1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7438-J081-106 (EZH-106)
Study Protocol Title:	A Phase 1 Study of Tazemetostat in Patients With Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma
Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112-8088 Japan
Investigational Product Name:	E7438/tazemetostat (INN)
Indication:	B-cell non-Hodgkin's lymphoma
Phase:	1
Approval Date:	V5.0 18 Oct 2018
GCP Statement:	This study is to be performed in full compliance with all applicable local Good Clinical Practice (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 Eisai (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.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7438

Name of Active Ingredient: Tazemetostat (INN)

Study Protocol Title

A Phase 1 Study of Tazemetostat in Patients With Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma

Investigators

See the Attachment separately provided to each site.

Sites

Study centers: 2 sites (planned)
Study location: Japan

Study Period and Phase of Development

Study period: 24 months (planned)
Phase of development: Phase 1

Objectives

Primary objective:
To assess the tolerability of tazemetostat in patients with B-cell non-Hodgkin's lymphoma (NHL).

Secondary objectives:
(1)To assess the safety of tazemetostat.
(2)To assess the pharmacokinetics (PK) profile of tazemetostat.
(3)To assess the preliminary anti-tumor activity of tazemetostat.

Exploratory objectives:

CCI [redacted]

Study Design

This is a multicenter, single-arm, phase 1 study to assess tolerability, safety, PK and preliminary anti-tumor activity of tazemetostat in patients with relapsed or refractory B-cell NHL.
This study will be conducted in the following 4 phases: Pre-treatment Phase, Treatment Phase, Extension Phase, and Follow-up Phase.
The Pre-treatment Phase will last no longer than 28 days and include a period to obtain informed consent, screening, enrollment and a baseline assessment. After screening assessments, the patient who meets the inclusion criteria and does not meet the exclusion criteria will be enrolled. The baseline assessment will be conducted within 3 days before the treatment in order to confirm that the patient continues to meet the inclusion criteria and does not meet the exclusion criteria before moving to the Treatment Phase.
The Treatment Phase consists of Cycle 0 (4 days) for tazemetostat single-dose oral administration and Cycle 1 of 28 days for tazemetostat twice daily (BID) oral administration on a continuous basis. Considering visit schedule and safety, subjects will be hospitalized from Cycle 0/Day 1 (C0D1) to Cycