CLINICAL STUDY PROTOCOL

Protocol Number:	E7438-G000-101
Study Protocol Title:	An Open-Label, Multicenter, Phase 1/2 Study of Tazemetostat (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B Cell Lymphomas and Tazemetostat in Combination With Prednisolone in Subjects With Diffuse Large B Cell Lymphoma
Sponsor:	Epizyme, Inc. 400 Technology Square – 4th Floor Cambridge, Massachusetts 02139 USA
Investigational Product Name:	Tazemetostat (formerly EPZ-6438 and E7438)
Indication:	Relapsed or refractory diffuse large B cell or follicular lymphoma
Phase:	1/2
Approval Date:	Original protocol: 01 Nov 2012

Amendment 1:	11 Feb 2013	*Amendment 9.1 (US only):*	*15 Apr 2016*
Amendment 2:	24 Apr 2013	Amendment 10:	21 Nov 2016
Amendment 3:	19 Jun 2013	*Amendment 10.1 (US only):*	*21 Nov 2016*
Amendment 4:	22 Oct 2013	*Amendment 10.2 (UK only):*	*28 Feb 2017*
Amendment 5:	24 Feb 2014	Amendment 11.0:	24 Sep 2018
Amendment 6:	29 Aug 2014	*Amendment 11.1 (UK only):*	*07 Nov 2018*
Amendment 6.1:	14 Oct 2014	*Amendment 11.2 (Canada only):*	*08 Nov 2018*
Amendment 7:	19 Feb 2015	*Amendment 11.3 (France only):*	*09 Dec 2019*
Amendment 7.1 (site-specific):	*21 May 2015*	*Amendment 12.0 (US only; **not implemented**):*	*25 Aug 2020*
Amendment 8 (first US):	15 Sep 2015	**Amendment 13.0:**	**10 Aug 2021**
Amendment 8.1 (US only):	*03 Nov 2015*	*Amendment 13.1 (UK only):*	*10 Aug 2021*
Amendment 9:	15 Apr 2016	*Amendment 13.2 (Canada only):*	*10 Aug 2021*
		Amendment 13.3 (France only):	*10 Aug 2021*

EudraCT Number:	2012-004083-21
IND Number:	124025
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of 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.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Epizyme (the Sponsor). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title: An Open-Label, Multicenter, Phase 1/2 Study of Tazemetostat (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B Cell Lymphoma and Tazemetostat in Combination With Prednisolone in Subjects With Diffuse Large B Cell Lymphoma

Protocol Number: E7438-G000-101

Approved by:

Responsible Sponsor Medical Officer:

Signature: PPD

Date: 10-Aug-2021 | 11:31 EDT

Epizyme, Inc.

Responsible Sponsor Medical Monitor:

Signature: PPD

Date: 10-Aug-2021 | 10:11 EDT

Epizyme, Inc.

INVESTIGATOR AGREEMENT PAGE

Protocol Title: An Open-Label, Multicenter, Phase 1/2 Study of Tazemetostat (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B Cell Lymphoma and Tazemetostat in Combination With Prednisolone in Subjects With Diffuse Large B Cell Lymphoma

Protocol Number: E-7438-G000-101

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

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

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

I have read and agree to the following Confidentiality Statement:

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

Principal Investigator:

Name: _____

Title: _____

Signature: _____ **Date:** _____

Name/Address of Institution: _____

_____

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 13.3 (France only)	*10 Aug 2021*
Amendment 13.2 (Canada only)	*10 Aug 2021*
Amendment 13.1 (UK only)	*10 Aug 2021*
Amendment 13.0	**10 Aug 2021**
*Amendment 12.0 (US only; **not implemented**)*	*25 Aug 2020*
Amendment 11.3 (France only)	*09 Dec 2019*
Amendment 11.2 (Canada only)	*08 Nov 2018*
Amendment 11.1 (UK only)	*07 Nov 2018*
Amendment 11.0	24 Sep 2018
Amendment 10	21 Nov 2016
Amendment 10.2 (UK only)	*28 Feb 2017*
Amendment 10.1 (US only)	*21 Nov 2016*
Amendment 09.1 (US only)	*15 Apr 2016*
Amendment 09	15 Apr 2016
Amendment 08.1 (US only)	*03 Nov 2015*
Amendment 08 *(first in US)*	15 Sep 2015
Amendment 07.1 (site-specific)	*21 May 2015*
Amendment 07	19 Feb 2015
Amendment 06.1	*14 Oct 2014*
Amendment 06	29 Aug 2014
Amendment 05	24 Feb 2014
Amendment 04	22 Oct 2013
Amendment 03	19 Jun 2013
Amendment 02	24 Apr 2013
Amendment 01	11 Feb 2013
Original protocol	01 Nov 2012

Amendment 13.0 (10 August 2021)

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

PLEASE NOTE: Because Protocol Amendment No 12.0 was specific to the US and was not implemented, this amendment describes changes from global Protocol Amendment No 11.0.

Overall Rationale for the Amendment:

This amendment is being made primarily for the following reasons:

- To remove the requirement of survival follow-up globally, as the primary efficacy outcome assessment has been met.
- To update contraception requirements for both male and female subjects, and to update prohibited medications and medications to be used with caution to ensure consistency with the US FDA approved tazemetostat label.

- To update the process for recording and reporting special situations, and to update the adverse event of special interest (AESI) assessment procedure and safety information to align with IBv11.0.
- To adjust record retention requirements.

Substantial changes to the protocol are detailed in the table below:

Section # and Name	Description of Substantial Change	Rationale
Section 1 Synopsis Section 7.1 Overall Study Design and Plan Section 7.3.4.4 Concomitant Medications to be Used with Caution Section 7.4.1.4 Exploratory Assessments Section7.4.2.2 Description of Assessment Schedule Section 7.4.5 Completion/Discontinuation of Subjects	Removed the requirement of overall survival (OS) follow-up, as of this protocol amendment.	No further OS follow-up in FL cohorts is required because the primary efficacy outcome assessments for the study are met.
Section 1 Synopsis Section 5.1.1.2 Nonclincal Experience with Tazemetostat Section 7.2.1 Inclusion Criteria	Updated contraception requirement as follows: - For women of childbearing potential: for 6 months after study drug discontinuation. - For male subjects: for 3 months after study drug discontinuation.	To ensure consistency with the US FDA approved tazemetostat label.
Section 7.3.4.3 Prohibited Concomitant Therapies and Drugs Section 7.3.4.4 Concomitant Medications to be used with Caution	Updated prohibited medications and medications to be used with caution with regard to CYP3A.	To ensure consistency with the US FDA approved tazemetostat label.
Section 7.3.2.2 Criteria for Retreatment, Temporary Discontinuation of Treatment, Dose Reduction, and Resumption of Treatment	Updated procedures for AESI assessment by the Epizyme Quarterly Safety Review committee and discontinuing tazemetostat in subjects who experience an AESI of MDS/AML or other myeloid malignancies like MPN.	To ensure consistent assessment of AESIs across Epizyme sponsored clinical trials and discontinuation of tazemetostat in subjects with MDS/AML or other myeloid malignancies like MPN.
Section 7.4.4.9 Adverse Events of Special Interest	Updated to align with tazemetostat IBv11.0 as follows: - Number of myeloid malignancy updated - Criteria of discontinuation for myeloid malignancy added	To ensure consistency with the approved tazemetostat IB v11.0.
Section 7.4.4.10.1 Special Situations: Overdose, Misuse, Abuse and Medication Error	Updated process for recording and reporting abuse, medication error, and overdose as follows:	To ensure consistent recording and reporting of special situations across

Section # and Name	Description of Substantial Change	Rationale
Section 7.4.6.3 Reporting of Special Situations	- Implemented a special situations form to capture these events in the safety database. - Provided clear steps for accurate recording of these events in the clinical and safety databases	Epizyme sponsored clinical trials.
Section 8.3.6 Retention of Records	Adjusted record retention requirements.	To ensure record retention for the full ICH retention period.

Abbreviations: AML = acute myeloid leukemia; AESI = adverse event of special interest; FDA = Food and Drug Administration; FL = follicular lymphoma; IB = Investigator's Brochure; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasms; OS = overall survival.

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

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

Section # and Name	Description of Non-Substantial Change	Brief Rationale
Title Page	Corrected previous amendment descriptions on title page. Specified that amendment 12.0 (US only) was not implemented.	To correct typographical errors. To add clarity concerning amendment 12.0.
Section 1 Synopsis Section 7.1 Overall Study Design and Plan	Specified "Enrollment Closed" for Phase 2.	To update study status for phase 2.
Section 5 Introduction	More accurately defined "mutant" and "wild-type" EZH2	To add clarity.
Section 7.6.1.1 Definition of Analysis Sets	Added a definition for the PGx Analysis Set.	To correct an error of omission in previous protocol versions.
Section 1 Synopsis Section 7.4.1.8 Other Assements Section 7.4.2 Schedule of Procedures/Assessments	As previously communicated to sites, removed the annual PK requirement. Also removed the redundant requirement of assessments to be performed annually while on study.	To align with previous communication of 16 May 2018 to sites that annual PK assessments were no longer required. To eliminate redundant assessments, as AESI and tumor response assessments are conducted at routine timepoints.

Abbreviations: AESI = adverse event of special interest; EZH2 = enhancer of zeste homolog 2; PGx = pharmacogenomics.

1 CLINICAL PROTOCOL SYNOPSIS

Compound Name

Tazemetostat (formerly known as EPZ-6438 and E7438)

Name of Active Ingredient

N-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-yl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4-yl)amino]-4-methyl-4'-(morpholin-4-ylmethyl)biphenyl-3-carboxamide hydrobromide

Study Protocol Title

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Sites

Phase 1: 2 sites (Institut Bergonie [IB] and Institut Gustave Roussy [IGR] sites in France only)
Phase 2: Up to 50 sites

Study Period and Phase of Development

Phase 1: First subject in 2Q2013; Last subject in 4Q2015. Enrollment closed.

Phase 2: First subject in 3Q2015; Last subject in 4Q2019. Enrollment closed.

Objectives

Primary Objectives

Phase 1

- To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of tazemetostat as a single agent administered orally twice daily (BID), continuously in 28-day cycles, in subjects with advanced solid tumors or with relapsed and/or refractory B cell lymphomas

Phase 2

- To determine the objective response rate (ORR; complete response + partial response [CR + PR]) of tazemetostat in subjects with enhancer of zeste homolog 2 (EZH2) gene mutation positive or negative (wild-type) with histologically confirmed diffuse large B cell lymphoma (DLBCL) or follicular lymphomas (FL), with relapsed or refractory disease and the ORR of tazemetostat in combination with prednisolone in subjects with EZH2 wild-type DLBCL

Secondary Objectives

Phase 1

- To assess the effect of a high-fat meal on the bioavailability of tazemetostat
- To assess the effect of tazemetostat on exposure of midazolam, a cytochrome P450 (CYP)3A4 substrate
- To assess the preliminary activity of tazemetostat

Phase 2

- To assess the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on progression-free survival (PFS)
- To assess the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on duration of response (DOR)

All Phases and Cohorts

- To assess the safety and tolerability of tazemetostat monotherapy and tazemetostat in combination with prednisolone
- To assess the pharmacokinetic (PK) profile of tazemetostat monotherapy and tazemetostat in combination with prednisolone

Exploratory Objectives

All Phases and Cohorts

- To explore the PK and pharmacodynamic (PD) relationship of tazemetostat
- To identify and investigate biomarkers and their correlation with biological activity for tazemetostat
- To explore the effects of tazemetostat on histone H3K27 methylation, target gene expression, and phenotypic markers including those for differentiation, apoptosis, cell proliferation, and changes in the tumor microenvironment
- To explore the role of DNA sequence variability on absorption, metabolism, excretion, and susceptibility to adverse events of tazemetostat
- To explore the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on overall survival

Study Design

Overall Design:

This is a multicenter, open-label, Phase 1/2 study that will be conducted in 2 parts. The Phase 1 part (dose escalation and expansion parts have completed enrollment) is comprised of dose escalation and expansion parts to establish the MTD and/or RP2D when tazemetostat is given BID orally on a continuous basis in subjects with histologically and/or cytologically confirmed advanced or metastatic solid tumors or B cell lymphomas that have progressed after treatment with approved therapies or for which there are no standard therapies available. Additionally, in separate cohorts in Phase 1, the effect of food on the bioavailability of tazemetostat will be evaluated as well as the drug-drug interaction (DDI) potential as evaluated by the effect of tazemetostat on the PK of midazolam, a CYP3A4 substrate. The effect of food on bioavailability cohort was initiated after safety of the 200 mg tazemetostat dose (highest available tablet dosage strength) was evaluated. The DDI potential cohort was initiated at the RP2D of 800 mg BID. The Food Effect (FE) and DDI cohorts were performed once the dose escalation was completed. The Phase 2 part was initiated once the MTD and/or RP2D was established. Phase 2 will enroll subjects with DLBCL (Cohorts 1-3 and 6) and FL (Cohorts 4 and 5) for the determination of efficacy and safety of tazemetostat monotherapy (Cohorts 1-5) and of tazemetostat in combination with prednisolone (Cohort 6) with placement determined by centrally confirmed histology, cell of origin (COO), and EZH2 mutation status as shown in the schematic below.

Phase 1

Subjects with advanced solid tumors or B cell lymphomas

Dose Escalation tazemetostat single agent

→ **Food Effect Substudy**
(13 subjects enrolled)
- Randomized to either fasted or fed tazemetostat treatment
- 200 mg single dose on Day -8 and Day -1
- Tazemetostat 400 mg BID beginning on Day 1

→ **DDI Substudy**
(13 subjects enrolled)
- Midazolam single dose on Day -1 and 15
- Tazemetostat (fasted) MTD/RP2D BID beginning on Day 1

→ **Phase 2**
Subjects with B cell lymphomas
Tazemetostat Monotherapy Cohorts
- Cohort 1: DLBCL (GCB subtype) EZH2 mutation positive (-enrollment closed)
- Cohort 2: DLBCL (GCB subtype) EZH2 wild-type (enrollment closed)
- Cohort 3: DLBCL non-GCB subtype (enrollment closed)
  Note: Upon cohort closure, up to 5 DLBCL non-GCB EZH2 mutation positive subjects can be enrolled in Cohort 1
- Cohort 4: FL (Grades 1 to 3) EZH2 mutation positive (up to 45 subjects) (enrollment closed)
- Cohort 5: FL (Grades 1 to 3) EZH2 wild-type (enrollment closed)

Tazemetostat/Prednisolone Combination Cohort
- Cohort 6: DLBCL GCB or non-GCB subtype EZH2 wild-type (enrollment closed)

BID = twice daily, DDI = drug-drug interaction, DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste- homolog 2, FL = follicular lymphoma, GCB = germinal-center B-cell-like, MTD = maximum tolerated dose, RP2D = recommended Phase 2 dose

Number of Subjects

Phase 1 (IB and IGR sites in France only):

Dose Escalation (closed to enrollment)

Thirty-eight subjects with advanced solid tumors or B cell lymphomas were enrolled.

Food Effect and Drug-Drug Interaction (closed to enrollment):

Thirteen evaluable subjects with advanced solid tumors or B cell lymphomas were enrolled in each FE and DDI cohort (for a total of 26 subjects).

Phase 2:

Up to 45 subjects will be enrolled in Cohort 4 FL (Grades 1-3) EZH2 mutation positive. All other cohorts have completed enrollment. Approximately 420 subjects will be enrolled in the entire study.

Sample Size Rationale

For Phase 1, the sample size of 6 to 45 subjects is considered adequate for the purposes of selecting a dose. Per Food and Drug Administration (FDA) guidance, 12 subjects are considered adequate to evaluate food effect. The sample size for the DDI cohort was not based on statistical considerations.

For Phase 2, the original study design planned enrollment of up to 30 subjects in each cohort. The initial assessment of efficacy was to be conducted within each cohort when 10 subjects had been enrolled (stage 1). For each DLBCL cohort, if zero responders (with CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 30% and there is a 2.8% probability of observing no responders among 10 subjects. For each FL cohort, if 1 or zero responders (CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 40% and there is a 4.6% probability of observing ≤ 1 responder among 10 subjects. Subsequent to the futility analysis in the DLBCL cohorts, the Data Monitoring Committee (DMC) endorsed a study design change to a modified 2-stage Green-Dahlberg design. The resulting expanded sample size is shown in the table below.

Up to 70 subjects with DLBCL (GCB or non-GCB, EZH2 wild-type) will be enrolled in an additional combination therapy cohort (tazemetostat and prednisolone), after completion of the accrual of the corresponding monotherapy cohort (2 or 3). A 2-stage Green-Dahlberg design will be used to terminate enrollment for futility. Prior to full enrollment of stage 1, initial tolerability of 800 mg BID tazemetostat in combination with prednisolone (40 mg/m^2 once daily on Days 1 to 5 and Days 15 to 19 in a 28-day cycle for a total duration of 16 weeks) will be assessed in the first 6 subjects enrolled based on the same set of dose limiting toxicity (DLT) criteria used in Phase 1. If a DLT is observed in no more than 1 of the 6 subjects, enrollment will continue to the end of stage 1. If a DLT is observed in more than 1 of the 6 subjects, lower dose level(s) of prednisolone may be evaluated. Subjects treated at the dose found to be tolerable during the initial safety run-in assessment will be included as part of the 35 subjects enrolled for stage 1.

	Monotherapy					**Combination Therapy**
	DLBCL GCB EZH2 Mutant	**DLBCL GCB EZH2 Wild-Type**	**DLBCL non-GCB**	**FL EZH2 Mutant**	**FL EZH2 Wild-Type**	**DLBCL GCB or non-GCB EZH2 Wild-Type**
Stage 1	10	10	10	10	10	35
Stage 2	50	50	50	35	35	35
Total	60	60	60	45	45	70

DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste- homolog 2, FL = follicular lymphoma, GCB = germinal-center B-cell-like

Inclusion Criteria

All Subjects:

1. Phase 1: Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Phase 2: ECOG performance status of 0 to 2 (Appendix 1).
2. Life expectancy ≥ 3 months before starting tazemetostat.
3. Subjects with a history of hepatitis B or C are eligible on the condition that subjects have adequate liver function as defined by Inclusion Criterion #6 and are hepatitis B surface antigen negative and/or have undetectable hepatitis C virus (HCV) RNA.
4. Adequate renal function defined as calculated creatinine clearance ≥ 40 mL/min per the Cockcroft and Gault formula (Appendix 2) or local institutional standard formula.

5. Adequate bone marrow function:
   a. Absolute neutrophil count (ANC) ≥ 750/mm^3 (≥ 0.75 × 10^9/L)
      - Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days
   b. Platelets ≥ 75,000/mm^3 (≥ 75 × 10^9/L)
      - Evaluated after at least 7 days since last platelet transfusion
   c. Hemoglobin ≥ 9.0 g/dL
      - May receive transfusion
6. Adequate liver function:
   a. Total bilirubin ≤ 1.5 × the upper limit of normal (ULN) except for unconjugated hyperbilirubinemia of Gilbert's syndrome
   b. Alkaline phosphatase (ALP) (in the absence of bone disease), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if subject has liver metastases)
7. Time between prior anticancer therapy and first dose of tazemetostat as below:
   - Cytotoxic chemotherapy – At least 21 days
   - Non-cytotoxic chemotherapy (eg, small molecule inhibitor) – At least 14 days
   - Nitrosoureas – At least 6 weeks
   - Monoclonal antibody(ies) – At least 28 days
   - Radiotherapy
     - At least 14 days from local site radiation therapy;
     - At least 6 weeks from prior radioisotope therapy;
     - At least 12 weeks from 50% pelvic or total body irradiation
   - High-dose therapy with autologous hematopoietic cell infusion – At least 60 days
   - High-dose therapy with allogeneic transplant – At least 90 days (if graft versus host disease [GVHD] is present, must be < Grade 2) and on no prohibited medications, per Exclusion Criterion #3)
     - **NOTE:** Starting at Cycle 1 Day 1, subjects may receive no more than 10 mg of prednisone daily (or equivalent corticosteroid, excluding protocol-defined prednisolone dosing for subjects enrolled in Cohort 6) when used for treatment of lymphoma-related symptoms, with the intent to taper by the end of Cycle 1.
8. Males or females aged ≥ 18 years at the time of informed consent (Phase 2). Males and females aged ≥16 years of age at time of informed consent (Phase 1).
9. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. All females will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutively amenorrheic, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). Females of childbearing potential must not have had unprotected sexual intercourse within 30 days prior to study entry and must agree to use a highly effective method of contraception, from the last menstrual period prior to randomization, during Treatment Cycles, and for 6 months after the final dose of study drug, and have a male partner who uses a condom. Highly effective contraception includes:
   a. Double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.
   b. Placement of an intrauterine device.
   c. Established hormonal contraceptive methods: oral, injectable, or implant. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and

for 6 months after study drug discontinuation.

Female subjects exempt from this requirement are subjects who practice total abstinence or have a male partner who is vasectomized. If currently abstinent, the subject must agree to use a highly effective method of contraception as described above if they become sexually active during the Treatment Cycles, and for 6 months after study drug discontinuation.

10. Male subjects must have had either a successful vasectomy **OR** they and their female partner must meet the criteria above (ie, not of childbearing potential **OR** practicing highly effective contraception and use a condom throughout the study period and for 3 months after study drug discontinuation).
11. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.

Phase 1 only (IGR and IB sites in France only):

12. Histologically and/or cytologically confirmed advanced or metastatic solid tumor or B cell lymphomas that have progressed after treatment with approved therapies or for which there are no standard therapies available.

Phase 2:

13. Subjects must satisfy all of the following criteria:
    a. Have histologically confirmed DLBCL (including primary mediastinal B cell lymphoma), with relapsed or refractory disease following at least 2 lines of prior standard therapy, including alkylator/anthracycline (unless anthracycline–based chemotherapy is contraindicated)/anti-CD20-based therapy (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] or equivalent) AND must be considered unable to benefit from intensification treatment with autologous hematopoietic stem cell transplantation (ASCT), as defined by meeting at least 1 of the following criteria:
        - Relapsed following, or refractory to, previous ASCT
        - Did not achieve at least a partial response to a standard salvage regimen (eg, rituximab, ifosfamide, carboplatin, and etoposide phosphate [R-ICE] or rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP])
        - Ineligible for intensification treatment due to age or significant comorbidity
        - Ineligible for intensification treatment due to failure to mobilize an acceptable number of hematopoietic stem cells
        - Refused intensification treatment and/or ASCT

        or

    b. Have histologically confirmed FL, all grades. Subjects may have relapsed/refractory disease following at least 2 standard prior systemic treatment regimens where at least 1 anti-CD20-based regimen was used. Subjects with prior radiotherapy will be included; however, radiotherapy alone will not be considered a separate systemic treatment regimen.
    c. Have provided sufficient archival tumor tissue that has been successfully tested for EZH2 mutation status and cell of origin (DLBCL only) at study specific laboratories allowing for allocation into an open cohort.
    d. Have measurable disease as defined by International Working Group-Non-Hodgkin's Lymphoma (IWG-NHL [Cheson, 2007]).

Exclusion Criteria

All Subjects:

1. Prior exposure to tazemetostat or other inhibitor(s) of EZH2.
2. Subjects with known leptomeningeal metastases or brain metastases or history of previously treated brain metastases.
3. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE 4.03 criteria) and any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS).
4. Has a prior history of T-LBL/T-ALL.
5. Subjects taking medications that are known potent CYP3A4 inducers/inhibitors (including St. John's wort) (see Section 7.3.4.3 and

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm; http://medicine.iupui.edu/clinpharm/ddis/).

6. Subjects unwilling to exclude Seville oranges, grapefruit juice, and grapefruit from their diet.
7. Any prior treatment-related (ie, chemotherapy, immunotherapy, radiotherapy), clinically significant toxicities have not resolved to ≤ Grade 1 per CTCAE version 4.03, or prior treatment-related toxicities are clinically unstable and clinically significant at time of enrollment.
8. Major surgery within 4 weeks before the first dose of study drug.
    - **NOTE**: Minor surgery (eg, minor biopsy of extracranial site, central venous catheter placement, shunt revision) is permitted within 3 weeks prior to enrollment.
9. Inability to take oral medication, or malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, or vomiting) that might impair the bioavailability of tazemetostat.
10. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug; or cardiac ventricular arrhythmia (Appendix 3).
11. Prolongation of corrected QT interval using Fridericia's formula (QTcF) to > 480 msec.
12. Venous thrombosis or pulmonary embolism within the last 3 months before starting tazemetostat.
13. Active infection requiring systemic therapy.
14. Known hypersensitivity to any component of tazemetostat, prednisolone/prednisone (combination cohort only), or inability to be treated with a *Pneumocystis* prophylaxis medication (combination cohort only).
15. Immunocompromised subjects, including subjects known to be infected with human immunodeficiency virus (HIV).
16. Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the subject's participation in this study.
17. Females who are pregnant or breastfeeding.
18. Subjects who have undergone a solid organ transplant.

Phase 2 only:

19. Subjects with noncutaneous malignancies other than B cell lymphomas.
    - **Exception:** Subjects with another malignancy who have been disease-free for 5 years, or subjects with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible.

Study Drugs

Study Drugs: Tazemetostat and Prednisolone (combination only)

Tazemetostat is available as tablets in strengths of 100 (Phase 1 only) and 200 mg and supplied in white high-density polyethylene bottles.

Prednisolone will be sourced by the Investigator through the site pharmacy. In this study prednisolone is considered background therapy.

Dosage and Administration: Tazemetostat and Prednisolone (combination only)

Tazemetostat is administered orally with or without food. The doses being administered in each part of the study are as follows:

Phase 1 Dose Escalation **(closed to enrollment)** – Five dose levels were explored: 100 mg BID, 200 mg BID, 400 mg BID, 800 mg BID and 1600 mg BID starting on Cycle 1 Day 1.

Phase 1 Food Effect **(closed to enrollment)** – A single 200 mg dose administered on Day -8 and Day -1. Starting on Cycle 1 Day 1 400 mg BID is administered.

Phase 1 Drug-Drug Interaction **(closed to enrollment)** – Midazolam 2 mg is given orally on Day -1 and Day 15. Starting on Cycle 1 Day 1, tazemetostat 800 mg BID is administered.

Phase 2 – In the monotherapy cohorts, 800 mg BID is administered starting on Cycle 1 Day 1. In the combination cohort, tazemetostat is administered at 800 mg BID starting on Cycle 1 Day 1 continuously and prednisolone is administered at 40 mg/m^2 (rounding can be done per local standard practice) once daily on Days 1 to 5 and Days 15 to 19 in a 28-day cycle for a total duration of 16 weeks. After the combination treatment, tazemetostat will be continued as a monotherapy at 800 mg BID continuously. There will be a run-in of up to 6 subjects to evaluate the tolerability of the combination treatment. If the tolerability is not acceptable, lower dose(s) of prednisolone may be evaluated.

Duration of Treatment

The Treatment Phase for the Phase 1 Dose Escalation part will last for 1 cycle. In the Extension Phase, subjects may remain on study until they have disease progression, development of unacceptable toxicity that leads to tazemetostat treatment withdrawal, or withdrawal of consent.

Food Effect and DDI cohorts were initiated as part of the Phase 1 study after safety of the 200 mg tazemetostat dose (highest available tablet dosage strength) was evaluated, and at the RP2D of 800 mg BID, respectively. The Treatment Phase for both cohorts will last until the end of Cycle 1.

Subjects will continue to receive study treatment per study design until disease progression, development of unacceptable toxicity that leads to study treatment withdrawal, or withdrawal of consent. Investigators who note subjects with disease progression that are receiving continued clinical benefit without clinical deterioration should contact the Medical Monitor to discuss the assessment of risk/benefit of keeping the subject on study.

As of Amendment 13.0, long-term survival follow-up is no longer required for subjects after discontinuation of study treatment. Also, annual PK sample collections for assessment were no longer required as of as of 16 May 2018.

Rollover Study: All subjects in Phase 1 who remain on tazemetostat for 9 months or longer, and are eligible to continue receiving tazemetostat, will transfer to a Rollover Study for monitoring and continued study drug at the Investigator's and the Medical Monitor's discretion. All subjects in Phase 2 who remain on tazemetostat for 24 months or longer, and are eligible to continue receiving tazemetostat, also will transfer to a Rollover Study for monitoring and continued access to study drug at the Investigator's and the Medical Monitor's discretion.

2 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
^{18}FDG-PET	^{18}fluorodeoxyglucose-positron emission tomography
ABC	activated B-cell-like
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	autologous hematopoietic stem cell transplantation
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from zero extrapolated to infinity
AUC_{0-12}	area under the concentration-time curve from zero time to 12 hours
AUC_{0-24}	area under the concentration-time curve from zero time to 24 hours
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BP	blood pressure
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
C_{max}	maximum drug concentration
CL	total body clearance
CLr	renal clearance
CNS	central nervous system
COO	cell of origin
COP	CHOP without doxorubicin
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EZH2	enhancer of zeste homolog 2
EU	European Union
FDA	Food and Drug Administration
fe	fraction excreted
FE	food effect
FFPE	formalin fixed paraffin embedded
FL	follicular lymphoma
GCB	germinal-center B-cell-like

Abbreviation	Term
GCP	Good Clinical Practice(s)
GVHD	graft versus host disease
H3K27	histone H3 lysine 27
H3K27me3	trimethylated state of histone H3 lysine 27
HAT	histone acetyltransferase
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HMT	histone methyltransferase
HR	heart rate
IB	Institut Bergonie (when referring to study site in France) Investigator's Brochure (when referring to document)
IC_{90}	90% of the maximal inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGR	Institut Gustave Roussy
IHC	immunohistochemistry
IRB	Institutional Review Board
IV	intravenous
IWG-NHL	International Working Group-Non-Hodgkin's Lymphoma
LNH	low/normal/high classification
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NE	not evaluable
NHL	non-Hodgkin lymphoma
NYHA	New York Heart Association
ORR	objective response rate
PCR	polymerase chain reaction
PD	pharmacodynamic(s) or progressive disease
PET	positron-emission tomography
PFS	progression-free survival
PI	Principal Investigator
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)
PMBCL	primary mediastinal B cell lymphoma
PR	partial response
PT	preferred term
QT	the time interval from the beginning of the cardiac QRS complex to the end of the T wave
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
R	accumulation ratio
R-CHOP	rituximab plus CHOP
R-DHAP	rituximab, dexamethasone, cytarabine, and cisplatin
RECIST	Response Evaluation Criteria in Solid Tumors
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide phosphate
RP2D	recommended Phase 2 dose

Abbreviation	Term
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
tazemetostat (EPZ-6438 and E7438)	investigational study drug: *N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-yl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4-yl)amino]-4-methyl-4'-(morpholin-4-ylmethyl)biphenyl-3-carboxamide hydrobromide
T-ALL	T-cell acute lymphoblastic leukemia
T-LBL	T-cell lymphoblastic lymphoma
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum concentration (following drug administration)
ULN	upper limit of normal
US/USA	United States/United States of America
UTX	ubiquitously transcribed tetratricopeptide repeat, X chromosome
UV	ultraviolet
V_d	volume of distribution

4 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Epizyme (the Sponsor) at up to 5 investigational sites in the European Union (EU) for the Phase 1 part of the study. Investigational sites for Phase 2 are being identified globally.

The name of the Sponsor's medical monitor, along with the telephone and fax numbers of the other contact persons at the Sponsor and, if applicable, any contract research organization (CRO), will be listed in the Investigator File provided to each site.

5 INTRODUCTION

Tazemetostat is a selective small molecule inhibitor of the histone lysine methyltransferase enhancer of zeste homolog 2 (EZH2). Posttranslational modifications of core histone proteins of chromatin play an important role in controlling the fidelity of gene transcription patterns in cells. Paramount among these transcription-controlling modifications is methylation events at lysine and arginine residues, catalyzed by histone methyltransferases (HMTs). Genetic alterations in a number of HMTs have been identified in human cancers where they are purported to play a causal role in malignancies. Of note, non-Hodgkin lymphoma (NHL) shows a high propensity in mutations in chromatin modifying enzymes, including HMTs (EZH2, MLL2), histone demethylases (for instance ubiquitously transcribed tetratricopeptide repeat, X chromosome, UTX) and histone acetyltransferases (HATs), perturbing the state of chromatin leading to aberrant gene expression (Morin, 2011). EZH2 is the catalytic subunit of the multi-protein HMT complex known as polycomb repressive complex 2, which is responsible for mono-, di-, and tri-methylation of histone H3 lysine 27 (H3K27); hypertrimethylation of H3K27 is known to silence tumor suppressor genes and thus to be tumorigenic. MLL2, in contrast, methylates H3K4, a histone modification associated with actively transcribed chromatin (Milne, 2005). Loci of genes bivalently modified at H3K27 and H3K4 are poised for rapid expression regulation in either direction (Voigt, 2013), and perturbation of the correct methylation balance can lead to cancer (Béguelin, 2013). Multiple mechanisms have been shown to lead to hypertrimethylation of H3K27 in cancer, including mutation, amplification and overexpression of EZH2, and inactivating mutations of the H3K27 demethylase UTX. Somatic mutations in the catalytic SET (Su(var)3-9, Enhancer-of-zeste and Trithorax) domain of the EZH2 gene at 3 hotspot residues (Y646, A682, and A692 [NM_001203247]) are present in follicular and diffuse large B cell lymphomas (FL, DLBCL) and lead to high levels of H3K27 trimethylation (H3K27me3) in these lymphomas. These gain-of-function (GOF) mutations of EZH2 render the enzyme constitutively active and, therefore, have been proposed to be required for the development and maintenance of EZH2 mutation-bearing lymphomas. Inhibition of EZH2 leads to reduction in H3K27me3 and cell death in lymphoma cell lines bearing the mutation. In addition, loss of function of MLL2 and HATs may generate abnormal methylation states of H3K27, potentially leading to a dependency

on EZH2. In nonclinical models, inhibition of EZH2 leads to reduction in H3K27me3 in all lymphoma cell lines irrespective of their EZH2 mutation status. While cells with wild-type EZH2 (operationally defined here as lacking any of the GOF mutations within the SET domain that define "mutant" EZH2 [specifically, lacking any of the following mutations within codons Y646, A682, and A692 of the EZH2 gene: Y646F, Y646N, Y646S, Y646H, Y646C, A682G, and/or A692V (Bodor, 2013). While cells with wild-type EZH2 are growth inhibited with EZH2 inhibition in vitro, only mutation bearing cells undergo cell death in culture (Béguelin, 2013; Knutson, 2014a).

Changes to the tumor microenvironment, for instance those affecting antitumor immunity, are increasingly recognized as an important mechanism in lymphomagenesis, affecting all types of NHL (Scott, 2014). Epigenetic therapy has been suggested to release repression of molecules important for immune recognition on tumor cells (Wrangle, 2013), and EZH2 inhibition may induce similar effects. In addition, loss of EZH2 has been described as affecting T helper cell plasticity (Tumes, 2013) and is proposed to inhibit the function of regulatory T cells (Arvey, 2014; DuPage, 2015; Yang, 2015), suggesting that EZH2 inhibition may contribute to enhancing antitumor immunity.

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

Diffuse large B cell lymphoma (DLBCL) and FL are the 2 most common lymphoid malignancies with annual incidences of 3.8 and 2.2/100,000, respectively, in Europe (Sant, 2010) and 6.9 and 3.7/100,000, respectively, in the United States (US) (National Cancer Institute, 2014). For both DLBCL and advanced FL, chemoimmunotherapy with rituximab has substantially improved long-term disease control (Dreyling, 2014; Tilley, 2012). There are 3 histologically indistinguishable molecular subtypes of DLBCL: the activated B-cell-like (ABC) subtype, the germinal-center B-cell-like (GCB) subtype, and the primary mediastinal B cell lymphoma (PMBCL) subtype. These subtypes differ in terms of gene expression and are believed to originate in B cells at different stages of differentiation. In addition, the process of malignant transformation differs for each subtype, resulting in distinctive patterns of genetic abnormality. Clinical presentation and responsiveness to targeted therapies also vary across the subtypes (Foon, 2012).

Gene expression in GCB lymphomas is characteristic for germinal-center B cells, with deletion of the tumor suppressor gene PTEN and p53 mutations being specific to GCB lymphomas. Genetic abnormalities that are characteristic for ABC DLBCL include deletion of the INK4α/ARF tumor suppressor locus on chromosome 9 and amplification of the 9-Mb region on

chromosome 19. Loss of these tumor suppressors impedes the action of chemotherapy and may contribute to the poor prognosis associated with this subtype. PMBCL may present with distinct clinical features, with disease thought to originate in the thymus, and often confined to the mediastinum. Gene expression profiling may provide additional information on characteristics of PMBCL such as deletion of SOCS1, a suppressor of JAK signaling, and gene profiling has identified similarities between PMBCL and classical Hodgkin's lymphoma (Foon, 2012; Rosenwald, 2003). FL is thought to arise from germinal-center B cells, and the majority of subjects have a t(14:18) translocation at the site of the BCL-2 oncogene and 1 of the 3 immunoglobulin genes. However, BCL-2 expression alone is not considered sufficient for FL development and other genetic mechanisms or host factors, such as epigenetic abnormalities, are considered required. FL is graded based on the proportion of centroblasts in the follicle with Grade 3b often being BCL-2 negative and displaying histological similarities to DLBCL. An integral part of the natural history of FL is progression to a higher grade histologic subtype such as DLBCL.

Of note, in the Phase 1 Dose Escalation part of the present study, objective responses have been observed in both subjects lacking EZH2 GOF mutations (ie, wild-type) and subjects with mutant EZH2 NHL. In addition, objective responses have been noted in subjects with both GCB and non-GCB cell of origin (COO), determined by immunohistochemistry (IHC), including 1 subject with a classical clinical presentation of PMBCL. Based on these findings, the design of the Phase 2 part of this study has been modified to include a new cohort to evaluate the activity of tazemetostat in subjects with the non-GCB DLBCL subtype (inclusive of subjects with PMBCL), in addition to the previously described cohorts for mutation-bearing and non-mutation-bearing GCB DLBCL.

5.1 Investigational Product

Tazemetostat is under investigation as a treatment for subjects with relapsed or refractory DLBCL or FL for the Phase 2 portion of the protocol. Prednisolone in combination with tazemetostat will also be assessed as a treatment for subjects with relapsed or refractory DLBCL.

5.1.1 Tazemetostat

Active ingredient: *N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-yl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4-yl)amino]-4-methyl-4'-(morpholin-4-ylmethyl)biphenyl-3-carboxamide hydrobromide

5.1.1.1 Therapeutic Pathway or Mechanism of Action

Tazemetostat inhibits EZH2, both wild-type (ie, lacking EZH2 GOF mutations) and mutation-bearing, with nanomolar affinity. The compound shows 36-fold selectivity over the closest

family member, EZH1, and greater than 4500-fold selectivity over other HMTs. It selectively inhibits intracellular histone H3K27 methylation in a concentration and time-dependent manner. Incubation with tazemetostat inhibits the proliferation of lymphoma cell lines, with those bearing EZH2 activating mutations being on average more sensitive. Administration of tazemetostat to mice bearing human DLBCL xenografts (4/5 EZH2 mutant DLBCL and 2/3 EZH2 wild-type DLBCL tested so far) induced significant antitumor effects, ranging from tumor growth inhibition to complete and durable tumor regressions (Knutson, 2014b; and unpublished). To determine the combination potential of tazemetostat with DLBCL standard of care, in vitro and in vivo studies of tazemetostat were performed with the constituent components or active metabolites of CHOP (Knutson, 2014b; and unpublished). In the in vitro studies, an additive or modest synergy benefit was seen for the DNA alkylating agent mafosfamide (a cyclophosphamide analogue), the DNA intercalating agent hyroxyldaunorubicin, and tubulin disrupting agent vincristine in DLBCL cell lines containing EZH2 GOF mutations at SET domain residues Y646, A682, or A692 that result in constitutive EZH2 activity and elevated levels of H3K27me3. Dramatic in vitro synergy was observed when tazemetostat was combined with glucocorticoid receptor agonist prednisolone (the active metabolite of prednisone) or dexamethasone in DLBCL cell lines containing either wild-type (ie, lacking EZH2 GOF mutations) or mutant EZH2.

These in vitro results were extended into in vivo studies with 3 different EZH2 mutant lymphoma xenograft models. Combination treatments with CHOP or COP (CHOP without doxorubicin) were well-tolerated and significant synergy with regards to antitumor responses and/or tumor regressions were observed when tazemetostat was co-administered with either CHOP or COP. In line with the in vitro data, the combination benefit was also observed when tazemetostat was combined with prednisone alone. These in vitro and in vivo combination results provide a basis for investigating a new combination therapy in patients with DLBCL.

5.1.1.2 Nonclinical Experience with Tazemetostat

Nonclinical safety assessments of tazemetostat included in vitro and monkey safety pharmacology studies, genotoxicity studies, and single- and repeat-dose toxicity studies in Sprague-Dawley rats and cynomolgus monkeys of 4- and 13-weeks duration. No notable cardiovascular, central nervous system (CNS), or respiratory risks were identified in nonclinical safety pharmacology assessments. Tazemetostat was not genotoxic in standard in vitro and in vivo assays. The following potential risks were identified for tazemetostat based on nonclinical safety data: T-LBL (rat), increased bone formation in bone and teeth (rat), non-progressive bile duct hyperplasia (monkey), teratogenicity (rat and rabbit), lymphoid depletion (rat and monkey), and phototoxic potential (in vitro). Other effects at high,

non-tolerated doses, toxicities included bone marrow effects (hypocellularity, rat), and gastrointestinal toxicity (distention, ulceration, and degeneration, rat).

Steady-state exposures (area under the concentration–time curve from 0 to 24 hours [AUC_{0-24}]) in rats at the lowest dose (100 mg/kg/day) at which no T-LBL occurred in the 13-week adolescent rat study were 2.5- to 7.5-fold greater than that observed in humans at the recommended Phase 2 dose (RP2D; 800 mg twice daily [BID]) from the ongoing Phase 1/2 Study E7438-G000-101. No incidences of abnormal bone formation have been observed in the ongoing clinical study. Female subjects of reproductive age will provide blood and urine samples for pregnancy testing at screening.

All subjects must agree to use a reliable birth control method during the study, and for for 6 months (female subjects) or 3 months (male subjects) after the last tazemetostat dose, and additionally will be actively monitored for signs or symptoms of abnormal bone formation.

5.1.1.3 Clinical Experience with Tazemetostat

This clinical study (Phase 1/2) is the first-in-human study with tazemetostat. The study parts and dose levels of the Phase 1 study are: Dose Escalation at 100 mg BID, Dose Escalation at 200 mg BID, Dose Escalation at 400 mg BID, Dose Escalation at 800 mg BID, Dose Escalation at 1600 mg BID, Dose Expansion at 800 mg BID, Dose Expansion at 1600 mg BID, Food Effect (FE) at 400 mg BID, and Drug-Drug Interaction (DDI) at 800 mg BID. The Phase 1 dose escalation and expansion parts have been completed and the recommended Phase 2 dose (RP2D) was defined as 800 mg BID. The Phase 1 part also determined the relationship between exposure and H3K27me3 reduction in skin, and provided a preliminary assessment of activity.

As of 7-Nov. 2015, 58 subjects were enrolled into the study (dose escalation, dose expansion, food effect, and drug-drug interaction), including 21 NHL subjects (14 DLBCL, 6 follicular lymphoma [FL], and 1 marginal zone lymphoma [MZL]). Adverse events (AE) occurring in ≥ 10% of the 58 subjects regardless of attribution were asthenia, anorexia, thrombocytopenia, nausea, diarrhea, and vomiting. There were 4 Grade ≥ 3 related AEs: thrombocytopenia, neutropenia, hypertension, and transaminase elevation. The median age of the NHL subjects enrolled was 63 years (range: 24-84) and 71% of subjects were male. Among the 16 response-evaluable NHL subjects, objective responses were seen in 5/10 DLBCL, 3/5 FL and 1/1 MZL subjects.

As of 19-Aug. 2016, 106 subjects were enrolled to the 5 monotherapy cohorts in the Phase 2 portion of the study. The safety profile of subjects in Phase 2 was generally consistent with that observed for subjects in Phase 1. As part of safety surveillance reporting, 6% of subjects were observed to experience Grade 3 or higher infection/infestation in the entire study (n = 170, with 64 subjects in Phase 1), of which only 1% experienced an opportunistic pneumonia

(*Pneumocystis jirovecii* pneumonia). Based on the review of safety and efficacy data, the DMC concluded on 6-Sep. 2016 that futility hurdles had been surpassed in all 5 monotherapy cohorts and no safety issues preclude the continued enrollment of study subjects.

Further information on clinical efficacy and safety can be found in the tazemetostat Investigator's Brochure (IB).

5.1.1.4 Common Serious Adverse Events Expected to Occur in the Study Population Even in the Absence of Study Drug Exposure

Lymphomatous meningitis, superior vena cava syndrome, compression syndromes, spinal cord compression, and pathologic fractures are known to occur in this study population.

5.1.2 Prednisolone

Prednisolone, an active metabolite of prednisone, is widely used for managing many types of disorders including aggressive lymphoma. Although its single-agent efficacy has been rarely documented, prednisolone has been integrated in important combination regimens in NHL, such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (Cunningham, 2013). While prednisolone is generally well tolerated, chronic administration has been associated with adverse reactions including but not limited to fluid and electrolyte disturbances, muscle weakness, osteoporosis, peptic ulcer, pancreatitis, impaired wound healing, thin fragile skin, headache, convulsion, endocrine disorder (such as Cushingnoid state), etc. In this protocol, prednisolone will be administered in combination with tazemetostat to be assessed as a treatment for subjects with relapsed or refractory DLBCL.

5.2 Study Rationale

The proposed clinical study is a multicenter, open-label, Phase 1/2 study that will be conducted in 2 parts.

The Phase 1 part (Institut Bergonie [IB] and Institut Gustave Roussy [IGR] sites in France only) will comprise dose escalation and establishment of the maximum tolerated dose (MTD) and/or RP2D when tazemetostat is given BID orally on a continuous basis in subjects with histologically and/or cytologically confirmed advanced or metastatic solid tumors or B cell lymphomas that have progressed after treatment with approved therapies or for which there are no standard therapies available. Additionally, in separate cohorts in Phase 1, the effect of food on the bioavailability of tazemetostat will be evaluated as well as the DDI potential as evaluated by the effect of tazemetostat on the pharmacokinetics (PK) of midazolam, a cytochrome P450 (CYP)3A4 substrate. The effect of food on bioavailability will be initiated at 200 mg tazemetostat dose (highest available tablet dosage strength). DDI potential will be initiated at

800 mg BID (RP2D). The FE and DDI cohorts may be performed in parallel and may subsequently continue in parallel with Phase 2.

The Phase 2 part will be initiated at a recommended dose of 800 mg BID. Based upon both the in vitro responses to tazemetostat of both EZH2 wild-type and mutant DLBCL cell lines and Phase 1 objective responses seen to date (Knutson, 2014a; Ribrag, 2015). Phase 2 will enroll subjects with DLBCL (Cohorts 1-3 and 6) or FL (Cohorts 4 and 5) for the determination of efficacy and safety of tazemetostat monotherapy (Cohorts 1-5) and of tazemetostat in combination with prednisolone (Cohort 6) with placement determined by centrally confirmed histology, COO, and EZH2 mutation status.

There are a limited number of treatment options for patients with relapsed/refractory DLBCL who may have poor bone marrow reserve after multiple prior treatments with chemotherapy. This study will evaluate the activity of the combination of tazemetostat and prednisolone in these patients (see Section 5.1.1.1 for in vitro and in vivo data on this combination). The combination will first be tested in a safety evaluation (safety run-in) and then expanded to a larger cohort for further safety confirmation and efficacy futility assessment (stage 1). The safety data of tazemetostat and prednisolone were carefully reviewed to identify potential areas of overlap for the most commonly reported adverse events. Based on the mechanisms of action and safety profiles of tazemetostat and prednisolone, the likelihood of overlapping toxicities of tazemetostat and prednisolone is considered low, with the exception of infection given the potential for immune suppression with steroid therapy or the combination therapy. This potential risk will be mitigated by prophylactic treatment with sulfamethoxazole and trimethoprim. Investigators should monitor subjects for infections and administer necessary treatments per their medical judgment. Prednisolone has a half-life of ~2 hours and is a CYP3A substrate and inducer. The risk of decreased tazemetostat exposure by prednisolone is acceptable given the intermittent dosing schedule of prednisolone. It is also plausible that the prednisolone exposure may be decreased by tazemetostat. Nevertheless, study drug exposure will be monitored throughout the study to evaluate for a DDI effect, allowing for potential future dosing revisions.

The preclinical demonstration of therapeutic synergy of tazemetostat and prednisolone, balanced with the implementation of protocol designated risk mitigation and safety monitoring for potential areas of overlapping toxicity support the rationale for the assessment of this treatment combination in patients with relapsed DLBCL.

5.2.1 Rationale for Dosage Selection

5.2.1.1 Tazemetostat

The first-in-human dose selected for tazemetostat is 100 mg BID or 200 mg daily. This dose has been intentionally chosen as a conservative starting point to maximize safety margins since,

according to the standard DeGeorge method, 1/10 of the severely toxic dose in rats resulted in a suggested starting dose of 150 mg BID (300 mg/day) in humans.

Twice-daily administration of tazemetostat was selected based on the nonclinical studies in nude and severe combined immunodeficiency mice xenograft models, wherein BID dosing resulted in maximal tumor growth inhibition and sustained inhibition of intratumoral H3K27me3.

In a nonclinical study, the tazemetostat mean bioavailability in the fed state was roughly 5-fold lower than that in fasted state in cynomolgus monkeys. Thus, this study was originally designed to administer tazemetostat in the fasted state, defined as no food for 2 hours before and after study drug ingestion. The effect of food on tazemetostat bioavailability in humans was explored in the Phase 1 part of this study to inform tazemetostat dosing in the Phase 2 part.

Tazemetostat is metabolized primarily by CYP3A4. Tazemetostat was also shown to be a time-dependent CYP3A4 inhibitor and a CYP3A4 inducer. To assess the effect of tazemetostat coadministration on drugs metabolized by CYP3A4, a DDI cohort with midazolam, a probe CYP3A4 substrate, is included in this study. Assessment of the effect of tazemetostat on exposure to midazolam and its metabolites will be used to guide coadministration of tazemetostat with drugs metabolized by CYP3A4.

Tazemetostat was initially supplied as an oral suspension. Tazemetostat was subsequently made available as tablets in strengths of 50, 100, and 200 mg and supplied in white high-density polyethylene (HDPE) bottles. The first cohort (100 mg BID) included 3 subjects dosed with tazemetostat suspension and 3 subjects dosed with the tazemetostat tablet formulation. Tablet strengths of 200 mg will be made available during the Phase 2 part of the study.

Inclusion of subjects 16 years of age and older in Phase 1 (FE and DDI cohorts only):

PK modeling has been conducted using a GastroPlus PBPKPlus module that is integrated with age-related population data for body weight, height, body mass index, and bioelectrical impedance resistance measured at 50 KHz for humans from the US population 0 to 85 years of age. Using tazemetostat concentration-time data from the completed Phase 1 Dose Escalation/Expansion part of the current study, the predicted mean steady-state AUC and steady-state maximum drug concentration (C_{max}) values were 4900 ng•h/mL and 1500 ng/mL, respectively, for subjects 12 to 18 years of age after administration of 800 mg BID. These predicted PK exposure values are within the range of observed values in subjects after administration of 800 or 1600 mg BID. The 1600 mg BID dose was tolerated without a MTD being reached.

5.2.1.2 Prednisolone

Prednisolone (40 mg/m^2 once daily) was a component of R-CHOP14 (Cunningham, 2013), a dose intense immunochemotherapy regimen which was administered once every 2 weeks for a total of 6 cycles (12 weeks). In a separate Phase 3 study (Delarue, 2013), prednisone was used in the R-CHOP14 regimen for a total duration of 8 cycles (16 weeks). There was no significant difference in the safety or efficacy profile when R-CHOP was administered every 2 weeks vs 3 weeks, and no significant toxicity was associated with the glucocorticoid use in either of the R-CHOP regimens (Cunningham, 2013; Delarue, 2013). In addition, a Phase 1b/2 study (EudraCT 2016-001499-31) is being initiated by the French Lymphoma Study Association evaluating the combination treatment of tazemetostat with 8 cycles of R-CHOP in DLBCL subjects who have not received anticancer treatment. To synchronize with the current dosing schedule of tazemetostat (28-day cycle), prednisolone will be dosed for a total period of 16 weeks in this proposed study.

Prednisolone concentrations of 1 µM (~360 ng/mL) resulted in a 7-fold enhancement of the potency of tazemetostat against an EZH2-mutant cell line (Knutson, 2014b). Enhancement of the effect of tazemetostat on tumor growth in mice bearing an EZH2-mutant lymphoma xenograft was observed after oral administration of 0.15 mg/kg prednisone twice daily. El Dareer et al. (1977) demonstrated that a 10 mg/kg oral dose of prednisone to mice resulted in a mean serum prednisolone C_{max} of approximately 3000 ng/mL. The estimated prednisolone C_{max} after administration of 0.15 mg/kg to mice is approximately 45 ng/mL assuming that systemic exposure to prednisolone increases in proportion to the dose of prednisone. A single oral dose of 50 mg (~30 mg/m^2 in a 1.75 m^2 subject) prednisolone administered to healthy volunteers resulted in a mean plasma C_{max} of approximately 1000 ng/mL (Luippold, 2001). These results suggest that a dose of 40 mg/m^2 in subjects with lymphoma will result in plasma concentrations greater than those that resulted in enhancement of tazemetostat activity in preclinical models.

5.2.2 Rationale for Phase 2 Dose

Oral tazemetostat doses of 100 mg to 1600 mg BID were investigated in the Dose Escalation part of this study. As of 09-Jul. 2015, 45 subjects with advanced or metastatic solid tumors or B cell lymphomas had been included in the Phase 1 Dose Escalation part of the study. Clinical activity of tazemetostat was observed at dose levels of 100, 200, and 800 mg BID, including objective responses observed in 9 of 15 evaluable subjects with B cell lymphoma who have had tumor assessments while on study drug. Objective responses were observed in 5/9 DLBCL, 3/5 FL, and 1/1 MZL subjects. An MTD was not established with tazemetostat doses of up to 1600 mg BID.

Inhibition of H3K27Me3 in skin was utilized as a measure of target engagement. A relationship between tazemetostat AUC on Day 15 and inhibition of H3K27 methylation in skin was

observed in the Dose Escalation part of Study E7438-G000-101. Results of preliminary pharmacokinetic/pharmacodynamic (PK/PD) modelling predicted that a tazemetostat Day 15 AUC of approximately 4000 ng•h/mL will result in 90% of the maximal inhibition (IC_{90}) of H3K27Me3 in the skin. The mean tazemetostat area under the concentration-time curve from zero time to 12 hours (AUC_{0-12}) on Day 15 in the 800 mg BID cohort (n = 13) was 3670 ng•h/mL, which is similar to the predicted IC_{90}.

The safety, tolerability, clinical activity, PK, and pharmacodynamic (PD) assessments from the subjects treated in the Dose Escalation part of the study were used to select the RP2D. The greatest number of objective responses was observed in the 800 mg BID cohort during the Dose Escalation part of the study. Administration of 800 mg tazemetostat BID also resulted in a mean AUC_{0-12} similar to the AUC predicted to result in 90% of the maximal inhibition of H3K27Me3 in skin. Therefore, the RP2D of 800 mg BID was selected. This RP2D has been endorsed by the investigators and an independent Data Monitoring Committee (DMC). A summary of the preliminary PK parameters from the food effect portion of this study is displayed in Table 1.

Table 1 Geometric Mean [(%CV), (range)] for Preliminary Tazemetostat Pharmacokinetic Parameters after Administration Fasted or Immediately After a High-Fat Breakfast in Study E7438-G000-101 (n = 11)

Meal State	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng*h/mL)	t_{max}[a] (h)
Fed	232 (107) (65.7 – 752)	1080 (85.3) (317.7 – 3070)	4.0 (1.0 – 6.0)
Fasted	322 (130) (59.6 – 1470)	1140 (135) (179.3 – 6251)	1.0 (0.5 – 6.0)

$AUC_{0-\infty}$ = area under the concentration-time curve from zero extrapolated to infinity, C_{max} = maximum drug concentration, CV = coefficient of variation, n = number of subjects, t_{max} = time to reach maximum concentration (following drug administration)

a t_{max} presented as median (range)

Administration of tazemetostat with a high-fat meal decreased geometric mean area under the concentration-time curve from zero extrapolated to infinity ($AUC_{0-\infty}$) and C_{max} values approximately 6% and 28%, respectively, relative to administration in the fasted state. However, for both C_{max} and $AUC_{0-\infty}$, all values observed after administration of tazemetostat following a high-fat meal were within the range of values observed after administration in the fasted state. Administration of tazemetostat with a high-fat meal also resulted in a 4-fold increase in median time to reach maximum concentration (following drug administration) (t_{max}) relative to administration in the fasted state. The relationship between tazemetostat AUC on Day 15 and inhibition of H3K27 methylation in skin observed in the Dose Escalation part of Study E7438-G000-101 indicates that target inhibition is related to AUC. The decrease in

systemic exposure as measured by $AUC_{0-\infty}$ is not clinically significant, and therefore, tazemetostat can be taken without regards to meals.

Further information on the rationale for the RP2D can be found in the tazemetostat IB.

6 STUDY OBJECTIVES

6.1 Primary Objectives

The primary objectives of this study are:

Phase 1

- To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of tazemetostat as a single agent administered orally twice daily (BID), continuously in 28-day cycles in subjects with advanced solid tumors or with relapsed and/or refractory B cell lymphomas

Phase 2

- To determine the objective response rate (ORR; complete response + partial response [CR + PR]) of tazemetostat in subjects with enhancer of zeste homolog 2 (EZH2) gene mutation positive or negative (wild-type) with histologically confirmed diffuse large B cell lymphoma (DLBCL) or follicular lymphomas (FL) with relapsed or refractory disease and the ORR of tazemetostat in combination with prednisolone in subjects with EZH2 wild-type DLBCL

6.2 Secondary Objectives

The secondary objectives of this study are:

Phase 1

- To assess the effect of a high-fat meal on the bioavailability of tazemetostat
- To assess the effect of tazemetostat on exposure of midazolam, a cytochrome P450 (CYP)3A4 substrate
- To assess the preliminary activity of tazemetostat

Phase 2

- To assess the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on progression-free survival (PFS)
- To assess the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on duration of response (DOR)

All Phases and Cohorts

- To assess the safety and tolerability of tazemetostat monotherapy and tazemetostat in combination with prednisolone
- To assess the pharmacokinetic (PK) profile of tazemetostat monotherapy and tazemetostat in combination with prednisolone

6.3 Exploratory Objectives

The exploratory objectives of this study are:

All Phases and Cohorts

- To explore the PK and pharmacodynamic (PD) relationship of tazemetostat
- To identify and investigate biomarkers and their correlation with biological activity for tazemetostat
- To explore the effects of tazemetostat on histone H3K27 methylation, target gene expression, and phenotypic markers including those for differentiation, apoptosis, and cell proliferation, and changes in the tumor microenvironment
- To explore the role of DNA sequence variability on absorption, metabolism, excretion and susceptibility to adverse events of tazemetostat
- To explore the effect of tazemetostat monotherapy and tazemetostat in combination with prednisolone on overall survival

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

This is a multicenter, open-label, Phase 1/2 study that will be conducted in 2 parts (see Section 7.3.2). The Phase 1 part (dose escalation and expansion parts have completed enrollment) comprised of dose escalation and expansion to establish the MTD and/or RP2D when tazemetostat is given BID orally on a continuous basis in subjects with histologically and/or cytologically confirmed advanced or metastatic solid tumors or B cell lymphomas that have progressed after treatment with approved therapies or for which there are no standard therapies available. Additionally, in separate cohorts in Phase 1 (IB and IGR sites in France only), the effect of food on the bioavailability of tazemetostat will be evaluated as well as the DDI potential as evaluated by the effect of tazemetostat on the pharmacokinetics of midazolam, a CYP3A4 substrate. The effect of food on bioavailability was initiated after safety of the 200 mg tazemetostat dose (highest available tablet dosage strength) was evaluated. The DDI potential cohort was initiated at the RP2D of 800 mg BID. The FE and DDI cohorts were performed once

the dose escalation was completed. The Phase 2 part was initiated once the MTD and/or RP2D was established. Phase 2 will enroll subjects with DLBCL (Cohorts 1-3 and 6) and FL (Cohorts 4 and 5) for the determination of efficacy and safety of tazemetostat monotherapy (Cohorts 1-5) and tazemetostat in combination with prednisolone (Cohort 6) with placement determined by centrally confirmed histology, COO, and EZH2 mutation status as described below:

- **Subjects with histologically confirmed DLBCL (including PMBCL and transformed FL) (all enrollment of these Cohorts is closed)**
  - DLBCL Cohort 1: Subjects with GCB subtype and the following EZH2 mutations: Y646F, Y646N, Y646S, Y646H, Y646C, A682G, and/or A692V
  - DLBCL Cohort 2: Subjects with GCB subtype and EZH2 wild-type
  - DLBCL Cohort 3: Subjects with non-GCB subtype (including PMBCL)

    Note: Upon cohort closure, up to 5 non-GCB subtype EZH2 mutation positive subjects can be enrolled in Cohort 1
  - DLBCL Cohort 6: EZH2 wild-type DLBCL subjects (GCB and non-GCB subtypes) can be enrolled after the accrual of the corresponding monotherapy cohort (2 or 3) is completed

or

- **Subjects with histologically confirmed FL, all grades**
  - FL Cohort 4: Subjects with the following EZH2 mutations: Y646F, Y646N, Y646S, Y646H, Y646C, A682G, and/or A692V (enrollment closed)
  - FL Cohort 5: Subjects with EZH2 wild-type (enrollment closed)

Subjects will be required to undergo EZH2 mutation testing of their tumor tissue. An EZH2 mutation result will be determined at designated study laboratory testing sites using a cobas® EZH2 Mutation Test (under development, Roche Molecular Systems, Inc.), which is a real-time allele-specific polymerase chain reaction (PCR) test to detect the following GOF mutations within codons Y646, A682, and A692 of the EZH2 gene (Bodor, 2013) in formalin fixed paraffin embedded (FFPE) NHL tumor tissue specimens: Y646F, Y646N, Y646S, Y646H, Y646C, A682G, and/or A692V; results for codons Y646S, Y646H, and Y646C are not reported individually (grouped as Y646X). For the purposes of this protocol, the term “wild-type” refers to the absence of detection of the above-specified mutations. Subjects with tumors that are wild-type for EZH2 will be enrolled in the EZH2 wild-type cohort. The EZH2 mutation test is intended to be used as an Investigational Use Only assay.

Cell-of-origin status will be determined for DLBCL subjects by the Hans method (Hans, 2004) using available tumor tissue at designated study laboratory testing sites. Further details of EZH2 mutation and COO testing are provided in the Laboratory Manual.

The tumor tissue EZH2/COO testing can be performed prior to other screening procedures, for example, during wash-out of the second line anticancer therapy, after the subject is consented for the prescreening testing.

This study will be conducted in 3 phases: a Pretreatment Phase, a Treatment Phase, and an Extension Phase. The Pretreatment Phase consists of Screening and Baseline Visits (see Table 8 and Table 9).

The Treatment Phase for the Phase 1 Dose Escalation and Expansion parts last for 1 cycle. Subjects were enrolled using a dose-escalation algorithm (3+3 subjects per dose level) to identify the MTD and/or RP2D.

Each 28-day period will be considered 1 treatment cycle. PK sampling will be performed on every subject and samples will be collected predose and at protocol-defined intervals as described in the Schedule of Visits and Procedures (see Table 8 and Table 9).

The treatment cycle will begin with the first dose of study drug administration and continue for 1 cycle (28 days [4 weeks]). Treatment may continue in the Extension Phase with Cycle 2 and beyond until completion of the Off-Treatment Visit (30 days after the last study drug administration).

The enrollment for the Phase 1 part of the study commenced in June 2013. Using a standard 3+3 design and increasing in 100% increments, enrollment of 5 dose cohorts of 3 to 6 subjects was completed with tazemetostat at 100, 200, 400, 800, and 1600 mg BID, with 1 dose-limiting toxicity (DLT) reported at 1600 mg BID. As of 07-Nov. 2014, the maximum delivered dose was 1600 mg BID, and hence, an MTD had not been reached. The RP2D was therefore 800 mg BID because of the safety, PK, biological activity, and responses at this dose.

Dose escalation (complete): Dose escalation proceeded in 100% increments in subsequent cohorts unless 1 Grade ≥ 2 nonhematological toxicity during Cycle 1 was assessed as related to the study drug in 2 or more subjects at a dose level. For dose escalation purposes, toxicities assigned as DLTs during the first cycle were assessed (see Table 4). After completion of Cycle 1 in each cohort, all available safety data were reviewed jointly by the Sponsor and the investigators and the decision to proceed to the next dose cohort was made. If 0 of 3 or 1 of 6 subjects demonstrated DLT(s), then enrollment proceeded to the next dose level. If 1 DLT was reported for the first 3 (or 4) subjects, the cohort expanded to a total of 6 subjects. If 2 subjects in any cohort demonstrate DLT(s) during Cycle 1, enrollment into that cohort stopped and a dose reduction took place. In the first and second cohorts only, the first subject in each dose level must have completed at least 2 weeks of treatment during Cycle 1 without experiencing any DLTs before additional subjects were treated at that dose level. A dose-escalation meeting occurred when 3 evaluable subjects (for DLTs) completed 1 cycle of treatment. If a fourth subject in this

cohort experienced a DLT after a decision had been made to escalate to the next dose level, then this dose cohort (of the fourth subject) was expanded to a total of 6 subjects. Any subject initiated at a higher dose level continued to receive the same dose. If 2 subjects in the expanded cohort experience a DLT(s), a dose reduction took place. Additionally, any subject being treated at a higher dose level had the dose reduced to below the dose level that exceeded the tolerable dose level. The highest dose level below the dose level that exceeds a tolerable dose level (ie, results in ≥ 2 of 6 subjects with DLTs was considered the MTD of Phase 1 and was used to determine the RP2D). Dose escalation continued until the MTD is reached, or up to a maximum feasible dose of 1600 mg BID, whichever comes first. If no DLTs are observed, the RP2D was determined based on safety, tolerability, activity, PK, and PD assessments. Two dose cohorts were expanded up to 12 subjects each in the Dose Expansion part.

In the Extension Phase of the Dose Escalation and Expansion parts, subjects may remain on study until disease progression, development of unacceptable toxicity that leads to tazemetostat treatment withdrawal, or withdrawal of consent. Investigators who note subjects with disease progression that are receiving continued clinical benefit without clinical deterioration should contact the Medical Monitor to discuss the assessment of risk/benefit of keeping the subject on study.

Food Effect and DDI cohorts were initiated as part of the Phase 1 study after safety of the 200 mg tazemetostat dose (highest available tablet dosage strength) was evaluated, and at the RP2D of 800 mg BID, respectively. The Treatment Phase for both cohorts will last until the end of Cycle 1. In the Extension Phase, subjects may remain on study until disease progression, development of unacceptable toxicity that leads to tazemetostat treatment withdrawal, or withdrawal of consent.

Randomization will be used in the Phase 1 FE cohort in this study.

The Phase 2 study was initiated after a minimum of 6 subjects complete dosing at the RP2D. The RP2D has been determined as 800 mg BID. The Phase 2 proof-of-concept part of the study will enroll subjects with B cell lymphoma for the determination of efficacy and safety of tazemetostat in 5 separate cohorts determined by centrally confirmed histology, COO, and EZH2 mutation status. In addition, up to 70 subjects with DLBCL will be enrolled to a combination therapy cohort with a starting dose of tazemetostat 800 mg BID and prednisolone 40 mg/m^2 once daily on Days 1-5 and 15-19 of Cycles 1-4. The tolerability of the combination treatment will be assessed in the first 6 subjects using the same DLT evaluation criteria as in Phase 1 (see Section 7.3.2). In order to observe preliminary safety of the study drug combination, there will be at least a 2-week delay in start of treatment between the first and second subjects in the safety run-in. Provided there are no initial safety concerns, subsequent subjects in the safety run-in may be enrolled as available. If a DLT is observed in no more than 1 of the initial 6 subjects, enrollment

will continue to the end of stage 1. If a DLT is observed in more than 1 of the 6 subjects, lower dose level(s) of prednisolone may be evaluated using a similar approach. The Treatment Phase in Phase 2 will end when the last subject completes assessments following a minimum of 6 cycles or discontinues treatment due to disease progression, development of unacceptable toxicity that leads to tazemetostat treatment withdrawal, or withdrawal of consent.

In the Extension Phase in both the Phase 1 and Phase 2, subjects will continue to receive study drug until disease progression, development of unacceptable toxicity that leads to study treatment withdrawal, or withdrawal of consent. An Off-Treatment Visit will occur up to 30 days after final administration of study drug, or initiation of a new anticancer treatment, whichever occurs earlier, after which subjects will enter the Follow-up Period.

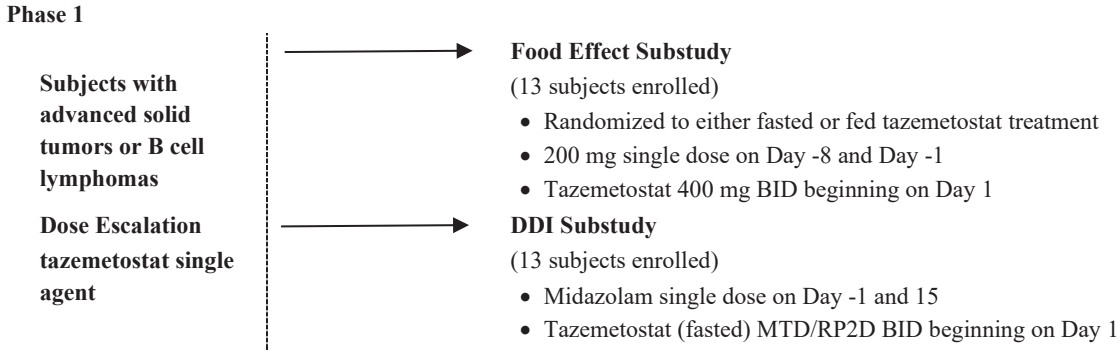
During the Follow-up Period, survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. As of Protocol Amendment 13.0, no further survival follow-up is necessary for remaining subjects because the primary outcome assessment for all subjects has been met.

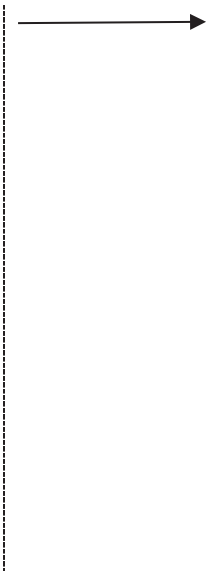
Rollover Study: All subjects in Phase 1 who receive tazemetostat for 9 months or longer, and are eligible to continue receiving tazemetostat, will transfer to a Rollover Study for monitoring and continued study drug at the Investigator's and the Medical Monitor's discretion. All subjects in Phase 2 who remain on tazemetostat for 24 months or longer, and are eligible to continue receiving tazemetostat, also will transfer to a Rollover Study for monitoring and continued study drug at the Investigator's and the Medical Monitor's discretion.

This study will include PD assessments of the effects of tazemetostat in a variety of matrices, including plasma, PBMCs, skin, bone marrow, and malignant tissue as appropriate, which may help confirm the mechanism of action of tazemetostat, predict responses, and guide further development and optimize use of tazemetostat. See Section 7.4.1.6 for further information on PD assessments.

An overview of the study design is presented in Table 2.

Table 2 Study Design for E7438-G000-101





Phase 2

Subjects with B cell lymphomas

Tazemetostat Monotherapy Cohorts

- Cohort 1: DLBCL (GCB subtype) EZH2 mutation positive (enrollment closed)
- Cohort 2: DLBCL (GCB subtype) EZH2 wild-type (enrollment closed)
- Cohort 3: DLBCL non-GCB subtype (enrollment closed)

  Note: Upon cohort closure, up to 5 DLBCL non-GCB EZH2 mutation positive subjects can be enrolled in Cohort 1
- Cohort 4: FL (Grades 1 to 3) EZH2 mutation positive (up to 45 subjects) (enrollment closed)
- Cohort 5: FL (Grades 1 to 3) EZH2 wild-type (up to 45 subjects) (enrollment closed)

Tazemetostat/Prednisolone Combination Cohort

- Cohort 6: DLBCL GCB or non-GCB subtype EZH2 wild-type (enrollment closed)

BID = twice daily, DDI = drug-drug interaction, DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste homolog 2, GCB = germinal-center B-cell-like, FL = follicular lymphoma, MTD = maximum tolerated dose, RP2D = recommended Phase 2 dose

The end of study is defined as last subject last follow-up visit or the last subject transferred to the Rollover Study (EZH-501).

7.2 Selection of Study Population

Approximately 420 subjects will be enrolled in the entire study. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

In Phase 1, a total of 64 subjects with advanced solid tumors or B cell lymphomas were enrolled. Two dose levels were expanded (to 14 subjects at 800 mg BID and 12 subjects at 1600 mg BID) to support the determination/confirmation of the RP2D per joint decision of the Sponsor and the investigators.

Thirteen evaluable subjects with advanced solid tumors or B cell lymphomas were enrolled in each FE and DDI cohort (IB and IGR sites in France only). Enrollment is closed for both cohorts.

In Phase 2, approximately 340 subjects with histologically confirmed DLBCL or FL with relapsed or refractory disease will be enrolled (monotherapy: up to 60 subjects in each of the 3 DLBCL cohorts and up to 45 subjects in each of the 2 FL cohorts; combination therapy: up to 70 subjects with relapsed or refractory DLBCL).

7.2.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

All Subjects:

1. Phase 1: Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
   Phase 2: Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Appendix 1).
2. Life expectancy ≥ 3 months before starting tazemetostat.
3. Subjects with a history of hepatitis B or C are eligible on the condition that subjects have adequate liver function as defined by Inclusion Criterion #6 and are hepatitis B surface antigen negative and/or have undetectable HCV RNA.
4. Adequate renal function defined as calculated creatinine clearance ≥ 40 mL/min per the Cockcroft and Gault formula (Appendix 2) or local institutional standard formula.
5. Adequate bone marrow function:
   a. Absolute neutrophil count (ANC) ≥ 750/mm^3 (≥ 0.75 × 10^9/L)
      - Without growth factor support (filgrastim or pegfilgrastim) for at least 14 days
   b. Platelets ≥ 75,000/mm^3 (≥ 75 × 10^9/L)
      - Evaluated after at least 7 days since last platelet transfusion
   c. Hemoglobin ≥ 9.0 g/dL
      - May receive transfusion
6. Adequate liver function:
   a. Total bilirubin ≤ 1.5 × the upper limit of normal (ULN) except for unconjugated hyperbilirubinemia of Gilbert's syndrome
   b. Alkaline phosphatase (ALP) (in the absence of bone disease), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if subject has liver metastases)
7. Time between prior anticancer therapy and first dose of tazemetostat as below:
   - Cytotoxic chemotherapy – At least 21 days
   - Non-cytotoxic chemotherapy (eg small molecule inhibitor) – At least 14 days
   - Nitrosoureas – At least 6 weeks

- Monoclonal antibody(ies) – At least 28 days
- Radiotherapy
    - At least 14 days from local site radiation therapy;
    - At least 6 weeks from prior radioisotope therapy;
    - At least 12 weeks from 50% pelvic or total body irradiation
- High-dose therapy with autologous hematopoietic cell infusion – At least 60 days
- High-dose therapy with allogeneic transplant – At least 90 days (if graft versus host disease [GVHD] is present, must be < Grade 2) and on no prohibited medications, per Exclusion Criterion #3)
- **NOTE:** Starting at Cycle 1 Day 1, subjects may receive no more than 10 mg of prednisone daily (or equivalent corticosteroid, excluding protocol-defined prednisolone dosing for subjects enrolled in Cohort 6) when used for treatment of lymphoma related symptoms, with the intent to taper by the end of Cycle 1.

8. Males or females aged ≥ 18 years at the time of informed consent (Phase 2). Males or females aged ≥ 16 years at the time of informed consent (Phase 1).
9. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. All females will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutively amenorrheic, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). Females of childbearing potential must not have had unprotected sexual intercourse within 30 days prior to study entry and must agree to use a highly effective method of contraception, from the last menstrual period prior to randomization, during Treatment Cycles, and for 6 months after the final dose of study drug, and have a male partner who uses a condom. Highly effective contraception includes:
    a. Double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.
    b. Placement of an intrauterine device.
    c. Established hormonal contraceptive methods: oral, injectable, or implant. Females who are using hormonal contraceptives must have been on a stable dose of the same

hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 6 months after study drug discontinuation.

Female subjects exempt from this requirement are subjects who practice total abstinence or have a male partner who is vasectomized. If currently abstinent, the subject must agree to use a highly effective method of contraception as described above if they become sexually active during the Treatment Cycles, and for 6 months after study drug discontinuation.

10. Male subjects must have had either a successful vasectomy **OR** they and their female partner must meet the criteria above (ie, not of childbearing potential **OR** practicing highly effective contraception and use a condom throughout the study period and for 3 months after study drug discontinuation).
11. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.

Phase 1 only (IB and IGR sites in France only):

12. Histologically and/or cytologically confirmed advanced or metastatic solid tumor or B cell lymphomas that has progressed after treatment with approved therapies or for which there are no standard therapies available.

Phase 2:

13. Subjects must satisfy all of the following criteria:

    a. Have histologically confirmed DLBCL (including primary mediastinal B cell lymphoma), with relapsed or refractory disease following at least 2 lines of prior standard therapy, including alkylator/anthracycline (unless anthracycline –based chemotherapy is contraindicated)/ anti-CD20-based therapy (R-CHOP or equivalent) AND must be considered unable to benefit from intensification treatment with autologous hematopoietic stem cell transplantation (ASCT), as defined by meeting at least 1 of the following criteria:

    - Relapsed following, or refractory to, previous ASCT
    - Did not achieve at least a partial response to a standard salvage regimen (eg, rituximab, ifosfamide, carboplatin, and etoposide phosphate [R-ICE] or rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP])
    - Ineligible for intensification treatment due to age or significant comorbidity
    - Ineligible for intensification treatment due to failure to mobilize an acceptable

number of hematopoietic stem cells

- Refused intensification treatment and/or ASCT

or

b. Have histologically confirmed FL, all grades. Subjects may have relapsed/refractory disease following at least 2 standard prior systemic treatment regimens where at least 1 anti-CD20-based regimen was used. Subjects with prior radiotherapy will be included; however, radiotherapy alone will not be considered a systemic treatment regimen.

c. Have provided sufficient archival tumor tissue that has been successfully tested for EZH2 mutation status and cell of origin (DLBCL only) at study specific laboratories allowing for allocation into an open cohort.

d. Have measurable disease as defined by International Working Group-Non-Hodgkin's Lymphoma (IWG-NHL [Cheson, 2007]).

7.2.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

All Subjects:

1. Prior exposure to tazemetostat or other inhibitor(s) of EZH2.
2. Subjects with known leptomeningeal metastases or brain metastases or history of previously treated brain metastases.
3. Has thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE 4.03 criteria) and any prior history of myeloid malignancies, including myelodysplastic syndrome (MDS).
4. Has a prior history of T-Cell lymphoblastic lymphoma(T-LBL) or T-Cell lymphoblastic leukemia (T-ALL).
5. Subjects taking medications that are known potent CYP3A4 inducers/inhibitors (including St. John's wort) (see Section 7.3.4.3 and http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm; http://medicine.iupui.edu/clinpharm/ddis/).
6. Subjects unwilling to exclude Seville oranges, grapefruit juice, and grapefruit from their diet.
7. Any prior treatment-related (ie, chemotherapy, immunotherapy, radiotherapy) clinically significant toxicities have not resolved to ≤ Grade 1 per CTCAE version 4.03, or prior treatment-related toxicities are clinically unstable and clinically significant at time of enrollment.
8. Major surgery within 4 weeks before the first dose of study drug.

- **NOTE**: Minor surgery (eg, minor biopsy of extracranial site, central venous catheter placement, shunt revision) is permitted within 3 weeks prior to enrollment.

9. Inability to take oral medication, or malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, or vomiting) that might impair the bioavailability of tazemetostat.
10. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug; or cardiac ventricular arrhythmia (Appendix 3).
11. Prolongation of corrected QT interval using Fridericia's formula (QTcF) to > 480 msec.
12. Venous thrombosis or pulmonary embolism within the last 3 months before starting tazemetostat.
13. Active infection requiring systemic therapy.
14. Known hypersensitivity to any component of tazemetostat, prednisolone/prednisone (combination cohort only), or inability to be treated with a *Pneumocystis* prophylaxis medication (combination cohort only).
15. Immunocompromised subjects, including subjects known to be infected with human immunodeficiency virus (HIV).
16. Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the subject's participation in this study.
17. Females who are pregnant or breastfeeding.
18. Subjects who have undergone a solid organ transplant.

Phase 2 only:

19. Subjects with noncutaneous malignancies other than B cell lymphomas.

- **Exception:** Subjects with another malignancy who have been disease-free for 5 years, or subjects with a history of a completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible.

7.3 Treatments

7.3.1 Identity of Investigational Product

Tazemetostat is available as tablets in strengths of 100 (Phase 1 only) and 200 mg and supplied in white HDPE bottles.

7.3.1.1 Chemical Name, Structural Formula of Tazemetostat

Test drug code: EPZ-6438 (for free base)

International non-proprietary name (INN) name: tazemetostat

Chemical name: *N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-yl)methyl]-5-[ethyl(tetrahydro-2*H*-pyran-4-yl)amino]-4-methyl-4'-(morpholin-4-ylmethyl)biphenyl-3-carboxamide hydrobromide

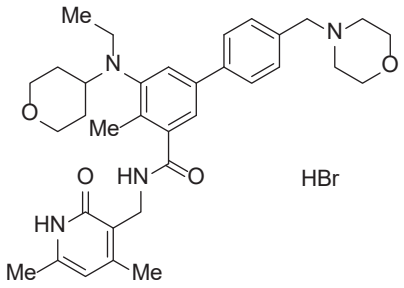
Molecular formula: $C_{34}H_{45}BrN_4O_4$ (Hydrobromide salt)

$C_{34}H_{44}N_4O_4$ (Free base)

Molecular weight: 653.65 (Hydrobromide salt)

572.74 (Free base)

Structural formula:



7.3.1.2 Labeling for Study Drug

Tazemetostat will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

7.3.1.3 Storage Conditions

Tablets: Tazemetostat tablets will be stored in accordance with the labeled storage conditions. See pharmacy manual.

7.3.2 Treatments Administered

Tazemetostat will be administered orally in Phase 1 and Phase 2.

Midazolam will only be administered in the Phase 1 DDI cohort and will be administered orally according to the Summary of Product Characteristics (SmPC).

Phase 1 Dose Escalation and Expansion (closed to enrollment): In the Phase 1 Dose Escalation and Expansion parts, 38 subjects with advanced solid tumors or B cell lymphomas were given tazemetostat orally, starting at 100 mg BID (200 mg total daily dose) continuously starting Cycle 1 Day 1 in 28-day cycles. Dose escalation proceeded in 100% increments in subsequent cohorts unless 1 Grade ≥ 2 nonhematological toxicity during Cycle 1 was assessed as related to the study drug in 2 or more subjects at a dose level until the MTD and/or RP2D was established. Tazemetostat can be taken with or without food.

Phase 1 Food Effect (IB and IGR sites in France only, closed to enrollment): In the Phase 1 FE cohort, 13 subjects with advanced solid tumors or B cell lymphomas were randomized to receive the tazemetostat 200 mg as a single oral dose on Day -8 after fasting for 8 hours before dosing and immediately after consuming a high-fat breakfast (see Appendix 6). For 7 subjects, 200 mg was dosed as a single dose on Day -8 after fasting for 8 hours before tazemetostat dosing, and for 6 subjects, 200 mg was dosed immediately after consuming a high-fat breakfast. Because tazemetostat was to be taken in a fasting state, subjects were required to record the time at which they ate food. Following a 7-day wash-out period subjects crossed over to receive the second tazemetostat 200 mg single oral dose on Day -1. Subjects consumed the high-fat breakfast within a 30-minute period before study drug administration. Each 28-day period was considered 1 treatment cycle.

If a subject did not consume the full breakfast (when appropriate) and complete all PK assessments, this subject was replaced to ensure that there were 6 subjects in each sequence (fed/fasted and fasted/fed) with all PK assessments.

Beginning on Day 1 of Cycle 1, tazemetostat 400 mg was administered BID for 28-day cycles and could be taken with or without food.

Phase 1 CYP3A4 DDI with Midazolam (IB and IGR sites in France only, closed to enrollment): In the Phase 1 DDI cohort, 13 subjects with advanced solid tumors or B cell lymphoma were enrolled for a DDI study with midazolam to determine the effect of tazemetostat on CYP3A4. Subjects received 800 mg tazemetostat BID, continuously starting on Day 1. Subjects received a single oral dose of midazolam on Day -1 and Day 15. Subjects fasted 2 hours before and 1 hour after tazemetostat dosing. Once the DDI evaluation was completed in Cycle 1 (after Day 15), continuous dosing of tazemetostat 800 mg BID continued, and tazemetostat was taken with or without food.

Midazolam: Midazolam was administered only in the Phase 1 CYP3A4 DDI cohort of the study. A single 2-mg dose of midazolam was administered orally on Days -1 and Day 15, according to the instructions contained in the SmPC. On Day 15, midazolam was administered concurrently with tazemetostat administration.

Phase 2: Subjects with B cell lymphoma will be administered 800 mg BID of tazemetostat. Tazemetostat will be dosed BID beginning on Cycle 1 Day 1 for continuous 28-day cycles, with or without food.

In the DLBCL tazemetostat and prednisolone combination cohort, prednisolone will be administered as open-label commercial product at a starting dose of 40 mg/m^2 (rounding can be done per local standard practice) orally once daily on Days 1 to 5 and Days 15 to 19 of each 28-day cycle for 4 cycles, without regard to food. Tazemetostat will be administered orally, continuously from Cycle Day 1 without break, at a starting dose of 800 mg BID. On days when both drugs are administered, prednisolone should be taken immediately after the morning dose of tazemetostat.

Subjects enrolled in the cohort receiving the combination treatment of tazemetostat and prednisolone will receive a prophylaxis treatment for *Pneumocystis jirovecii* (eg, sulfamethoxazole 800 mg plus trimethoprim 160 mg 3 times a week or acceptable alternative) for a total of 24 weeks, starting on Cycle 1 Day 1.

Each dose of tazemetostat should not be given any earlier than 8 hours after the previous dose or 8 hours before the next dose. If a tazemetostat dose is missed (ie, not taken within 4 hours after the scheduled dosing time), that dose should not be made up and the subject should resume dose administration with the next scheduled dose. Each dose of prednisolone should not be given later than 12 hours before the next dose. If a prednisolone dose is missed (ie, not taken within 12 hours after the scheduled dosing time), that dose should not be made up and the subject should resume dose administration with the next scheduled dose.

If a subject vomits within 30 minutes of study treatment dose administration, anti-emetics should be given and a second dose of study treatment should be administered.

Study treatment in Phase 2 will continue until disease progression, development of unacceptable toxicity, or withdrawal of consent. Subjects may be permitted to continue study treatment if they meet the IWG-NHL (Cheson, 2007) criteria for PD as well as the following criteria:

- Absence of symptoms and signs (including worsening of laboratory values, eg, new or worsening hypercalcemia) that indicate unequivocal PD
- No decline in ECOG performance status
- Absence of tumor growth at critical anatomical sites (eg, leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

At the time of apparent PD per the IWG 2007, subjects for whom approved treatment exists must provide written consent to acknowledge their choice to continue to receive study treatment.

Subjects whose radiographic PD is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the Investigator if they have evidence of clinical benefit and continue to meet the above criteria. Investigators who note subjects with disease progression that are receiving continued clinical benefit without clinical deterioration should contact the Medical Monitor to discuss the assessment of risk/benefit of keeping the subject on study.

7.3.2.1 Dose-Limiting Toxicity

Dose-limiting toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE v4.03 [Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, 2009], see Appendix 5) and are defined in Table 3. Final determination of whether a subject was counted as having experienced a DLT for dose escalation purposes or MTD and/or RP2D confirmation purposes, and whether the dose escalation proceeded in 100% increments, was made jointly by the Sponsor and the investigators.

Table 3 Dose-Limiting Toxicities

Toxicity Category	Toxicity/CTCAE Grade
Hematological	• Grade 4 neutropenia for ≥ 7 days or Grade 3 neutropenia with fever (> 38.5 °C in axilla) • Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or lasting > 7 days
Other Nonhematological Toxicity	• Grade 3 fatigue, or a 2-point decline in Eastern Cooperative Oncology Group (ECOG) performance status that persists for > 7 days • Grade 3 aspartate transaminase ([AST], also referred to as serum glutamic oxaloacetic transaminase [SGOT]) or Grade 3 alanine aminotransferase ([ALT], also referred to as serum glutamic pyruvic transaminase [SGPT]) elevation of > 7 days or Grade 4 AST or ALT of any duration • ≥ Grade 2 neurotoxicity or cardiotoxicity • Grade 2 hypersensitivity reaction • Nausea, vomiting, or diarrhea that persists at Grade 3 or 4 despite maximal medical therapy • Any Grade 3 or higher nonhematological laboratory abnormalities that require hospitalization

CTCAE = Common Terminology Criteria for Adverse Events

The MTD and/or RP2D was determined based on the incidence of DLTs in Cycle 1, although toxicities occurring during subsequent cycles were also reviewed. If serious toxicities were observed at this dose level in later cycles, a reduction of the MTD and/or RP2D was to be considered.

For subjects who required a dose interruption due to tazemetostat-related toxicity during Cycle 1 in the Dose Escalation part of the study, the treatment was re-started once the toxicity resolved to Grade ≤ 1 or baseline. Treatment was according to the criteria listed below:

- If the observed toxicity was determined to be a DLT according to Table 3, the subject resumed treatment at the next lower dose level.
- If the observed toxicity was not considered to be a DLT according to Table 3, the subject resumed treatment as described in the Dose Reduction and Interruption Instructions in Table 4.

All available safety, PK and PD data were reviewed to decide whether to explore intermediate dose and/or alternative dose regimens. As PK were observed to be linear, the dosing schedule and dose escalation scheme was not modified during the dose escalation part of the study. Treatment will continue until disease progression, development of unacceptable toxicity, or withdrawal of consent.

An independent DMC was established to review available safety data supporting the MTD and/or RP2D once a minimum of 6 subjects at the MTD or highest feasible dose complete 1 cycle of treatment in Dose Escalation. The DMC reviewed safety data including, but not limited to, AEs, serious adverse events (SAEs), laboratory parameters, investigational product dosing records, treatment delays or reductions, and treatment discontinuation due to toxicity. One DLT was observed at the dose level of 1600 mg BID; thus, the protocol-defined MTD was not reached. Based on evaluation of safety, tolerability, activity, PK, and PD assessments from the 24 subjects treated in the Dose Escalation part of the study, an RP2D of 800 mg BID has been determined. The RP2D has been endorsed by the investigators and a DMC.

The rules listed in Table 3 will be applied to the safety run-in DLT assessment of the combination therapy of tazemetostat and prednisolone. In addition, any Grade 3 or higher non-hematological toxicities that require hospitalization will also be considered DLTs. For toxicities assessed by the Investigator to be attributed to prednisolone, the dose interruption and reduction of prednisolone should follow the same guidance above. The suggested dose reduction of prednisolone, if deemed necessary by the Investigator, is from 40 mg/m^2 to 30 mg/m^2. If further dose reduction of prednisolone is considered necessary to manage prednisolone-related toxicities, the recommended dose level is 22.5 mg/m^2. A discussion with the Sponsor's medical monitor is needed if further reduction is considered for prednisolone. A discussion with the Sponsor's medical monitor is needed if dose interruption or reduction is considered for tazemetostat.

7.3.2.2 Criteria for Retreatment, Temporary Discontinuation of Treatment, Dose Reduction, and Resumption of Treatment

Tazemetostat dose reductions and interruptions will be allowed in Phase 1 and Phase 2; however, an interruption in the administration of tazemetostat for more than **14 days** must be discussed with the Medical Monitor before treatment can be resumed.

Toxicity will be managed by concomitant medication (as appropriate), treatment interruption, dose reduction, and treatment discontinuation, or a combination of these. During treatment with tazemetostat, dose interruption and reduction for subjects who experience tazemetostat-related toxicity will be in accordance with the Dose Reduction and Interruption Instructions in Table 4. If a case of adult T-LBL/T-ALL occurs enrollment will be suspended and the benefit-risk of the drug will be assessed at an ad hoc Epizyme Quarterly Safety Review Committee and the results will be communicated to all Health Authorities and Ethics Committees as applicable. For any MDS/AML or other myeloid malignancies like MPN, tazemetostat will be discontinued in that subject.

For subjects who require dose interruption due to tazemetostat-related toxicity in Phase 1 or in Phase 2, the treatment may re-start once the toxicity has been resolved to Grade ≤ 1 or baseline according to the Dose Reduction and Interruption Instructions in Table 4.

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

- Platelet count must be ≥ 75×10^9/L
- ANC must be ≥ 0.75×10^9/L, and
- Any Grade 3 or higher toxicity must have resolved to Grade 1 or baseline, unless otherwise noted.

The same set of rules of treatment interruption and resumption will be applied to the cohort receiving combination therapy of tazemetostat and prednisolone. A discussion with the Sponsor's medical monitor is needed if dose interruption or reduction is considered, either for both or only one of the drugs. The suggested initial dose reduction of prednisolone, if deemed necessary by the Investigator, is from 40 mg/m^2 to 30 mg/m^2. If further dose reduction of prednisolone is considered necessary, the recommended dose level is 22.5 mg/m^2. A discussion with the Sponsor's medical monitor is needed if further reduction is considered for prednisolone. Dose reduction of tazemetostat will follow the guidelines in Table 4.

Table 4 Tazemetostat Dose Reduction and Interruption Instructions

	During Therapy	Approximate Dose Adjustment[b]
Grade 1		
All occurrences	Continue tazemetostat	Maintain dose level
Grade 2[c]		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Maintain dose level
2nd occurrence (same or new toxicity)		Restart at 600 mg BID
3rd occurrence (same or new toxicity)		Restart at 400 mg BID
4th occurrence (same or new toxicity)		Discuss with medical monitor
Grade 3[c] not including neutropenia and thrombocytopenia		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 600 mg BID
2nd occurrence (same or new toxicity)		Restart at 400 mg BID
3rd occurrence (same or new toxicity)	Discontinue tazemetostat	Not applicable
Grade 3 Neutropenia (ANC: < 1 – 0.5 × 10^9/L)		
ANC < 0.75 × 10^9/L 1st occurrence	Interrupt tazemetostat until resolved to ANC ≥ 0.75 × 10^9/L	Restart at 600 mg BID
2nd occurrence		Restart at 400 mg BID
3rd occurrence	Discontinue tazemetostat	Not applicable
Grade 3 Thrombocytopenia		
1st occurrence	Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[b]	Restart at 600 mg BID
2nd occurrence		Restart at 400mg BID
3rd occurrence	Discontinue tazemetostat	Not applicable
Grade 4		
Any occurrence	Interrupt study drug until resolved to Grade 2 or less	Discuss with medical monitor

ANC = absolute neutrophil count, BID = twice daily

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 Sponsor before treatment can be resumed.

c Excluding Grade 2 and 3 anemia: Subjects are allowed to continue tazemetostat at their current dose level with transfusion per investigator discretion.

7.3.3 Method of Assigning Subjects to Treatment Groups

For the Phase 1 Dose Escalation part, subjects with advanced solid tumors or B cell lymphoma were enrolled using a dose-escalation algorithm (3+3 subjects per dose level) to identify the MTD and/or RP2D. Food Effect cohort subjects with advanced solid tumors or B cell lymphoma were randomized to 1 of 2 treatment sequences (either fed/fasted or fasted/fed) according to a

randomization scheme. Subjects will be enrolled sequentially in the Dose Escalation component and DDI cohort.

For Phase 2, DLBCL subjects will be allocated into cohorts (Cohorts 1-3 and 6) prior to tazemetostat dosing based on the results of the EZH2 mutation and COO testing. In Cohort 6, the safety run-in (DLT assessment) needs to be completed in the first 6 subject before other subjects can be enrolled. DLBCL subjects with wild-type EZH2 can be enrolled to Cohort 6 after the accrual of the Cohort 2 or 3 is completed. FL subjects will be allocated into cohorts (Cohorts 4 and 5) prior to tazemetostat dosing based on the results of EZH2 mutation testing. The tumor tissue EZH2/COO testing can be performed prior to other screening procedures, for example, during wash-out of the second line anticancer therapy, after the subject is consented for the prescreening testing.

7.3.4 Prior and Concomitant Therapy

Prior and concomitant medications include all prescription and nonprescription medications, vitamins, herbals, and transfusions.

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug will be recorded. In the Phase 1 part of the study any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study drug will be recorded. In the Phase 2 part of the study any concomitant therapy administered to the subject during the course of the study (starting at the date of first dose of study drug) until 30 days after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded.

7.3.4.1 Permitted and Concomitant Medication

Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with tazemetostat may be continued during the study.

Subjects may receive prednisone (or equivalent corticosteroid) for systemic or local symptom control prior to and while on study. Starting at Cycle 1 Day 1 however, subjects may receive no more than 10 mg of prednisone daily (or equivalent corticosteroid, excluding protocol-defined prednisolone dosing for subjects enrolled in Cohort 6) when used for treatment of lymphoma related symptoms, with the intent to taper by the end of Cycle 1.

Subjects enrolled in the cohort receiving the combination treatment of tazemetostat and prednisolone will receive a prophylaxis treatment for *Pneumocystis jirovecii* (eg, sulfamethoxazole 800 mg plus trimethoprim 160 mg 3 times a week or acceptable alternative) for a total of 24 weeks, starting on Cycle 1 Day 1.

Treatment of complications or AEs or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs, etc.) may be given at the discretion of the Investigator, unless it is expected to interfere with the evaluation of (or to interact with) tazemetostat. The Investigator will record any AE on the AE case report form (CRF) for which the concomitant medication/therapy was administered.

Over the counter medications, nutritional supplements, vitamins, and herbal preparations are permitted under physician recommendation only. Aspirin, nonsteroidal anti-inflammatory drugs, and low-molecular-weight heparin or prophylactic doses of heparin are permissible but should be used with caution. Granulocyte colony-stimulating factor or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines.

7.3.4.2 Permitted Radiation Therapy

Palliative radiotherapy may be given for the control of pain or for other reasons (ie, bronchial obstruction, ulcerating skin lesions) with no curative intent. The irradiated area should be as small as possible and should never involve more than 10% of the bone marrow in any given 4-week period for distribution of active bone marrow). The irradiated area cannot be used as a parameter for response assessment. Treatment with tazemetostat should be delayed in subjects receiving palliative radiotherapy after discussion with the Medical Monitor. In addition, other palliative procedures intended for symptom control and concurrent dose interruptions may be permitted after discussion with the Medical Monitor. These procedures will be limited to non-target lesions only.

7.3.4.3 Prohibited Concomitant Therapies and Drugs

Subjects must not receive other antitumor therapies while on study. Prohibited medications during this study are any other experimental or unapproved drugs, other anticancer therapies unless otherwise stated, and known strong CYP3A inhibitors and strong or moderate CYP3A inducers within 14 days prior to the first dose of tazemetostat and for the duration of the study.

If subjects receive any of the prohibited antitumor medications, this will be judged as evidence of disease progression, and study drug will be discontinued. These subjects should complete all off-treatment assessments and be followed for survival in the Follow-up Period. (Note: As of Protocol Amendment 13.0, no further survival follow-up is necessary for remaining subjects because the primary outcome assessment for all subjects has been met.)

Examples of medications that are strong inhibitors and strong or moderate inducers of CYP3A include, but are not limited to, those listed in Table 5.

Table 5 Medications that are Potent Inhibitors and Inducers of CYP3A4

CYP Enzymes	Strong Inducers	Strong Inhibitors
CYP3A	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, elaprevir, telithromycin, voriconazole

Please refer to the following websites for a comprehensive list of these medications or contact the Medical Monitor for additional questions:

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. 2020; https://drug-interactions.medicine.iu.edu/MainTable.aspx

US Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. March 2020; https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

7.3.4.4 Concomitant Medications to be used with Caution

The following medications are to be used with caution:

- CYP3A sensitive substrates
- Moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the dose of tazemetostat as shown below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the tazemetostat dose that was being taken prior to initiating the inhibitor, as listed in Table 6.

Table 6 Tazemetostat Adjustment for Coadministration of a Moderate CYP3A Inhibitor

Current Dosage	Adjusted Dosage
800 mg twice daily	400 mg twice daily
600 mg twice daily	400 mg for first dose and 200 mg for second dose

Current Dosage	Adjusted Dosage
400 mg twice daily	200 mg twice daily

Please refer to the following websites for a list of these medications or contact the medical monitor for additional questions:

- Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. 2020; https://drug-interactions.medicine.iu.edu/MainTable.aspx
- US Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. March 2020; https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

7.3.5 Prohibitions and Restrictions during Study Period

Grapefruit and grapefruit juice-containing products and Seville oranges are not permitted for 1 week before dosing and throughout the study.

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

7.3.6 Treatment Compliance

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

7.3.7 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the Investigator until the following documentation has been received by the Sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page signed and dated by the Investigator

- Written proof of approval of the protocol, the informed consent form(s) (ICFs), and any other information provided to the subjects by the Institutional Review Board or Independent Ethics Committee (IRB/IEC) for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required) and the Import License (if required)
- An investigator-signed and dated Form Food and Drug Administration (FDA) 1572, a signed and dated curriculum vitae for the principal investigator (PI) including a copy of the PI's current medical license (required in the US) or medical registration number on curriculum vitae
- Financial Disclosure Form for the PI listed on Form FDA 1572
- A signed and dated clinical trials agreement.

The Investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following the Sponsor's instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local and regional requirements.

Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled in the study. An accurate and timely record of the receipt of all clinical supplies, dispensing of study drug to the subject, collection and reconciliation of used and unused supplies that are either returned by the subject or shipped to the site but not used, subsequent return of unused study drug to the Sponsor or designated central or local depot, and (where applicable) destruction of study drug at the site must be maintained. This includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) study drug dispensing/return reconciliation log, (c) study drug accountability log, (d) all shipping service receipts, (e) documentation of drug returned to the Sponsor, and (f) certificates of destruction for any destruction that occurs at site. All forms will be provided by the Sponsor. Any comparable forms that the investigational site wishes to use must be approved by the Sponsor.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor or a representative of any national health authority. All used and unused study drugs, including empty containers, are to be returned to the Investigator by the subject and ultimately to the Sponsor's designated contractor or depot by the conclusion of the study, unless approval is given by the Sponsor for destruction of supplies and containers at

the investigational site. Upon completion of drug accountability and reconciliation procedures by investigational site personnel and documentation procedures by the Sponsor's personnel, study drug that is to be returned to the Sponsor's approved contract vendor must be boxed and sealed and shipped back to the Sponsor's approved contract vendor following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the Sponsor's specified location by sponsor representatives.

Drug accountability will be reviewed during investigational site visits and at the completion of the study.

7.4 Study Assessments

7.4.1 Assessments

7.4.1.1 Screening Assessments and Demography

Demographic information will be collected at the Screening Visit. Standard demography parameters include age, gender, and race/ethnicity (recorded in accordance with prevailing regulations). The Screening Visit will occur in the period specified in Table 8 and Table 9. The purpose of the Screening Period is to obtain informed consent and establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 8.2.1.

7.4.1.2 Medical History and Physical Examinations

Medical and surgical histories will be obtained during the Pretreatment Phase, along with a record of prior and concomitant medications. Significant findings before the start of study drug will be recorded on the Medical History and Current Medical Conditions CRF. A standard-of-care clinical examination for lymphoma, including assessment of B symptoms, will also be performed at the Screening Visit and at all disease assessments.

Physical examinations (comprehensive or symptom-directed) will be performed as specified in the Schedule of Visits and Procedures (Table 8 and Table 9). Documentation of the physical examination will be included in the source documentation at the investigational site. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AE CRF.

7.4.1.3 Tumor Assessments

Solid tumors: Tumor assessment will be performed based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1 [Eisenhauer, 2009]); see Appendix 4. Investigator-determined response assessments at each assessment time point will be entered onto the appropriate CRF.

B cell lymphoma: Tumor assessments will be performed based upon IWG-NHL (Cheson, 2007) criteria at each assessment time point and entered onto the appropriate CRF. Investigator-determined response assessments at each assessment time point will be entered onto the appropriate CRF. For the Phase 2 part of the study, scans will be performed according to guidelines provided by the imaging core laboratory designated for this study (see Imaging Manual). All tumor assessment scans will be sent, as soon as they have been performed, to the imaging core laboratory for quality assessment and archival for potential independent imaging review.

For additional tumor assessment details, see the Schedules of Procedures and Assessments (Table 8 and Table 9).

During the **Screening Period:**

All subjects: Computed tomography (CT) scans of the chest; and CT or magnetic resonance imaging (MRI) scans of the brain, abdomen, pelvis, and other known sites of disease (as well as photographs of skin lesions that will be followed as target and nontarget lesions), will be performed at Screening. Standard of care scans performed within 28 days before Cycle 1 Day 1 using the protocol-specified parameters may be used as screening assessments.

Solid tumor only: Bone scans will be performed as clinically indicated

NHL only: An ^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) scan will be performed (NHL only). A bone marrow biopsy (including IHC) will be performed for all subjects with FL and if clinically indicated in subjects with DLBCL if these have not been performed within 42 days (an approval is needed from the Sponsor's medical monitor if the window has been beyond 42 days) of Cycle 1 Day 1.

During the **Treatment Phase:**

All subjects: CT scans of the chest, and CT or MRI of the brain (if clinically indicated), abdomen, pelvis, and other known sites of disease will be performed every 8 weeks (starting from Cycle 1 Day 1 of continuous tazemetostat dosing), or sooner if clinically indicated. If local regulatory authorities mandate less frequent imaging, minimum frequency must be every 12 weeks. Tumor assessments will be carried out every 8 weeks (or sooner, if clinically indicated) during treatment cycles in both the Treatment Phase and the Extension Phase. For subjects who remain on study drug for 24 weeks or more, radiologic disease assessments will be performed every 12 weeks.

Solid tumor only: Possible PR and CR (according to RECIST 1.1 criteria) must be confirmed at least 4 weeks after the initial response assessment.

NHL only: At the first notation of possible PR and CR, a whole body ^{18}FDG-PET scan should be performed. At the first notation of CR, a repeat bone marrow biopsy will be performed if lymphoma involvement in the bone marrow was reported at Screening. Repeat bone marrow biopsies will be performed if clinically indicated (if progressive disease or relapse is suspected).

All Subjects: The CT scan should be a diagnostic quality spiral or multidetector CT with oral and iodinated intravenous (IV) contrast, and the MRI scan should be performed with IV gadolinium chelate. Scans of the neck, abdomen, pelvis, and other areas of the body may be performed with MRI instead of CT, but evaluation of the chest must be done with CT. If iodinated IV contrast is contraindicated, the chest evaluation should be done with noncontrast CT, and the abdomen and pelvis evaluation should be performed using either CT with oral contrast (without IV contrast) or MRI with gadolinium chelate IV contrast (the latter is preferred). Spiral/multidetector CT should be performed with a 5-mm contiguous slice reconstruction algorithm. If body MRI scans are performed, contiguous slices of 5 mm are also recommended.

The same imaging modality and image-acquisition protocol (including use or nonuse of IV contrast) should be used consistently across all time points to allow consistent comparison of lesions. Low-dose noncontrast CT transmission scans from a positron emission tomography-CT (PET-CT) combination scanner are not acceptable. Ultrasound should not be used for radiographic tumor assessment. A chest x-ray or skeletal x-ray that clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT or MRI scans.

Brain scans should be performed by MRI pre- and post-contrast enhancement or CT with contrast enhancement, with 5-mm contiguous slices recommended (maximum inter-slice gap of 1 mm on MRI).

Solid tumor subjects only: The recommended bone scan technique is ^{99}m-technetium methylene polyphosphonate (ie, methylene diphosphonate or hydroxymethylene diphosphonate scintigraphy or whole body-bone MRI, or ^{18}F-sodium fluoride PET. The same methodology and scan acquisition techniques used at Screening should be used throughout the study to ensure comparability. If a bone lesion is to be followed as a nontarget lesion (RECIST 1.1 criteria), it is preferable that this be performed using CT or MRI. For bone nontarget lesions that can be followed only on bone scans, a time point response other than not evaluable (NE) will be allowed despite an individual lesion assessment of NE for weeks when bone scans are not required.

Whole body ^{18}FDG-PET scans should be performed using institutional guidelines for Phase 1 and according to the imaging core laboratory guidelines for the Phase 2 part.

If subcutaneous masses or nodes are palpable (eg, bulky) and are assessable by both clinical and radiographic techniques, the radiographic (CT or MRI) technique should be used for the assessment of target and nontarget lesions.

Assessments are to be performed at the site by appropriately qualified personnel and results of the site interpretation are to be recorded on the appropriate CRFs.

7.4.1.4 Exploratory Assessments

Overall survival

Overall survival is the duration measured from the date of first dose until the date of death from any cause. Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Anti-cancer therapies and AESI information will also be collected at this time. As of Protocol Amendment 13.0, no further survival follow-up is necessary for remaining subjects because the primary outcome assessment for all subjects has been met.

7.4.1.5 Pharmacokinetic Assessments

Phase 1: Blood samples for PK analyses will be collected during Cycle 1 in the Phase 1 Dose Escalation part, on Day -8 and Day -1 of the FE cohort, Day -1 and Day 15 of the DDI cohort, and Cycles 1 and 2 in the Phase 1 FE and DDI cohorts.

Urine samples for PK analyses will be collected during the Phase 1 Dose Escalation part only during Cycle 1.

Phase 2: Sparse PK blood samples will be collected during Cycle 1 and Cycle 2 of the Phase 2 study until sample size needed for population PK analysis has been met.

Refer to Laboratory Manual and see Table 8 and Table 9 for additional details.

7.4.1.6 Biomarker and Pharmacogenomic Assessments

Biomarker and Pharmacogenomic Assessments

Biomarker discovery and validation may be performed through all phases of this clinical study. The goal of these studies is to assay biomarkers in blood, normal, and malignant tissue to confirm the mechanism of action of tazemetostat and discover biomarkers that may predict response to tazemetostat.

Phase 1 Dose Escalation and Food Effect Cohort (Closed to Enrollment)

Blood samples and skin punch biopsies (Dose Escalation only: closed), will be obtained predose and at various specified times postdose and may be assessed for molecular changes associated with exposure to tazemetostat, such as changes in histone methylation, gene expression (protein

and/or mRNA), or other markers with the potential to confirm the mechanism of action of tazemetostat (PD biomarker). Results will be correlated with PK and safety data.

Archival, FFPE tumor tissue from all enrolled subjects will also be collected (if available) for assessment of EZH2 mutation status, for confirmation of COO in DLBCL cohorts, and for exploratory response biomarker analysis. Biomarker assays for analysis of markers identified in nonclinical studies and/or the scientific literature may include DNA mutation assessment, gene-expression profiling, proteomics, or IHC analysis. Results may be correlated with efficacy data.

During the FE cohort, paired tumor biopsies or bone marrow samples (for FL cases) may be obtained, with appropriate subject consent, to examine tumor tissue for molecular evidence of the downstream consequences of EZH2 inhibition (see below under Phase 2).

For details regarding the Phase 1 PD analyses, see Schedule of Visits and Procedures (Table 8) and the Laboratory Manual.

Phase 2

Blood samples will be obtained predose and at various specified times postdose and assessed for molecular changes induced by exposure to tazemetostat, such as changes in histone methylation, gene expression (protein and/or mRNA), or other markers with the potential to elucidate or confirm the mechanism of action of tazemetostat.

Paired tumor biopsies and/or bone marrow (FL cohorts) may be obtained, with appropriate subject consent, to examine tumor tissue for molecular evidence of the downstream consequences of EZH2 inhibition using relevant PD biomarkers such as H3K27 methylation status or others as assayed by appropriate methodologies. The aim is to obtain paired tumor tissue from a minimum of 4-6 subjects from each of the planned cohorts in Phase 2, FE, and Dose Expansion cohorts. Depending on tissue availability, assessment of the drug's effect on both tumor and stromal cells is planned, as changes in 1 or both tissue types may predict tumor response. Lymphoma cell-specific markers can include, but are not limited to, differentiation markers, markers of immune cell recognition, and markers of proliferation and apoptosis. The general tumor/stromal architecture will be examined to study the drug's effects on the interaction of lymphoma cells with the tumor microenvironment. Specific markers can include, but are not limited to, the presence and activation state of regulatory T cells, the Th1/Th2 profile of intra-tumoral T helper cells, and expression of programmed death receptor 1 (PD1) and programmed death ligands (PDL1 and PDL2) on tumor and T cells. Refer to Section 7.4.1.8 for biopsy schedules.

A plasma sample for cell-free nucleic acid analysis (circulating tumor DNA) will be obtained predose and at various time points as specified in the Schedule of Visits and Procedures (Phase 2 only). Cell-free nucleic acid isolated from blood plasma samples may be used to explore tumor

genetic alterations, including mutations observed in archival tumor samples, mutations that may emerge with drug treatment, and candidate biomarkers of response to tazemetostat.

Archival, FFPE tumor tissue from all enrolled subjects must be collected for prospective assessment of EZH2 mutation status, for confirmation of COO in DLBCL cohorts. Additional exploratory response biomarker analysis may be performed retrospectively. Gene-expression profiling, proteomics, DNA mutation analysis, or IHC analysis may be performed, based on the amount of tumor tissue available, for analysis of markers identified in preclinical studies and/or the scientific literature. Gene expression profiling may be performed and correlated with PK, PD, or safety data.

An EZH2 mutation result will be determined at designated study laboratory testing sites using the **cobas®** EZH2 Mutation Test, which is a real time allele-specific PCR test to detect mutations within codons Y646, A682, and A692 of the EZH2 gene in FFPE NHL tumor tissue specimens: Y646F, Y646N, Y646S, Y646H, Y646C, A682G, and/or A692V; results for Y646S, Y646H, and Y646C are not reported individually (grouped as Y646X). The EZH2 mutation test is an Investigational Use Only assay.

COO will be determined for DLBCL subjects using the Hans method (Hans, 2004) at designated laboratory testing sites. Further details of EZH2 mutation and COO testing will be provided in the Laboratory Manual.

Applicable to both Phase 1 and Phase 2

Plasma samples from subjects receiving tazemetostat may undergo global proteomic and enzyme-linked immunosorbent assay-based analyses and multiplex bead-based immunoassay in an effort to identify protein markers.

Genomic DNA samples may be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion or the development of AEs. Variation in tazemetostat exposure or AEs may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety, or PD data. Collection of Genomic DNA will cease when sample size has been met.

Data obtained will be used only for research, to assist in developing safer and more effective treatments, and will not be used to change the diagnosis of the subject or alter the therapy of the subject. Biomarker specimens and any DNA, RNA, protein, or metabolites derived from the collected specimens may be stored for up to 15 years to assist in any research (eg, scientific questions related to tazemetostat, solid tumors, or B cell lymphoma) as well as for potential use in diagnostic development.

For additional information, see Appendix 7. Details of pharmacogenomic and biomarker sampling and analysis will be provided in the Laboratory Manual.

PHARMACODYNAMIC ASSESSMENTS

Blood samples, skin punch biopsies (for Dose Escalation only: closed), and optional tumor biopsies for PD assessments will be obtained predose and at various time points as specified in the Schedule of Visits and Procedures. Refer to Laboratory Manual and see Table 8 and Table 9 for additional details.

Pharmacokinetic/Pharmacodynamic Assessments

The PK/PD relationship between exposure to tazemetostat and histone methylation will be explored graphically and any emergent relationship will be followed by model-based PK/PD analysis.

PK/PD relationships will be assessed for exploratory biomarkers, safety, and preliminary efficacy.

PK/PD analysis will be performed to correlate best overall response with tazemetostat exposure.

The total volume of blood to be drawn per period or cycle can be found in the Laboratory Manual provided separately. Instructions for the processing, storage, and shipment of samples will be provided in a separate Laboratory Manual.

7.4.1.7 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE v4.03 [Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, 2009], see Appendix 5) (for both increasing and decreasing severity), and SAEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; and periodic measurement of vital signs, echocardiograms/ multiple-gated acquisition (MUGA) scans, electrocardiograms (ECGs), and physical examinations. Additionally, QT interval corrected for heart rate using Fridericia's formula (QTcF) will be evaluated.

For details, refer to the Schedule of Visits and Procedures (Table 8 and Table 9).

LABORATORY MEASUREMENTS

The clinical laboratory parameters that will be measured are detailed in Table 7.

Phase 1 only: Clinical laboratory tests will be performed by a central laboratory. All blood samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern or to guide clinical dosing, a local laboratory may be used in addition to a central laboratory. If central laboratory results are not available

within the necessary time frame to allow the subject to be enrolled, local laboratories may be used to perform laboratory tests to qualify subjects for entry into the study. Urinalysis may be performed at the investigational site by dipstick or sent to the central laboratory.

For the Phase 2 part of the study clinical laboratory tests will be performed locally.

The Schedules of Visits and Procedures (Table 8 and Table 9) show the visits at which blood and urine will be collected for clinical laboratory tests. A Laboratory Manual will be provided to detail handling, processing, and shipping procedures.

All hematology, blood chemistry (including pregnancy test, where applicable) samples are to be obtained before study drug administration and results reviewed before administration/dispensing of study drug at the beginning of each cycle. For the management of clinically significant laboratory abnormalities, refer to the Dose Reduction and Interruption Instructions for tazemetostat in Section 7.3.2.2 (Table 4).

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 7.4.4.2) and the CRF Completion guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the AE CRF.

For laboratory abnormalities meeting criteria as SAEs (Section 7.4.4.2), the study site must send the SAE report including the laboratory report to the Sponsor using the SAE fax number or email address provided in the Investigator File.

Table 7 Clinical Laboratory Tests

Category	Parameters
Hematology	• hematocrit, hemoglobin, red blood cell count (RBC), platelet count, white blood cell count (WBC) with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils) • Peripheral blood smear morphology assessment (If peripheral blood smear morphology is abnormal, then conduct bone marrow aspirate with cytogenic testing to closely monitor subjects with cytogenic abnormalities known to be associated with myelodysplastic syndrome (MDS) 9del 5q, chr 7, abn, etc.) and myeloproliferative neoplasm (MPN) (e.g. JAK2 V617F, etc.)
Chemistry	
Electrolytes	• bicarbonate, chloride, potassium, sodium
Liver function	• alkaline phosphatase (ALP), alanine aminotransferase (ALT [or serum glutamic pyruvic transaminase (SGPT)]), aspartate aminotransferase (AST [or serum glutamic oxaloacetic transaminase (SGOT)]), conjugated (direct) bilirubin[a], total bilirubin
Renal function	• blood urea or blood urea nitrogen (BUN), creatinine
Other	• albumin, amylase, calcium, cholesterol, , creatine phosphokinase (CPK), glucose, International Normalized Ratio (INR), lactate dehydrogenase (LDH), phosphorous, total protein, triglycerides, uric acid

a. The collection of conjugated bilirubin and globulin is not standard of care test across all institutions. Conjugated bilirubin should be collected whenever possible or if clinically indicated. Globulin is no longer required.

VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital signs and body weight (kg) will be collected at the visits designated in the Schedule of Visits and Procedures (Table 8 and Table 9) by a validated method. Vital sign measurements include blood pressure ([BP], systolic BP, diastolic BP), heart rate (HR, beats per minute), and body temperature (°C). Height will be measured at the Screening Visit only. Blood pressure and HR will be collected after subjects have been sitting for 5 minutes.

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

ECOG PERFORMANCE STATUS

An ECOG performance status should be done at each visit as designated in the Schedule of Visits and Procedures (Table 8 and Table 9).

PHYSICAL EXAMINATIONS

Comprehensive physical examinations and symptomatic physical examinations will be performed as designated in the Schedule of Visits and Procedures (Table 8 and Table 9). Documentation of the physical examination will be included in the source documentation at the investigational site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the AE CRF.

A comprehensive physical examination will include evaluation of the head, eyes, ears, nose, throat, neck, heart, chest, lungs, abdomen, extremities, skin, and neurological status.

Symptom directed physical examination will include health status assessed by a brief evaluation of the head, eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination.

ELECTROCARDIOGRAMS

Electrocardiograms will be complete, standardized, 12-lead recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format as designated in the Schedule of Visits and Procedures (Table 8 and Table 9). In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes before the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (Section 7.4.4.3) and the CRF instructions. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AE CRF.

For ECG abnormalities meeting criteria as SAEs (Section 7.4.6), the study site must send the SAE report including the ECG report to the number indicated in the Investigator File using the SAE reporting form.

7.4.1.8 Other Assessments

PREGNANCY TEST

A serum β-hCG test and/or urine β-hCG test will be performed at Screening for all women of child bearing potential. A urine or serum pregnancy test will be performed before the first tazemetostat dose and prior to dosing on Day 1 of each cycle. For the serum β-hCG test, a 6-mL sample of blood will be taken at designated time points on the Schedule of Visits and Procedures (Table 8 and Table 9).

PAIRED TUMOR BIOPSIES

Paired tumor biopsies (Phase 2 cohorts, Dose-Escalation cohorts, and FE cohort) and/or bone marrow biopsies (Phase 2 FL cohorts) may be obtained, with appropriate subject consent, from

4 to 6 subjects per cohort to examine tumor tissue for molecular evidence of the downstream consequences of EZH2 inhibition using relevant PD biomarkers assayed by appropriate methodologies. Paired tumor tissue will be obtained from the pool of subjects recruited to the Expansion Cohorts, FE cohort, and Phase 2 part. Tissue sample collection, for PD assessments will occur at the designated time point on the Schedule of Visits and Procedures (Table 9). Subjects should have the biopsy before administration of the first dose of tazemetostat and the second biopsy at Cycle 2 Day 1.

TUMOR BIOPSY AT DISEASE PROGRESSION

Tumor biopsy is requested, where medically feasible, at disease progression in subjects who achieve a PR or better with tazemetostat.

BONE MARROW BIOPSY WITH IHC

A bone marrow biopsy (including IHC) will be performed for all subjects with FL and in subjects with DLBCL if clinically indicated or if subject has history of bone marrow involvement if these have not been performed within 42 days (an approval is needed from the Sponsor's medical monitor if the window has been beyond 42 days) of Cycle 1 Day 1. At the first notation of CR, a repeat bone marrow biopsy should be performed if lymphoma involvement in the bone marrow was reported at Screening. For further details, see Table 9.

PERIPHERAL BLOOD SMEAR/ BONE MARROW BIOPSY

If peripheral blood smear morphology assessment is confirmed to be abnormal, the subject will be required to undergo bone marrow aspirate/biopsy for cytogenetic testing to closely monitor subjects with cytogenetic abnormalities known to be associated with MDS (9del 5q, chr 7, abn, etc.) and MPN (e.g. JAK2 V617F, etc.) If abnormal results, pause tazemetostat and after discussion with the Investigator modify the dose or discontinue the drug.

OPTIONAL CHEST ULTRASOUND

An optional chest ultrasound may be performed at screening and every 8 weeks at the Investigator's discretion to monitor for early signs of T-LBL/T-ALL.

ANNUAL ASSESSMENTS

Annual assessments will be conducted to review AESIs, PK and tumor response. A 3 mL blood sample will be required for annual PK assessments. Note: Annual assessments are no longer required as of Amendment 13.0. Annual PK sample collections that had been required in Cohorts 4 and 5 were no longer required as of 16 May 2018.

7.4.1.9 Safety Monitoring

Completed: Final determination of whether a subject should be counted as having experienced a DLT for dose escalation purposes or MTD and/or RP2D confirmation purposes, and whether the dose escalation will proceed in 100% increments or smaller, will be made jointly by the Sponsor and investigators. For additional details, see Section 7.3.2.1.

Completed: An independent DMC was established to review available safety data supporting the MTD and/or RP2D once a minimum of 6 subjects at the MTD or highest feasible dose complete 1 cycle in Dose Escalation. The DMC reviewed safety data including, but not limited to, AEs, SAEs, laboratory parameters, investigational product dosing records, treatment delays or reductions, and treatment discontinuation due to toxicity. Based on all data reviews, the Sponsor and the DMC concurred on the dose for Phase 2.

During Phase 2, in order to adequately monitor safety, data will be reviewed regularly by an independent DMC. The DMC Chair, in consultation with the Sponsor, will be responsible for determining the type and frequency of any additional DMC data review meetings. The DMC will review safety data including, but not limited to, AEs, SAEs, laboratory parameters, investigational product dosing records, treatment delays or reductions, and treatment discontinuations due to toxicity. Any treatment-related death will also trigger review by the DMC. The DMC will determine whether it is safe to proceed.

A full description of the membership and roles and responsibilities of the DMC will be provided in the DMC charter, and its end of Phase 1 assessment report will be transmitted to the approving Ethics Committees and Competent Authorities for this study.

Tazemetostat Safety Committee

A safety monitoring committee composed of internal and external medical experts will review all AESI cases, including T-LBL/acute lymphoblastic leukemia (ALL), MDS/acute myeloid leukemia (AML) and other myeloid malignancies like MPN (both related and unrelated), and other solid tumor malignancies. Cases will be evaluated for suspected relationship to tazemetostat and adjudicated by the experts. Recommendations for next steps per the risk management plan will be communicated to the CMO

7.4.2 Schedule of Procedures/Assessments

7.4.2.1 Schedule of Procedures/Assessments

Phase 1 Schedule of Visits and Procedures for assessments are presented in Table 8.

Phase 2 Schedule of Visits and Procedures for assessments are presented in Table 9.

7.4.2.2 Description of Assessment Schedule

Potential subjects will undergo a screening assessment within 28 days before the start of the study to evaluate their eligibility for the study. Before any procedures or assessments are performed, the nature of the study and the potential risks associated with the trial will be explained to all subject candidates, and written informed consent will be obtained. Once informed consent has been obtained, study procedures and evaluations will be performed.

The tumor tissue EZH2/COO testing can be performed prior to other screening procedures, for example, during wash-out of the second line anticancer therapy, after the subject is consented for the prescreening testing.

Efforts should be made to conduct study visits on the day scheduled (± 3 days). Clinical laboratory assessments (Table 7) may be conducted anytime within 72 hours before the scheduled visit, unless otherwise specified in the Schedule of Visits and Procedures. Whenever possible, subjects should be evaluated at approximately the same time of the day (eg, morning or afternoon) at each visit, and reasonable efforts should be made to conduct all evaluations in the same test order at each visit. Subjects on the Phase 1 part of the study who have completed at least 6 cycles of study drug and are considered clinically stable may, after prior agreement with the study medical monitor, have Day 15 assessments in additional cycles consisting of telephone contact to site and local clinical laboratory assessments. For the details of procedures, assessments, and timing of procedures and assessments that are to be conducted at each visit and cycle(s), refer to the Schedule of Visits and Procedures.

Table 8 Schedule of Visits and Procedures: Phase 1 Tazemetostat (all visits starting at Cycle 2 Day can have a +/- 3 day window)

Phase	Pretreatment		DDI only	Treatment		Extension		Extension	Off-Treatment[a]	Follow-up[b]
Period	Screening[c]	Baseline[c]		Cycle 1		Cycle 2 - 6		Cycle 7 and Beyond[d]		
Day	-28 to -4	-3 to -1	-1	1	15	1	15	1		
Procedures/Assessments										
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Medical history	X	X								
Prior and concomitant medications				Throughout study						
Comprehensive physical examination	X								X	
Symptom directed physical examination		X		X	X	X	X	X		
Pregnancy test[e]	X	X				X		X		
Body weight	X	X		X	X	X	X	X	X	
Height	X									
Vital signs[f]	X	X		X	X	X	X	X	X	
ECOG performance status	X	X				X		X	X	
12-lead ECGs[g]	X	X		X		X	X	X	X	
Hematology	X	X		X	X	X	X	X	X	
Blood chemistry	X	X		X	X	X	X	X	X	
Genomic DNA[j]		X								
PK blood samples[k]			X		X	X[k]				
PD blood samples[l]				X	X	X[l]				
Paired tumor biopsy[m]		X				X				
Archival tumor block or slides[n]		X								
Tumor assessments: CT (MRI)[o]	X			Tumor assessments must be performed every 8 weeks up to week 24				Tumor assessments performed every 12 weeks	X	
Bone scans (solid tumor	X			X						

Table 8 Schedule of Visits and Procedures: Phase 1 Tazemetostat (all visits starting at Cycle 2 Day can have a +/- 3 day window)

Phase	Pretreatment		DDI only	Treatment		Extension		Extension	Off-Treatment[a]	Follow-up[b]
Period	Screening[c]	Baseline[c]		Cycle 1		Cycle 2 - 6		Cycle 7 and Beyond[d]		
Day	-28 to -4	-3 to -1	-1	1	15	1	15	1		
Procedures/Assessments										
as indicated)										
^{18}FDG-PET Scan (NHL)[p]	X			Repeat PET at PR or CR						
Bone Marrow Biopsy (NHL if indicated)[q]	X									
CT or MRI of the brain[r]	Brain scans should be performed if clinically indicated both NHL and solid tumor.									
AEs/SAEs				Throughout study						
Tazemetostat administration[s]				Continuous 28-day cycle of tazemetostat twice daily. Tazemetostat can be taken with or without food.						
Midazolam administration (DDI only)[t]			X		X					
Survival status and subsequent anticancer therapy									X	X

AE = adverse event, BM = bone marrow, β-hCG = beta-human chorionic gonadotropin, BP = blood pressure, CR = complete response, CT = computed tomography, DDI = drug-drug interaction, DNA = deoxyribonucleic acid, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, ^{18}FDG-PET = ^{18}fluorodeoxyglucose-positron emission tomography, HR = heart rate, IV = intravenous, MRI = magnetic resonance imaging, NHL = non-Hodgkin lymphoma, PD = pharmacodynamic, PK = pharmacokinetic, PR = partial response, SAE = serious adverse event

Note: All table footnotes are presented on the following 2 pages.

PHASE 1 IS COMPLETED

a Off-treatment assessment may occur at time of treatment discontinuation or up to 30 days after the final dose of study drug. AE and concomitant medication data must be collected for 30 days after the final dose of study drug, or until the start of new therapy. This may occur prior to 30 days if new therapy is started within 30 days of last dose of study drug.

b Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Information on all anticancer therapies will be collected (the Sponsor may choose to stop the collection of therapies after the first anticancer treatment following tazemetostat). This may be done by telephone contact.

c The Screening Period extends from Day -28 to Day -4, except for signing of the informed consent form, which may be up to 8 weeks before the first dose of study drug. The baseline assessments may be performed from Day -3 to Day -2 (before the first dose of tazemetostat). The screening assessments (except tumor assessment) must be

Table 8 Schedule of Visits and Procedures: Phase 1 Tazemetostat (all visits starting at Cycle 2 Day can have a +/- 3 day window)

Phase	Pretreatment		DDI only	Treatment		Extension		Extension	Off-Treatment[a]	Follow-up[b]
Period	Screening[c]	Baseline[c]		Cycle 1		Cycle 2 - 6		Cycle 7 and Beyond[d]		
Day	-28 to -4	-3 to -1	-1	1	15	1	15	1		
Procedures/Assessments										

performed within 28 days before the first dose of study drug and may be used as baseline assessments if performed within 72 hours of the first dose of study drug. Tumor assessment must occur within 28 days of CT or MRI or photographs and within 42 days of bone scans (if a bone scan is appropriate for a tumor type).

d Starting at Cycle 7, a Day 15 visit is not required. On Day 15 of each cycle, subjects will have hematology and blood chemistry samples drawn at a local laboratory and telephone contact with the site to review AEs.

e A serum pregnancy test (β-hCG) will be performed at Screening for all women of childbearing potential. A urine or serum pregnancy test will be performed predose on Day 1 of each cycle.

f Vital signs include BP, HR, and body temperature. BP and HR will be collected after the subject has been sitting for 5 minutes.

g 12-Lead ECGs will be collected at the following time points: Screening (single) and Baseline (single unless abnormalities are observed or if clinically indicated, then in triplicate at 2-minute intervals); Day 1 of all cycles (before and after morning dose of study drug administration); at Day 15 from Cycle 2 until Cycle 6; and at Off-Treatment Visit. In case of any alteration, or if clinically necessary, an echocardiogram and/or cardiac enzymes should be performed.

i [Procedure no longer being performed.]

j Genomic DNA samples will be collected predose during Screening or Baseline. If it cannot be collected at the designated time point, it may be collected at a time point after baseline.

k Blood samples for PK analysis in the DDI cohort will be collected in Cycle 1 on Days -1 and 15 at Predose (0 hours), 0.5, 1, 2, 4, 6, 8, 10, and 12 and 24 hours postdose; and on Cycle 2 Day 1 Predose (0 hours), 0.5 to 2 hours, and 3 to 6 hours postdose.

l Blood samples for PD analysis will be collected at the following time points: Predose (0 hours) on Cycle 1 Days 1 and 15; and Predose (0 hours) on Cycle 2 Day 1. Blood samples should be collected on the day after Day 28 of Cycle 1, irrespective of the start of Cycle 2.

m Paired tumor biopsies and/or bone marrow biopsies may be obtained, with appropriate subject consent, from at least 4 to 6 subjects per cohort to examine tissue target inhibition, relevant PD biomarkers, and potential markers of response. Subjects will have the biopsy before administration of the first dose of tazemetostat and on Cycle 2 Day 1.

n Subjects will have collection of archived, tumor-biopsy sections for identification of predictive biomarkers unless no such material is available.

o Tumor assessments include CT scan of the chest, CT or MRI of abdomen, pelvis, and other known sites of disease or newly suspected disease (as well as photographs of skin lesions that will be followed as target and nontarget lesions) and should be performed at Screening and every 8 weeks (starting from Cycle 1 Day 1 through Cycle 6 and every 12 weeks from Cycle 7 and beyond), and as clinically indicated. Subjects with B Cell Lymphoma should be assessed for B symptoms at these time points. See Section 7.4.1.3. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be performed without IV contrast.

p Subjects with B Cell Lymphoma should have ^{18}FDG-PET Scan at Screening and at the first notation of possible PR or CR.

Table 8 Schedule of Visits and Procedures: Phase 1 Tazemetostat (all visits starting at Cycle 2 Day can have a +/- 3 day window)

Phase	Pretreatment		DDI only	Treatment		Extension		Extension	Off-Treatment[a]	Follow-up[b]
Period	Screening[c]	Baseline[c]		Cycle 1		Cycle 2 - 6		Cycle 7 and Beyond[d]		
Day	-28 to -4	-3 to -1	-1	1	15	1	15	1		
Procedures/Assessments										

q Subjects with B Cell Lymphoma should have a BM biopsy at Screening (unless performed within 42 days of Cycle 1 Day 1) and at first notation of CR if there was lymphoma involvement of BM at Screening. If a BM biopsy sample was provided for PD sample at Screening, subsequent BM biopsy samples will be requested for PD assessment.

r CT or MRI of the brain should be performed if clinically indicated. The same methodology and scan acquisition techniques used at Screening should be used throughout the study to ensure comparability.

s On visit days, subjects should not take study drug before evaluations are performed.

t A single oral dose of midazolam 2 mg will be given on Day -1 and Day 15 for subjects in the DDI cohort of the study only. See Section 7.3.2 for additional details.

Table 9 Schedule of Visits and Procedures: Phase 2 (All Visits Starting at Cycle 1 Day 15 Have ± 3-Day Window)

Period	Screening[a]	Cycles 1 and 2		Cycle 3 and Beyond		Off-Treatment[b]	Follow-up[c]
Day	-28 to -1	1 (± 3 days)	15 (± 3 days)	1 (± 3 days)	15[d] (± 3 days)		
Procedures/Assessments							
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history	X						
Prior and concomitant medications	Throughout study						
Comprehensive physical examination	X					X	
Symptom directed physical exam		X	X	X			
Pregnancy test[e]	X	X		X		X	
Body weight	X	X	X	X		X	
Height	X						
Vital signs[f]	X	X	X	X		X	
ECOG performance status	X	X		X		X	
12-lead ECGs[g]	X	X		X		X	
Hematology[u]	X	X	X	X	X	X	
Blood chemistry	X	X	X	X	X	X	
Genomic DNA[h, t]							
PK blood samples[i, t, w]		X[i]	X[i]				
PD blood samples[j]		X[j]	X[j]				
PD blood sample for nucleic acid[k]		X		X		X	
Sufficient tumor tissue available[l]	X						
Optional Paired tumor biopsies[m]		X					
Tumor biopsy at DP[n]						X	
Tumor assessments: CT (MRI), and assessments of B symptoms[o,w]	X	Radiologic tumor assessments (IWG-NHL [Cheson, 2007] criteria) **must be performed every 8 weeks during Cycles 2-6, and every 12 weeks starting at Cycle 7 and beyond**				X	X
Optional chest ultrasound[v,w]	X	Every 8 weeks while subject is receiving study drug					
CT or MRI of the brain[p]	Brain scans should be performed if clinically indicated.						
Bone marrow biopsy (with IHC)[q]	X	At first notation of CR if bone marrow involvement at Screening, and if clinically indicated (eg, suspicion of relapse or progressive disease)					

Table 9 Schedule of Visits and Procedures: Phase 2 (All Visits Starting at Cycle 1 Day 15 Have ± 3-Day Window)

Period	Screening[a]	Cycles 1 and 2		Cycle 3 and Beyond		Off-Treatment[b]	Follow-up[c]
Day	-28 to -1	1 (± 3 days)	15 (± 3 days)	1 (± 3 days)	15[d] (± 3 days)		
Procedures/Assessments							
^{18}FDG-PET scan[r]	X	Performed at first notation of possible PR or CR					
AEs/SAEs[w]	Throughout study treatment and off-treatment periods						
Tazemetostat administration[s]		Continuous 28-day cycle of tazemetostat twice daily. Tazemetostat can be taken with or without food.					
Prednisolone administration (Cohort 6 only)[s]		Prednisolone from Days 1 to 5 and Days 15 to 19 taken with or without food for a total of 4 cycles					
Survival status and subsequent anticancer therapy						X	X

AE = adverse event, β-hCG = beta-human chorionic gonadotropin, BP = blood pressure, CR = complete response, CT = computed tomography, DLBCL = diffuse large B cell lymphoma, DNA = deoxyribonucleic acid, DP = disease progression, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EZH2 = enhancer of zeste homolog 2, ^{18}FDG-PET = ^{18}fluorodeoxyglucose-positron emission tomography, FL = follicular lymphoma, HR = heart rate, IHC = immunohistochemistry, IWG-NHL = International Working Group-Non-Hodgkin's Lymphoma, MRI = magnetic resonance imaging, PD = pharmacodynamic, PK = pharmacokinetic, SAE = serious adverse event

a. The Screening Period extends from Day -28 to Day -1, except for signing of the informed consent form, which may be up to 8 weeks before the first dose of study drug. Screening laboratory assessments may be used as Day 1 assessments if performed within 72 hours of the first dose of study treatment, however subjects must continue to meet eligibility criteria prior to first dose of tazemetostat on Cycle 1 Day 1. The screening assessments (except tumor assessment) must be performed within 28 days before the first dose of study drug.

b. Off-treatment assessment may occur at time of treatment discontinuation (eg, at the visit at which the decision to discontinue treatment occurs) or up to 30 days after the final dose of study drug. AE and concomitant medication data must be collected for 30 days after the final dose of study drug, or until the start of new therapy. This may occur prior to 30 days if new therapy is started within 30 days of last dose of study drug. If subject is unable to return to the clinic for assessment of AEs this may be done by telephone.

c. Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Information on all subsequent anticancer therapies and AESIs will be collected throughout the survival follow up. This may be done by telephone contact. NOTE: As of Protocol Amendment 13.0, no further survival follow-up is necessary for remaining subjects because the primary outcome assessment for all subjects has been met.

d. Starting at Cycle 3, a Day 15 laboratory assessments are not required, but the telephone contact is still required. Laboratory assessments are to be performed as medically needed and can be either at the clinic or at a local laboratory. Any abnormal laboratory test result collected at Day 15, Cycle 3 and beyond will only need to be entered into the clinical database if they are associated to an AE. These results will be reported as an unscheduled visit.

e. A serum pregnancy test (β-hCG) will be performed at Screening for all women of childbearing potential. A urine or serum pregnancy test will be performed predose on Day 1 of each cycle starting at Cycle 2.

f. Vital signs include BP, HR and body temperature. BP and HR will be collected after the subject has been sitting for 5 minutes.

g. 12-Lead ECGs will be collected at the following time points: Screening (triplicate), Cycles 1 and 2 Day 1 (predose and 0.5 – 2 hours post dose immediately before PK sample), Day 1 of all subsequent cycles (before the morning dose of study drug administration), and at the Off-Treatment Visit. In case of any alteration or if clinically necessary, additional ECGs, an echocardiogram, and/or testing of cardiac enzymes should be performed.

h. Genomic DNA samples will be collected predose at Screening. If it cannot be collected at the designated time point, it may be collected at a time point prior to first dose.

i. Blood samples for PK analysis for tazemetostat (all cohorts) and prednisolone (Cohort 6 only) will be collected in Cycle 1 on Day 1 at 0.5 to 2 hours and 3 to 6 hours and Day 15 at predose (0 hours), 0.5 to 2 hours, and 3 to 6 hours; and Cycle 2 on Day 1 at predose (0 hours), 0.5 to 2 hours, and 3 to 6 hours. Blood samples should be collected on the day after Day 28 of Cycle 1, irrespective of start of Cycle 2.

j. This sample is no longer required.

k. Blood samples for nucleic acid analysis will be collected at the following time points: Predose (0 hours) on Cycle 1 Day 1, and Day 1 of every other cycle, and at the off-treatment visit.

l. Subjects will have collection of archived, tumor-biopsy sections for central testing of EZH2 mutation status (all subjects) and confirmation of cell of origin for DLBCL subjects.

m. Paired tumor biopsies (DLBCL cohorts) and/or bone marrow biopsies (FL cohorts) are optional and may be obtained, with appropriate subject consent, from at least 4 to 6 subjects per cohort to examine tissue target inhibition, relevant PD biomarkers, and potential markers of response. Subjects should have the biopsy before administration of the first dose of tazemetostat and the second biopsy on Cycle 2 Day 1. If sufficient tumor exists from archival, this could be considered the predose sample.

n. Tumor biopsy is to be requested, where medically feasible, at disease progression in subjects who achieve a PR or better with tazemetostat.

o. Tumor assessments include CT scan of the chest, CT or MRI of the abdomen, pelvis, and other areas of known disease or newly suspected disease and should be performed between Day -28 and Day -1 and every 8 weeks, irrespective of treatment delays, during Cycles 1 to 6, and every 12 weeks during Cycle 7 and beyond. If local regulatory authorities mandate less frequent imaging, minimum frequency must be every 12 weeks. For countries where CT scan of the chest, CT or MRI of abdomen, pelvis and other areas of known or newly suspected disease are part of Standard Of Care Assessment (SoC), the scan will be performed as per SoC schedule and evaluation of the result will be performed and reported as per the Protocol. The same parameters as the screening scans should be used. A standard-of-care clinical examination for lymphoma, including assessment of B symptoms, will also be performed at each visit.

p. CT or MRI of the brain should be performed if clinically indicated.

q. A bone marrow biopsy (including IHC) will be performed between Day -28 and Day -1 for all subjects with FL and in subjects with DLBCL if clinically indicated or if subject has history of bone marrow involvement if these have not been performed within 42 days (an approval is needed from the Sponsor's medical monitor if the window has been beyond 42 days) of Cycle 1 Day 1. At the first notation of CR, a repeat bone marrow biopsy should be performed if lymphoma involvement in the bone marrow was reported at Screening.

r. ^{18}FDG-PET scan should be performed at Screening and at the first notation of possible PR or CR.

s. On visit days when PK samples are collected, study drug(s) should be administered in clinic.

t. Effective 16 May 2018, the sample size for population PK and genomic DNA analysis has been met and additional samples are no longer being collected.

u. If peripheral blood smear morphology is abnormal, then conduct bone marrow aspirate with cytogenic testing to closely monitor subjects with cytogenic abnormalities known to be associated with MDS 9del 5q, chr 7, abn, etc.) and MPN (e.g. JAK2 V617F, etc.)

v. An optional chest ultrasound may be performed at the Investigator's discretion to monitor for early signs of T-LBL/T-ALL.

w. Annual assessments will be conducted to review AESIs, PK and tumor response. (Note: Annual assessments are no longer required as of Amendment 13.0. Also, annual PK sample collections for assessment were no longer required as of as of 16 May 2018.)

OFF-TREATMENT PROCEDURES

Off-treatment assessment may occur at time of treatment discontinuation or up to 30 days after the final dose of study drug or initiation of subsequent anticancer therapy. Adverse event and concomitant medication data must be collected for 30 days after the final dose of study drug, or until the start of new therapy. All subjects will be asked to return to the sites for discontinuation or off-treatment assessments, if possible. If a clinic visit is not feasible, follow up information may be obtained via telephone or written correspondence. This may occur prior to 30 days if new therapy is started within 30 days of last dose of study drug.

If a subject fails to appear for a scheduled study visit, the Investigator will make every attempt to contact the subject and determine the reason(s) for the missed visit as completely and accurately as possible. Subjects will only be judged as lost to follow-up if they cannot be reached after 3 documented attempts by the site to contact them (1 week apart).

Whenever possible, the following assessments should be performed within 30 days after subjects have received the final dose of study drug:

PHASE 1

- Comprehensive physical examination
- Body weight
- Vital signs (BP, HR, body temperature)
- ECOG performance status (Appendix 1)
- 12-lead ECGs
- Bone marrow biopsy, if clinically indicated
- Collect blood samples for hematology and blood chemistry analysis (see Table 7 for the tests to be performed)
- Tumor assessments: RECIST 1.1 criteria for solid tumors (Appendix 4) or IWG-NHL (Cheson, 2007) for B cell lymphoma
- Record AEs and SAEs
- Survival status and subsequent anticancer therapy

For details, refer to the Schedule of Visits and Procedures (Table 8 and Table 9).

PHASE 2

- Comprehensive physical examination
- Body weight

- Vital signs (BP, HR, body temperature)
- ECOG performance status (Appendix 1)
- 12-lead ECGs
- Collect blood samples for hematology and blood chemistry analysis (see Table 7 for the tests to be performed)
- Bone marrow biopsy for all FL subjects and if clinically indicated in DLBCL subjects with history of bone marrow involvement
- Tumor assessments: IWG-NHL (Cheson, 2007) criteria
- Record AEs and SAEs
- Survival status subsequent anticancer therapy (no longer applicable after Amendment 13.0) and AESI

For details, refer to the Schedule of Visits and Procedures (Table 8 and Table 9).

SURVIVAL STATUS AND SUBSEQUENT ANTICANCER THERAPY

Survival status will be collected on all subjects every 12 weeks, unless they withdraw consent. Information about all subsequent anticancer therapies after study drug discontinuation will be collected (the Sponsor may choose to stop the collection of therapies after the first post study drug discontinuation anticancer treatment). Note: As of Protocol Amendment 13.0, no further survival follow-up is necessary for remaining subjects because the primary outcome assessment for all subjects has been met.

TUMOR ASSESSMENTS DURING THE FOLLOW-UP PERIOD

Where possible, for subjects who discontinue study drug for reasons other than disease progression, scans performed during the post study drug discontinuation follow-up period should be performed on the same schedule and using the same imaging modality as defined in the study protocol.

7.4.2.3 Total Volume of Blood

The total volume of blood drawn per period or cycle can be found in the Laboratory Manual provided separately. Additional samples may be taken at the discretion of the Investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

7.4.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of solid tumors and hematological malignancies. The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, radiologic studies, and assessment of AEs, are standard International Conference on Harmonisation (ICH) GCP evaluations to ensure subject safety. The use of IWG-NHL (Cheson, 2007) for B cell lymphoma and RECIST 1.1 for solid tumor assessment and are widely accepted (Cheson, 2007; Eisenhauer, 2009).

7.4.4 Adverse Events and Serious Adverse Events, Pregnancy, and Other Events of Interest

7.4.4.1 Adverse Events and Other Events of Interest

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the investigational product. 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 investigational product, whether or not related to the investigational product.

In the Phase 1 part of the study all AEs, regardless of the relationship to the study drug or procedure, should be collected beginning from the time the subject signs the study consent. In the Phase 2 part of the study all AEs, regardless of the relationship to the study drug or procedure should be collected beginning from the time of first dose of the investigational product.

Worsening of a pretreatment event, after initiation of investigational product, must be recorded as a new AE. For example, if a subject experiences mild intermittent dyspepsia prior to dosing tazemetostat, but the dyspepsia becomes severe or more frequent after the first dose of tazemetostat, a new AE of worsening or more frequent dyspepsia (with the appropriate date of onset and severity) should be recorded in the eCRF.

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

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

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

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

All AEs will be collected for 30 days after the final dose of study drug, or until the start of subsequent anticancer therapy, whichever happens first. If subject is unable to return to the clinic for assessment of AEs this may be done by telephone.

7.4.4.2 Laboratory Abnormalities

An abnormal laboratory test result may be considered as an AE if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

A laboratory result should be considered by the Investigator to be an AE if it:

- Results in the withdrawal of study drug.
- Results in withholding of study drug pending some investigational outcome.
- Results in the initiation of an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia).
- Results in any out-of-range laboratory value that, in the Investigator's judgment, fulfills the definition of an AE with regard to the subject's medical profile.
- Increases in severity compared to baseline by ≥ 2 CTCAE grades (see Appendix 5), with the exception of lymphocytes, albumin, cholesterol, glucose, and phosphate. For these tests, a change of ≥ 2 grades will be evaluated by the Investigator to determine if they are of clinical significance and, if so, will be considered AEs.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the AE CRF.

It is the responsibility of the Investigator to review all laboratory findings in all subjects and determine if they constitute AEs. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

7.4.4.3 Other Safety Assessment Abnormalities

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is > 450 ms and there is an increase of > 60 ms from baseline. Any ECG abnormality that the Investigator considers as an AE should be reported as such.

7.4.4.4 Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v4.03 (Appendix 5). Investigators will collect all CTCAE grades for AEs (for both increasing and decreasing severity). All AEs reported using CTCAE classification and graded as 4 or 5 are to be considered serious. Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the study drug. In the event that an AE is not covered by the CTCAE, the assessment of severity will be determined by using the CTCAE general guidelines.

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 activities of daily living (ADL).

Grade 3 = Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4 = Life-threatening consequences: urgent intervention indicated.

Grade 5 = Death related to AE.

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”). See Section 7.4.4.8 for the definition of an SAE.

7.4.4.5 Assessing Relationship to Study Drug

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

Items to be considered when assessing the relationship of an AE to the study drug are:

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

- The presence of non-study drug-related factors which are known to be associated with the occurrence of the event.

7.4.4.6 Classification of Causality

Not Related: A causal relationship between the study drug and the AE is not a reasonable possibility.

Related: A causal relationship between the study drug and the AE is a reasonable possibility. The Investigator must further qualify the degree of certainty as "possible" or "probable."

7.4.4.7 Outcome Categorization

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

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

7.4.4.8 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, but when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent 1 of the outcomes in the definition of an SAE listed above should also be considered serious SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry
- An emergency room visit lasting longer than 24 hours but not resulting in hospitalization

Note: Disease progression is a study endpoint and should not be reported as an SAE term. However, AEs (eg, dyspnea) that meet seriousness criteria, although associated with disease progression, should be reported as SAE.

7.4.4.9 Adverse Events of Special Interest

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

7.4.4.9.1 T-LBL/T-ALL

Lymphoblastic lymphomas are considered thymus derived malignancies that have not yet completed T-cell maturations. Approximately 90% of lymphoblastic lymphomas are the T-cell phenotype and typically occur in young adults and adolescents, accounting for 29% of pediatric and 2% of adult NHL with a median age at diagnosis of 25 years (Lai, 2013; Cortelazzo, 2017; Lones, 2007). T-LBL is morphologically and immunophenotypically indistinct from T-ALL, with both diseases arising from precursor lymphoid cells of the T-cell lineage (Portell, 2012; Patel, 2014). Despite the similarities of the two diseases, significant yet unknown characteristics lead to differences in clinical presentations (Burkhardt, 2009). Initial clinical manifestation of both adult and pediatric T-LBL includes a mediastinal mass or lymphadenopathy with <25% bone marrow blasts. Adult T-LBL patients tend to have less thymic disease and greater lymph node disease and bone marrow involvement (Baleydier, 2008; Swerdlow, 2008; Campo, 2011). In contrast, T-ALL cases predominantly present with bone marrow and peripheral blood disease, and >25% bone marrow blasts (Swerdlow, 2008; Campo, 2011).

On 06 April 2018 an event of T-LBL was observed in a subject on study EZH-102. This event was reported to regulatory authorities as a 7-day SUSAR on 13 April 2018 (Case number 2018USEPZ64380299).

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

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

Based on this evaluation, we continue to believe that tazemetostat is a clinically active drug and has the potential to benefit both adult and pediatric patients across different tumor types where there are unmet medical needs. We also conclude that the risk assessment identifies a possible direct association between tazemetostat and T-LBL/T-ALL. Epizyme considers the risk for T-LBL/T-ALL in tazemetostat clinical trials to be largely concentrated in pediatric patients based on 1) higher $AUC_{0\text{-}24h}$ exposures in pediatric patients and 2) increases over time in age-related thymic involution, and 3) the known epidemiology / pathophysiology of T-LBL/T-ALL. The risk of T-LBL/T-ALL in adults is not known, however the incidence of treatment-related T-LBL/T-ALL in adults is expected to be uncommon. To date, over 958 subjects (adults and pediatric) have been treated with tazemetostat as monotherapy and in combination with other anti-neoplastic therapies with no other observed cased of T-LBL/T-ALL.

T-LBL Case

The event of T-LBL in a 9-year-old (at the time of enrollment) female subject diagnosed with poorly differentiated chordoma occurred on Study Day 432 of treatment with tazemetostat 900 mg/m^2 BID. At the time of the event of T-LBL, the subject was in complete response of her target lesions of the disease under study, yet due to presence of 1 of 2 non-target lesion in her lung (1 lesion disappeared), was considered overall as a partial responder. The first response was observed and measured at Day 54 on treatment. The steady-state $AUC_{0\text{-}24h}$ at Cycle 1 Day 15 in this subject was 18,784 ng•h/mL and is similar to the mean $AUC_{0\text{-}24h}$ at Cycle 1 Day 15 for the 900 mg/m^2 dose group overall (21,000 ng•h/mL, n=5). The study medication was discontinued and the subject withdrawn from the study due to the event.

Induction therapy was initiated on 06 April 2018 with the following regimen: cytrarabine, daunorubicin, dexamethasone, dexrazoxane. Methotrexate was subsequently started on 13 April 2018. The 9-year-old subject has since experienced a partial clinical response following standard induction chemotherapy, and is expected to have a good overall prognosis as is typical of T-LBL in children when treated appropriately.

The SUSAR of T-LBL resulted in the Sponsor initiating a temporary global halt in enrollment for the pediatric study EZH-102. In addition, this event led to a partial clinical hold (PCH) on new subject enrollment for tazemetostat by the U.S. (FDA), France (ANSM), and Germany (BfArM) across all studies of the Tazemetostat Development Program. For further details, see the Investigator's Brochure, version 8.0. In the event of suspicion of T-LBL/T-ALL or related concerns, please refer to Section 7.3.2.2 for evaluation and dose adjustments.

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

7.4.4.9.2 MDS/AML/MPN

As of the 12 April 2021, seven (7) cases of MDS/AMLhave been reported in tazemetostat clinical trials. A summary of these cases please refer to the Investigator's Brochure, Version 11.0. In the event of suspicion of these malignancies or related concerns, please refer to Section 6.5 for evaluation and dose adjustments. Heightened surveillance will be conducted to monitor and identify early signs and symptoms (per local practice/standard of care) of any MDS/AML and other myeloid malignancies like MPN. For any MDS/AML or other myeloid malignancies like MPN, tazemetostat will be held, and after discussion with the Investigator, tazemetostat will be discontinued.

7.4.4.10 OTHER IDENTIFIED RISKS

Further events of interest include pregnancy or exposure to study drug through breastfeeding;

Laboratory abnormalities are not to be reported as AESI, laboratory abnormalities should be reported as standard AEs or SAEs if the seriousness criteria are met. These events of interest are to be captured using the SAE procedures but are to be considered as SAEs only if they met 1 of

the above criteria. All AEs associated with events of interest are to be reported on the CRF whether or not they meet the criteria for SAEs.

7.4.4.10.1 Special Situations: Overdose, Misuse, Abuse and Medication Error

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

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

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

All instances of special situations are to be reported using the SAE form regardless of presence or absence of an associated AE. Refer to Section 7.4.6.3 for detailed instructions on how to handle the reporting of special situations.

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

7.4.5 Completion/Discontinuation of Subjects

The Investigator may permanently discontinue treating a subject with study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to permanently discontinue study drug or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. The Study Disposition Treatment CRF page will be completed indicating the primary reason for discontinuation from treatment and the study

drug discontinuation procedures indicated in the Schedule of Visits and Procedures will be completed (if possible).

If a subject discontinues study drug, the subject will have an Off-Treatment Visit with protocol-specified procedures and enter the Survival Follow-up Period unless the subject or parent/guardian withdraws consent or is lost to follow-up.

The Investigator should confirm whether a subject or parent/guardian will permanently discontinue study drug but agree to continue protocol-specified procedures at the Treatment Visit and Survival Follow-Up or whether the subject or parent/guardian will withdraw consent. If consent is withdrawn, the Investigator will promptly explain to the subject involved that the subject will be withdrawn from the study and provide appropriate medical treatment and other necessary measures for the subject. If a subject or parent/guardian withdraws consent, the date will be documented in the source documents.

A subject who has ceased to return for visits will be followed up by mail, phone, or other means as much as possible to gather information such as the reason for failure to return and the status of treatment compliance, presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the CRF.

Note: As of Protocol Amendment 13.0, no further survival follow-up is necessary for remaining subjects because the primary outcome assessment for all subjects has been met.

A subject removed from the study for any reason may not be replaced, except if a subject is discontinued before completing the Treatment Phase, an additional subject should be enrolled in the Phase 1 Dose Escalation part, FE cohort, and DDI cohort in this study.

7.4.6 Reporting of Serious Adverse Events and Other Events of Interest

All serious adverse events, irrespective of their relationship to study drug, must be reported as soon as possible, but no later than 24 hours from when the Investigator becomes aware of the event.

Deaths and life-threatening events should be reported immediately. The immediate report should be followed-up within 1 business day of report via CRF into the clinical database or with a completed SAE form in case of no access to clinical database.

It is very important that the SAE is processed as completely as possible at the time of the initial report. This includes the Investigator’s assessment of causality.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the follow-up SAE form.

The detailed contact information for reporting of SAEs is provided in the Investigator File.

Serious adverse events, regardless of causality assessment, must be collected over the same time period as stated above for AEs through the last visit and for 30 days after last dose following study drug discontinuation.

All SAEs must be followed to resolution, or if resolution is unlikely, to stabilization.

Any SAE judged by the Investigator to be related to the study drug should be reported to the Sponsor regardless of the length of time that has passed since study completion.

For urgent safety issues, please ensure that all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator File.

The Investigator should notify his/her IRB/IEC of the occurrence of the SAE, in writing, in accordance with local requirements. A copy of this communication must be forwarded to the Sponsor or CRO monitor and filed in the Trial Master File.

7.4.6.1 Reporting of Adverse Events of Special Interest

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

All potential and identified AESIs must be discussed with the Medical Monitor.

7.4.6.2 Reporting of Pregnancy

Any pregnancy where the estimated date of conception occurs either before the last visit or within 30 days of the last study drug or any exposure to study drug through breastfeeding during study drug or within 30 days of last study drug must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study drug.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events Section 7.4.6).

Pregnancies or exposure to study drug through breastfeeding must be reported as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the pregnancy.

The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File.

The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but not later than 1 business day from the date the Investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

7.4.6.3 Reporting of Special Situations

Report the special situation(s) of overdose, misuse, abuse, and/or medication error (described in Section 7.4.4.10.1) using one of the following sets of instructions according to whether the special situation occurred without any associated AEs, with an associated non-serious AE, or with an associated SAE:

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

- Report to Epizyme using a paper Special Situations Form following the procedures for reporting SAE (Section 7.4.6).

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

- Enter the non-serious event on the AE eCRF and mark the SAE field, “no”. SAE related narrative fields should not be completed.
- Report to Epizyme using a paper Special Situations Form following the procedures for reporting SAE (Section 7.4.6).

Special situation(s) with an associated SAE:

- Complete the AE eCRF per protocol for the associated SAE term ONLY (Special situations are not adverse event terms in and of themselves); complete eCRF SAE fields.
- Report to Epizyme using both a paper Special Situations Form and a paper Serious Adverse Event Form following the procedures for reporting SAE (Section 7.4.6).

Adverse events associated with overdose, misuse, abuse, or medication error should be reported using the procedures detailed in Reporting of Serious Adverse Events (Section 7.4.6) even if the AEs do not meet serious criteria.

7.4.6.4 Expedited Reporting

The Sponsor must inform investigators or, as regionally required, the head of the medical institution and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason,

it is imperative that investigational sites provide complete SAE information in the manner described above.

7.4.6.5 Regulatory Reporting of Adverse Events

Adverse events will be reported by the Sponsor or a third party acting on behalf of the Sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with the European Clinical Trial Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions (SUSARs) will be reported as required to the Competent Authorities of all involved European member states.

7.4.7 Confirmation of Medical Care by Another Physician

The Investigator will instruct the subject to inform beforehand when the subject is going to receive medical care by another physician. At each visit, the Investigator will ask the subject whether the subject has done so since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the Investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

7.5 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating practices, working practice documents, and applicable regulations and guidelines. Site visit audits will be made periodically by the Sponsor's or CRO's qualified compliance auditing team, which is an independent function from the study conduct team.

7.5.1 Data Management

Data required by the protocol will be collected on a CRF and entered into a validated Electronic Data Capture clinical database that is compliant with all regulatory requirements. Data collected on the CRF must follow the instructions described in the CRF Completion Guidelines.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRF. The Investigator or designee as identified on Form FDA 1572 must sign the CRF to attest to its accuracy, authenticity, and completeness.

The completed, original CRF is the sole property of Epizyme and should not be made available in any form to third parties without written permission from Epizyme, except for authorized representatives of Epizyme or appropriate regulatory authorities.

The Data Management Plan defines and documents the procedures necessary to ensure data quality. These activities must be followed to ensure data are properly entered, validated, coded, integrated, reconciled, and reviewed.

7.5.2 Database Quality Assurance

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the investigational site. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

7.5.3 Bioanalytical Data Management and Quality Control

Samples will be shipped according to the Laboratory Manual. Tazemetostat will be quantified using a validated liquid chromatography/mass spectrometry/mass spectrometry method. Before the analysis of study samples, the assay sensitivity, specificity, linearity, and reproducibility will be documented. Details on the analytical methodology, the method of validation, and the analytical within-study quality control procedures will be included in the clinical study report for this protocol.

7.6 Statistical Methods

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released, a snapshot of the database is obtained and released, and randomization codes have been released for the Phase 1 FE cohort. Phase 1 (Dose Escalation and Cohort Expansion), FE, and DDI cohorts may be analyzed separately upon completion (ie, at an earlier time point) from the Phase 2 analysis. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

7.6.1 Statistical and Analytical Plans

The statistical analyses described in this section will be performed as further outlined in the SAP, which will be finalized before database lock and included in the clinical study report for this protocol.

Subjects are analyzed according to their initial dose level, with the exception of subjects in the FE cohort:

- Subjects in the FE cohort who took only 200 mg doses and withdrew before Cycle 1 Day 1 will be included in the 200 mg BID dosing level for analysis.

- Subjects in the FE cohort who completed both single 200 mg doses and started the 400 mg BID dosing level on Cycle 1 Day 1 will be included in the 400 mg BID dosing level for analysis.

7.6.1.1 Definitions of Analysis Sets

The per protocol analysis sets will be defined as follows:

- **Full Analysis Set** will include all subjects who received at least 1 dose of study drug. This will be the primary analysis set for efficacy evaluations, as well as for demographic and baseline characteristics.
- **Safety Analysis Set** will include all subjects who received at least 1 dose of the study drug and have at least 1 post-baseline safety evaluation. This will be the analysis set for all safety evaluations, except for the DLT analysis.
- **Dose-Limiting Toxicity (DLT) Analysis Set** will include all subjects in the Safety Analysis Set who:
    - Experience a DLT during Cycle 1 as defined in Section 7.3.2
      or
    - Are not removed from Cycle 1 for reasons other than toxicity.
- **Pharmacokinetic (PK) Analysis Set** will include all subjects who have received at least 1 dose of tazemetostat and have at least 1 evaluable plasma concentration.
- **Food Effect Analysis Set** will include all subjects for whom a full PK profile of tazemetostat is available after study drug administration in both the fed and fasted state and who consumed the prescribed breakfast before treatment in the “fed” state.
- **Drug-Drug Interaction Analysis Set** will include all subjects for whom a full PK profile of midazolam is available after midazolam administration.
- **Pharmacodynamic (PD) Analysis Set** will include all subjects who have received at least 1 dose of study drug and have evaluable PD data.
- **Pharmacogenomic (PGx) Analysis Set** will include all subjects who have received at least 1 dose of study drug and have evaluable PGx data.
- **Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis Set** will consist of all subjects in the Safety Analysis Set that also have evaluable serum PK and PD pretreatment assessment and at least 1 post treatment assessment.

The SAP will outline which analysis sets are to be used for the Phase 1 part, FE cohort, and DDI cohort and Phase 2 analyses.

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be summarized and listed. For continuous demographic/baseline variables including age, weight, and vital signs, results will be summarized and presented as N, mean, standard deviation, median, and minimum and maximum values. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

PRIOR AND CONCOMITANT MEDICATIONS

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class.

7.6.1.2 Efficacy Analyses

The efficacy endpoints in Phase 1 will be summarized and listed for each subject by the study part and initial dose level based upon the Full Analysis Set. No formal statistical comparison will be performed.

PHASE 2 PRIMARY EFFICACY ANALYSES

In Phase 2, the evaluation of the ORR (CR + PR) in subjects with B cell lymphomas will be based on IWG-NHL (Cheson, 2007) response criteria.

ORR will be presented with corresponding 2-sided Clopper–Pearson exact 95% confidence intervals (CIs). For each cohort, this analysis will be performed on the Full Analysis Set.

PHASE 2 SECONDARY EFFICACY ANALYSES

PFS is defined as the time from the date of first dose to the date of first documentation of relapse, disease progression, or date of death, whichever occurs first. PFS will be estimated using Kaplan-Meier method. If there are a sufficient number of PFS events (ie, relapses, progressions or deaths), median PFS, first and third quartiles and 2-sided 95% CIs, will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982) for each cohort. Figures and listings of PFS will also be provided.

For each subject with a CR or PR, DOR is defined as time from the first date of response (CR or PR, whichever is first recorded) to recurrence, objectively documented disease progression, or death, whichever occurs first. If there are a sufficient number of responders who subsequently progress or die due to any cause, the median DOR, first and third quartiles, will be calculated from the Kaplan-Meier estimates for each cohort. The associated 2-sided 95% CIs will be estimated using the Brookmeyer-Crowley method for each cohort. A listing of DOR will be provided.

ALL PHASES EXPLORATORY EFFICACY ANALYSES

Overall survival is the duration measured from the date of first dose until the date of death from any cause. The Kaplan-Meier estimate of the median survival time, first and third quartiles will be presented with 2-sided 95% CIs for each cohort.

7.6.1.3 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Analyses

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Pharmacokinetic

Phase 1

Plasma and urine concentrations of tazemetostat will be tabulated and summarized by dose level, day, and time. Tazemetostat PK parameters will be derived from plasma concentrations by noncompartmental analysis using actual times.

Minimally, the following PK parameters will be calculated:

- Maximum drug concentration (C_{max})
- Time to reach maximum concentration (following drug administration) (t_{max})
- Area under the concentration time curve (AUC)

If data permit:

- Elimination half-life ($t_{1/2}$)
- Total body clearance (CL)
- Volume of distribution (Vd)
- Renal clearance (CLr)
- Accumulation ratio (R)
- Fraction excreted (fe)

PK parameters (eg, C_{max}, AUC) for tablet and suspension formulations will be compared within a dose cohort that comprises subjects receiving both tazemetostat formulations to assess the relative performance of each formulation.

Pharmacokinetic parameters for midazolam and its metabolites, 1-OH-midazolam and 4-OH midazolam, and 4β-hydroxycholesterol will be derived from plasma concentrations by noncompartmental analysis using actual times. Minimally, the following PK parameters will be calculated: C_{max}, t_{max}, and AUC. The effect of tazemetostat on AUC and C_{max} of midazolam and

its metabolites will be evaluated using a mixed linear model of logarithmically transformed values of the primary PK parameters. Ratios of geometric means and associated 2-sided 90% CIs will be presented. Similar analyses will be conducted for the effect of food on the AUC and C_{max} of tazemetostat (fed/fasted comparison).

Phase 1 and Phase 2

Combined PK data from Phase 1 and Phase 2 will be subjected to population PK analysis. The PK model will be parameterized for clearance and volume(s) and exposure parameters such as C_{max} and AUC will be derived.

Pharmacodynamic

H3K27 trimethylation levels as measured in skin punch biopsies (Phase 1 Dose Escalation only) and tumor, bone marrow, and PBMCs using appropriate methodologies may be explored and summarized by dose for each time point. The effect of tazemetostat therapy on cytogenetic changes, changes in histone methylation or other soluble, tissue, genetic, and imaging biomarkers may be explored and summarized using descriptive statistics.

The percentage change in the sum of the diameters of tumor target lesions based on investigator assessment may be summarized and correlated with tazemetostat exposure and PD markers.

Pharmacokinetic/Pharmacodynamic Analyses:

PK/PD relationships between exposure to tazemetostat and histone methylation status; exposure and exploratory biomarkers of safety; and exposure and best overall response will be explored graphically. Any emergent relationship might be followed by model based PK/PD analysis.

Biomarker and Pharmacogenomics Analyses:

Details of the biomarker and pharmacogenomics data analysis plan will be defined and reported separately.

BIOANALYTICAL METHODS

Plasma and urine concentrations of tazemetostat will be determined using a validated assay. If appropriate, assay of plasma and urine samples for any metabolites of tazemetostat may be explored in the future.

Plasma concentrations of midazolam and its metabolites, 1-OH-midazolam and 4-OH-midazolam, and 4β-hydroxycholesterol will be determined using a validated assay.

7.6.1.4 Safety Analyses

All safety analyses, unless otherwise specified, will be performed on the Safety Analysis Set. ECG findings and the incidence of AEs and SAEs will be summarized. Laboratory test results, vital signs, bromide levels (bromide monitoring will not be prospectively conducted in the FE

and DDI cohorts in Phase 1 or Phase 2), and echocardiograms/MUGA scans (LVEFs), and their changes from baseline, will be summarized using descriptive statistics. Abnormal values will be flagged.

The effects of tazemetostat on cardiovascular repolarization will be evaluated via 12-hour, 12-lead continuous Holter/ECG monitoring on Day -1, and on Cycle 1 Day 1 (ie, amounting to a total of 24 hours continuous cardiac Holter monitoring around first dose administration on Cycle 1 Day 1) and Day 15 in the Dose Escalation part of the study only. Individual ECGs will be extracted in triplicate from the Holter recordings at specified time points and will be evaluated by a central laboratory. QT intervals will be measured from Lead II and will be corrected for HR (QTc) using Fridericia's (QTcF) correction factors. The primary QTc parameter will be QTcF. Secondary parameters (QT interval corrected for heart rate using Bazett's formula [QTcB], QT, QRS, and HR) and waveforms (T waves) will be evaluated.

Extent Of Exposure

The number of cycles/days on treatment, quantity of study drug administered, and the number of subjects requiring dose reductions, treatment interruption, and treatment discontinuation due to AEs will be summarized.

Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 15.1 or higher) lower level term closest to the verbatim term. The linked preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that

- Emerges during treatment, having been absent at Pretreatment (Baseline)
- Reemerges during treatment, having been present at Pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment-emergent and had a start date within the earlier of 30 days following study drug discontinuation or initiation of subsequent anticancer therapy (Section 7.4.4.1) will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Treatment-emergent AEs will be summarized by treatment group. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will

be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity by highest CTCAE grade.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (possibly related, probably related, and not related).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

The number (percentage) of subjects in the DLT Analysis Set with TEAEs designated as DLTs in the CRF will be summarized by MedDRA SOC and PT for each treatment group in the Dose Escalation and Expansion parts.

LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 7.4.1.7 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 7.4.1.7 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Vital Signs

Descriptive statistics for vital signs parameters (ie, diastolic and systolic BP, HR, RR, and body temperature) body weight, and changes from baseline will be presented by visit and treatment group.

Electrocardiogram Results

Electrocardiogram assessments will be performed as specified in the Schedule of Assessments (Table 8 and Table 9). Time-matched, central-read ECGs will be performed to evaluate RR, PR, QRS, QT intervals, and QTc at various time points throughout the study. All 12-lead ECG and Holter-ECG data will be listed, and changes will be summarized by dose group, for each cohort using descriptive statistics. The number and percentage of subjects with abnormal ECG findings at each visit will be reported for each dosing cohort. Descriptive statistics will be used to present the abnormal ECG findings overall. Results will be tabulated and listed in the study report.

Muga Scans And Echocardiograms

MUGA scans and echocardiogram results will be evaluated on an individual basis by subject. Abnormal readings will be identified as those outside (above or below) the reference range. MUGA scans and echocardiogram findings will be summarized.

Other Special Tests

Serum Bromide Levels

Clinical laboratory values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the clinical study report for this protocol. Serum bromide monitoring will not be prospectively conducted in the FE and DDI cohorts in Phase 1 or Phase 2.

Electrocardiogram Holter Monitoring

The effects of tazemetostat on cardiovascular repolarization will be evaluated via 12-hour, 12-lead continuous Holter ECG monitoring in Cycle 1, Day 1 and Day 15 of the Dose Escalation part of the study. Individual ECGs will be extracted in triplicate from the Holter recordings at specified time points and will be evaluated by a central laboratory. QT intervals will be measured from Lead II and will be corrected for heart rate (QTc) using Fridericia's (QTcF) correction factors. The primary QTc parameter will be QTcF. Secondary parameters (QTcB, QT, QRS, and HR) and waveforms (T-waves) will be evaluated.

SKIN PUNCH BIOPSY

Skin punch biopsy results will be evaluated on an individual basis by subject. Abnormal readings will be identified as those outside (above or below) the reference range. Skin punch biopsy findings will be summarized.

PAIRED TUMOR BIOPSIES

Paired tumor biopsy explorative analysis will be evaluated on an individual basis by subject. Paired tumor biopsy results will be summarized.

BONE MARROW BIOPSY

Bone marrow biopsy results will be evaluated on an individual basis by subject. Abnormal readings will be identified as those outside (above or below) the reference range. Bone marrow biopsy findings will be summarized.

BONE MARROW BIOPSY (WITH IMMUNOHISTOCHEMISTRY)

Bone marrow biopsy (with IHC) results will be evaluated on an individual basis by subject. Abnormal readings will be identified as those outside (above or below) the reference range. Bone marrow biopsy (with IHC) findings will be summarized.

7.6.2 Determination of Sample Size

For Phase 1, the sample size of 6 to 45 subjects is considered adequate for the purposes of selecting a dose. Per FDA guidance, 12 subjects are considered adequate to evaluate food effect. The sample size for the DDI cohort was not based on statistical considerations. A total of 64 subjects were enrolled in Phase 1.

For Phase 2, the original study design planned enrollment of up to 30 subjects enrolled in each cohort. The initial assessment of efficacy was to be conducted within each cohort when 10 subjects had been enrolled (stage 1). For each DLBCL cohort, if zero responders (with CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 30% and there is a 2.8% probability of observing no responders among 10 subjects. For each FL cohort, if 1 or zero responders (CR or PR) out of the initial 10 subjects was observed, further enrollment in the cohort was to be terminated for futility. This rule was based on the underlying assumption that the response rate is 40% and there is a 4.6% probability of observing ≤ 1 responder among 10 subjects. Subsequent to the futility analysis in the DLBCL cohorts, the DMC supported a study design change to a modified 2-stage Green-Dahlberg design for each cohort. The resulting expanded sample size is shown in Table 10.

Up to 70 subjects with DLBCL (GCB or non-GCB, EZH2 wild-type) will be enrolled in an additional combination therapy cohort (tazemetostat and prednisolone). A 2-stage Green

Dahlberg design will be used to terminate enrollment for futility (Table 10). Prior to full enrollment of stage 1, initial tolerability of 800 mg BID tazemetostat in combination with prednisolone will be assessed in the first 6 subjects enrolled based on the same set of DLT criteria used in Phase 1 (see Section 7.3.2). If a DLT is observed in no more than 1 of the 6 subjects, enrollment will continue to stage 1. If a DLT is observed in more than 1 of the 6 subjects, lower dose level(s) of prednisolone may be evaluated. Subjects treated at the dose found to be tolerable during the initial safety run-in assessment will be included as part of the 35 subjects enrolled for stage 1.

Table 10 2-Stage Green Dahlberg Design

	Monotherapy					Combination Therapy
	DLBCL GCB EZH2 Mutant	**DLBCL GCB EZH2 Wild-Type**	**DLBCL non-GCB**	**FL EZH2 Mutant**	**FL EZH2 Wild-Type**	**DLBCL EZH2 Wild-Type**
Ho: CR + PR	≤15%	≤15%	≤15%	≤20%	≤20%	≤20%
Ha: CR + PR	≥30%	≥30%	≥30%	≥40%	≥40%	≥35%
Stage 1 futility n	10	10	10	10	10	35[b]
Stage 1 rejection of treatment	0[a]	0[a]	0[a]	1[a]	1[a]	6[c]
Stage 2 total n	60	60	60	45	45	70
Stage 2 rejection of treatment	14	14	14	13	13	19

CR = complete response, DLBCL = diffuse large B cell lymphoma, EZH2 = enhancer of zeste homolog 2, FL = follicular lymphoma, GCB = germinal-center B-cell-like, Ha = Alternative Hypothesis, Ho = Null Hypothesis, n = sample size, PR = partial response
Note: Approximate alpha=0.025 and power =0.80

a. Stage 1 futility analysis has been conducted. Enrollment will continue to 60 subjects in each of the DLBCL arms and 45 subjects in each of the FL arms.
b. Includes subjects treated at the dose found to be tolerable during the initial safety run-in assessment.
c. The interim analysis planned at the end of stage 1 may occur sooner if the stage 1 rejection criterion is surpassed before all 35 subjects are treated and have completed at least the Week 24 assessment. In this scenario, the total sample size (stage 1 + stage 2) would still remain unchanged at 70 subjects.

To avoid disruptions in the study, enrollment and treatment of subjects will not be halted in order to conduct the futility analysis. If every cohort completes enrollment of stage 2, a total of 340 subjects will be enrolled in Phase 2.

For the purpose of calculating an expanded cohort size, a modified 2-stage Green-Dahlberg design was used where the stage 1 futility sample size was set to the original protocol design sample size of 10 subjects per cohort (for Cohorts 1-5) and the stage 1 rejection criteria were set to the original protocol defined rejection criteria (0 for the DLBCL cohorts and 1 for the FL cohorts).

For the DLBCL Monotherapy Cohorts (futility analysis completed):

- The probability of early stopping under the null hypothesis is 0.197.
- The probability of stopping under the alternative hypothesis is 0.028.

For the FL Monotherapy Cohorts (futility analysis completed):

- The probability of early stopping under the null hypothesis is 0.376.
- The probability of stopping under the alternative hypothesis is 0.046.

A 2-stage Green-Dahlberg design will be used to assess futility in the DLBCL combination therapy cohort. The stage 1 rejection criterion will be 6 or fewer responders (CR + PR).

- The probability of early stopping under the null hypothesis is 0.433.
- The probability of stopping under the alternative hypothesis is 0.017.

7.6.3 Interim Analyses

Phase 1 Dose Escalation data will be summarized and reported. All available safety and PK data will be evaluated before Phase 2 initiation.

At the end of the FE and DDI cohorts, the data may be analyzed. The results of these analyses will inform Phase 2 dosing.

There will be an interim analysis for futility in each cohort in Phase 2. While evaluating the response for the stage 1 subjects in each cohort, the enrollment and treatment of subsequent subjects will be continued. Timing, sample size, and rejection criteria for the stage 1 futility interim of each cohort are described in Section 7.6.2.

If enrollment in any cohort is terminated for futility, the final reporting for that cohort will be based on all subject data in the database.

In the combination therapy cohort, tolerability of study therapy will be evaluated in the initial 6 subjects based on the same set of DLT criteria used in Phase 1 (see Section 7.3.2).

7.6.4 Other Statistical/Analytical Issues

Not applicable.

7.6.5 Procedure for Revising the Statistical Analysis Plan

If the planned analysis needs to be revised after the study starts, the Sponsor will determine how the revision impacts the study and determine how the revision should be implemented. The details of the revision will be documented and described in the SAP and the clinical study report.

8 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

8.1 Changes to the Protocol

The protocol, ICF, and appropriate related documents must be reviewed and approved by an IRB or IEC constituted and functioning in accordance with ICH E6, Section 3, and any local regulations, ie, Code of Federal Regulations, Title 21 CFR Part 56. Any protocol amendment and/or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associates [CRAs] or change of telephone number[s]). Documentation of IRB/IEC compliance with ICH and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval from the IRB/IEC Chairman must be sent to the PI (if regionally required, the heads of the medical institutions) with a copy to the Sponsor before study start and the release of any study drug to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the Investigator (if regionally required, the heads of the medical institutions) will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to the IRB/IEC annually (or as required) by the Investigator or sponsor, depending on local regulatory obligations. If the Investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The Investigator(s) or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (if regionally required, the heads of the medical institutions) of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

8.2 Ethical Conduct of the Study

This study will be conducted in accordance with the standard operating practices of the Sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- In accordance to the principle of World Medical Association Declaration of Helsinki, 2008
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use

- US 21CFR, including parts 50 and 56 concerning Informed Patient Consent and IRB regulations, and applicable sections of US 21CFR Part 312
- European Clinical Trial Directive 2005/28/EC, for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states
- In accordance with Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- And other applicable regulatory authorities

8.2.1 Subject Information and Consent

As part of administering the ICF, the Investigator must explain to each subject (or guardian/legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an informed consent at the Screening Visit before any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC and sponsor-approved written informed consent must be prepared in accordance with ICH E 6, Section 4, and all applicable local regulations (eg, Code of Federal Regulations, Title 21, CFR Part 50) and provided to the Sponsor. Each subject must sign an approved informed consent before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the Sponsor and kept on file, according to local procedure, at the study center.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

8.3 Administrative Procedures

8.3.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRB/IEC of all investigational sites and, in some countries, by the regulatory authority. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Sponsor's appropriate study team member must be notified promptly and the IRB/IEC for the site must be informed immediately. Per 21 CFR 312.30, a protocol change intended to eliminate an immediate hazard may be implemented immediately, provided FDA is subsequently notified by protocol amendment.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC (if regionally required, the heads of the medical institutions) must be kept informed of such changes. In these cases, the Sponsor will send a letter to the IRB/IEC (if regionally required, the heads of the medical institutions) detailing such changes.

8.3.2 Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

8.3.3 Monitoring Procedures

The Sponsor's or CRO's CRA will maintain contact with the Investigator and designated staff by telephone, and/or letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the assigned CRA as described in the monitoring plan. The Investigator (if regionally required, the heads of the medical institutions) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCPs and

local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to the study protocol and data accuracy in accordance with federal regulations (or local regulations). All records at the investigational site are subject to inspection by the FDA or local regulatory agency.

In accordance with ICH E6, Section 6.10, source documents include but are not limited to the following:

- Clinic, office, hospital charts
- Copies or transcribed healthcare provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IVRS/IWRS, x-rays, and other imaging reports: eg, sonograms, CT scans, MRIs, nuclear medicine scans, ECGs, rhythm strips, electroencephalograms, polysomnographs, and pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives)
- Pain, quality of life, medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs: eg, urine pregnancy test result documentation
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRB/IEC
- CRF components: eg, questionnaires that are completed directly by subjects and serve as their own source

8.3.4 Recording of Data

A CRF is required for each subject and must be completed by qualified and authorized personnel. Only data required by the protocol for the purposes of the study should be reported on the CRF. All data on the CRF must reflect the corresponding source document. Any corrections to entries made on the CRF must be documented in a valid audit trail.

8.3.5 Identification of Source Data

The following items in the CRF will be handled as source data:

- Study drug compliance (eg, the reason for dose increase/reduction)
- Discontinuation information
- Sampling date and time for the drug concentration
- Sampling date and time for the clinical laboratory test
- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)

8.3.6 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 documents, including but not limited to the protocol, copies of CRFs, the IB, regulatory agency registration documents (eg, FDA 1572 form), ICFs, and IRB/IEC correspondence. To enable evaluations and/or audits from regulatory authorities or Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, eCRFs, SAE forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records must be retained by the Investigator according to ICH GCP, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. It is requested that at the completion of the required retention period or, should the Investigator retire or relocate, the Investigator (or if regionally required, the heads of the medical institutions) prospectively contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

8.3.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the Sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the Sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator must inform the Sponsor immediately that this request has been made.

8.3.8 Handling of Study Drug

All study drug will be supplied to the PI (or a designated pharmacist) by the Sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug label. The Investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. Once study drug has been received by the investigational site, the assigned CRA will review these documents along with all other study conduct documents at appropriate intervals during investigational site visits.

All drug supplies are to be used only for this protocol and not for any other purpose. The Investigator (or a designated pharmacist) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the Sponsor. At the conclusion of the study and as appropriate during the course of the study, the Investigator (or a designated pharmacist) will either return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the Sponsor's designated contractor or, where approval is given by the Sponsor, will destroy supplies and containers at the investigational site.

8.3.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor in advance of submission. The review is aimed at protecting the Sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results or other information, generated or created in relation to the study shall be set out in the agreement between each investigator (or if regionally required, the heads of the medical institutions) and the CRO or the Sponsor, as appropriate.

8.3.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the Investigator, the Investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will be utilized in any written work, including publications, without the written consent of the Sponsor. These obligations of confidentiality and non-use shall in no way diminish such

obligations as set forth in the Confidentiality Agreement between the Sponsor and the Investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the Investigator and the Sponsor (provided by the Sponsor).

8.3.11 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or for any other reason at any time. If the study is prematurely terminated or suspended, the Sponsor will promptly inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform the Sponsor and the IRB/IEC, and should provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

8.3.12 Subject Insurance and Indemnity

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study.

9 REFERENCE LIST

Arvey A, van der Veeken J, Samstein RM, Feng Y, Stamatoyannopoulos JA, Rudensky AY. Inflammation-induced repression of chromatin bound by the transcription factor Foxp3 in regulatory T cells. Nat Immunol. 2014 Jun;15(6):580-7.

Baleydier F, Decouvelaere AV, Bergeron J, et al. T cell receptor genotyping and HOXA/TLX1 expression define three T lymphoblastic lymphoma subsets which might affect clinical outcome. *Clin Cancer Res*. 2008;14(3):692-700.
Beccaria K, Sainte-Rose C, Zerah M, Puget S. Paediatric Chordomas. *Orphanet J Rare Dis*. 2015;10:116.

Béguelin W, Popovic R, Teater M, Jiang Y, Bunting KL, Rosen M, et al. EZH2 is required for germinal center formation and somatic EZH2 mutations promote lymphoid transformation. Cancer Cell. 2013 May 13;23(5):677-92.

Bodor C, Grossmann V, Popov N, et al. EZH2 mutations are frequent and represent an early event in follicular lymphoma. Blood. 2013;122(18):3165-3168.

Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics. 1982;38(1):29-41.

Burkhardt B, Reiter A, Landmann E, et al. Poor outcome for children and adolescents with progressive disease or relapse of lymphoblastic lymphoma: a report from the berlin-frankfurt-muenster group. *J Clin Oncol*. 2009;27(20):3363-3369.

Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011;117(19):5019-5032.

Cortelazzo S, Ferreri A, Hoelzer D, Ponzoni M. Lymphoblastic lymphoma. Crit Rev Oncol Hematol. 2017;113:304-317.

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [published 28 May 2009 (v4.03: June 14, 2010)]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_ 8.5x11.pdf.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb 10;25(5):579-86.

Cunningham D, Hawkes EA, Jack A, Qian W, Smith P, Mouncey P, Pocock C, Ardeshna KM, Radford JA, McMillan A, Davies J, Turner D, Kruger A, Johnson P, Gambell J, Linch D. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with

newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet. 2013 May 25;381(9880):1817-26.

Delarue R, Tilly H, Mounier N, Petrella T, Salles G, Thieblemont C, Bologna S, Ghesquières H, Hacini M, Fruchart C, Ysebaert L, Fermé C, Casasnovas O, Van Hoof A, Thyss A, Delmer A, Fitoussi O, Molina TJ, Haioun C, Bosly A. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. Lancet Oncol. 2013 May;14(6):525-33.

Dreyling M, Geisler C, Hermine O, Kluin-Nelemans HC, Le Gouill S, Rule S, et al. ESMO Guidelines Working Group. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014 Sep;25 Suppl 3:iii83-92.

DuPage M, Chopra G, Quiros J, Rosenthal WL, Morar MM, Holohan D, et al. The chromatin-modifying enzyme Ezh2 is critical for the maintenance of regulatory T cell identity after activation. Immunity. 2015 Feb 17;42(2):227-38.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

El Dareer SM, Struck RF, White VM, Mellett B, Hill DL. Distribution and metabolism of prednisone in mice, dogs, and monkeys. Cancer Treat Rep. 1977 61:1279-1289.

European Agency for the Evaluation of Medicinal Products. Committee for Veterinary Medicinal Products. Bromide, sodium salt. Summary Report. March 1997. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500011113.pdf. Accessed October 9, 2012.

Foon KA, Takeshita K, Zinzani PL. Novel therapies for aggressive B-cell lymphoma. Adv Hematol. 2012; (article 302570).

Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004;103(1):275-82.

Knutson SK, Kawano S, Minoshima Y, Warholic NM, Huang KC, Xiao Y, et al. Selective inhibition of EZH2 by EPZ-6438 leads to potent antitumor activity in EZH2-mutant non-Hodgkin lymphoma. Mol Cancer Ther. 2014 Apr;13(4):842-54.

Knutson SK, Warholic NM, Johnston LD, Klaus CR, Wigle TJ, Iwanowicz D, Littlefield BA, Porter-Scott M, Smith JJ, Moyer MP, Copeland RA, Pollock RM, Kuntz KW, Raimondi A,

Keilhack H. Synergistic Anti-Tumor Activity of EZH2 Inhibitors and Glucocorticoid Receptor Agonists in Models of Germinal Center Non-Hodgkin Lymphomas. PLoS One. 2014 Dec 10;9(12):e111840.

Luippold G, Schneider S, Marto M, Benöhr P, Mühlbauer B. Pharmacokinetics of two oral prednisolone tablet formulations in healthy volunteers. Arzneimittelforschung. 2001 Nov 51(11):911-5.

Lai C, Dunleavy K. NK/T-cell lymphomas in children. *Best Pract Res Clin Haematol*. 2013;26(1):33-41.

Lones MA, Heerema NA, Le Beau MM, et al. Chromosome abnormalities in advanced stage lymphoblastic lymphoma of children and adolescents: a report from CCG-E08. Cancer Genet Cytogenet. 2007;172(1):1-11.

Midazolam [summary of product characteristics]. Available from: http://www.medicines.org.uk/emc/medicine/15432/SPC/mimpara/. Updated February 22, 2012. Accessed August 30, 2012.

Milne TA, Dou Y, Martin ME, Brock HW, Roeder RG, Hess JL. MLL associates specifically with a subset of transcriptionally active target genes. Proc Natl Acad Sci U S A. 2005 Oct 11;102(41):14765-70.

Morin RD, Mendez-Lago M, Mungall AJ, Goya R, Mungall KL, Corbett RD, et al. Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. Nature. 2011;476(7360):298-03.

National Cancer Institute. Surveillance, Epidemiology and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1972-2011), Non-Hodgkins Lymphoma; 2014. Accessed 19 Aug 2014.

Patel B, Kang Y, Cui K, et al. Aberrant TAL1 activation is mediated by an interchromosomal interaction in human T-cell acute lymphoblastic leukemia. Leukemia. 2014;28(2):349-361.

Portell CA, Sweetenham JW. Adult lymphoblastic lymphoma. Cancer J. 2012;18(5):432-438

Ribrag V, Soria J, Reyderman L, et al. Phase 1 Study of E7438 (EPZ-6438), an Enhancer of Zeste-Homolog 2 (EZH2) Inhibitor: Dose Determination and Preliminary Activity in Non-Hodgkin Lymphoma. Hematological Oncology, Volume 33, Issue Supplement S1, page 179, June 2015.

Rosenwald A, Wright G, Leroy K, Yu X, Gaulard P, Gascoyne RD, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med. 2003;198(6):851-62.

Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood 2010;116(19):3724-34.

Scott DW, Gascoyne RD. The tumour microenvironment in B cell lymphomas. Nat Rev Cancer. 2014 Aug;14(8):517-34.

Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008. 2. Harris NL

Tilley H, Vitolo U, Walewski J, da Silva MG, Shpilberg O, Andre M, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(suppl 7):vii78-82.

Tumes DJ, Onodera A, Suzuki A, Shinoda K, Endo Y, Iwamura C, et al. The polycomb protein Ezh2 regulates differentiation and plasticity of CD4(+) T helper type 1 and type 2 cells. Immunity. 2013 Nov 14;39(5):819-32.

Voigt P, Tee WW, Reinberg D. A double take on bivalent promoters. Genes Dev. 2013 Jun 15;27(12):1318-38.

Wrangle J, Wang W, Koch A, Easwaran H, Mohammad HP, Vendetti F, et al. Alterations of immune response of non-small cell lung cancer with azacytidine. Oncotarget. 2013 Nov;4(11):2067-79.

Yang XP, Jiang K, Hirahara K, Vahedi G, Afzali B, Sciume G, et al. EZH2 is crucial for both differentiation of regulatory T cells and T effector cell expansion. Sci Rep. 2015 Jun 19;5:10643.

APPENDIX 1 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

ECOG = Eastern Cooperative Oncology Group.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

APPENDIX 2 COCKCROFT AND GAULT FORMULA

$$\text{Male} \quad \frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min}$$

$$\text{Female} \quad \frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min} \times 0.85$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

For serum creatinine measured in µmol/L:

$$\text{Male} \quad \frac{(140\text{-age}) \times \text{weight (kg)} \times 1.23}{\text{Creatinine (µmol/L)}}$$

$$\text{Female} \quad \frac{(140\text{-age}) \times \text{weight (kg)} \times 1.23 \times 0.85}{\text{Creatinine (µmol/L)}}$$

APPENDIX 3 NEW YORK HEART ASSOCIATION CARDIAC DISEASE CLASSIFICATION

The New York Heart Association (NYHA) Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for cardiac subjects. Based on NYHA definitions, subjects are to be classified as follows:

Class	**NYHA Status**
Class I:	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II:	Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III:	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV:	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

NYHA = New York Heart Association.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. NY: Little Brown;1994. p. 253-6.

APPENDIX 4 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

Tumor response assessments in this clinical trial will utilize Response Evaluation Criteria in Solid Tumors (RECIST 1.1) based on the following 2009 article: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

The modifications to RECIST 1.1 to be implemented in this trial are: 1) chest x-rays may not be used to follow disease; only CT scans may be used to follow chest disease, and 2) the minimum duration of stable disease (or non-CR/non-PD for subjects with nontarget lesions only) is 7 weeks following the date of first dose of study drug.

The Eisenhauer article, published in the *European Journal of Cancer*, is available online at: http://linkinghub.elsevier.com/retrieve/pii/S0959804908008733.

APPENDIX 5 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 4.03 published 28 May 2009) provides descriptive terminology to be used for adverse event (AE) reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE 4.03 have been correlated with single-concept Medical Dictionary for Regulatory Activities (MedDRA) terms.

For details regarding CTCAE v4.03, refer to Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [published 28 May 2009; v4.03: 14 June 2010], available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications /docs/ctcaev4.pdf.

For details regarding MedDRA, refer to the MedDRA website at: http://www.meddramsso.com.

APPENDIX 6 STANDARD HIGH-FAT BREAKFAST

Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate and fat, and has comparable meal volume and viscosity.

Item	Amount	Calories	Protein (g)	Fat (g)	Carbohydrate (g)
Eggs (fried)	2	191	14	15	-
Bacon (strip)	2	96	3.6	8.8	0.4
Toast (slice)	2	136	4	-	30
Butter (pat)	2	90	-	10	-
Hash browned potatoes	4 oz (100 g)	156	2	10	15
Whole milk	8 oz (200 mL)	170	8	10	12
Total		841	31.6	53.8	57.4

As recommended by FDA Guidance: Guidance for industry. Food-effect in bioavailability and fed bioequivalence studies, p. 1-9. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Rockville, MD, USA, 2002.

APPENDIX 7 PHARMACOGENOMICS/PHARMACODYNAMICS

Subjects enrolled in this clinical study will have samples collected for pharmacogenomic and biomarker analysis. The aim of the analysis is to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

Collection of the samples for pharmacogenomic analysis will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for pharmacogenomic and biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws. If regionally required, subjects' consent form for collection of samples in which DNA will be analyzed will be prepared separately from the informed consent form for study participation. In these regions, subjects who do not consent to DNA sample collection can be enrolled without collection of these samples.

SAMPLE COLLECTION AND HANDLING

The samples will be collected according to the study flow chart and laboratory manual.

SECURITY OF THE SAMPLES, USE OF THE SAMPLES, RETENTION OF THE SAMPLES

Sample processing, including DNA extraction and genotyping, sequencing or other analysis will be performed by a laboratory under the direction of the Sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol by the Sponsor. Laboratories contracted to perform the analysis on behalf of the Sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The Sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a Health Authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not

possible to prospectively define every avenue of future testing, all samples collected will be single- or double-coded (according to the ICH15 guidelines) in order to maintain subject privacy.

RIGHT TO WITHDRAW

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples, if they can still be identified (not anonymized). Once samples have been anonymized, it will not be possible to identify which samples have come from a particular individual. Therefore, it will not be possible to destroy subject samples after anonymization. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

SUBJECT PRIVACY AND RETURN OF DATA

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. Samples that are processed for analysis (DNA extracted) may be double-coded. Double-coding involves removing the initial code and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded (the first code being the subject number) as long as the initial tube does not carry any personal identifiers or the random code assigned by the central laboratory or biorepository. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

Sample anonymization may occur by destruction of the "key." Once the "key" is destroyed, it will not be possible to trace the pharmacogenomics assay results back to an individual. The Sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The Sponsor and its representatives and agents may share anonymized data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the Sponsor
- Independent ethics committees or institutional review boards that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report that can include part or all of the anonymized data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the planned analysis, it will not be possible to return individual data to subjects participating in the pharmacogenomics analysis.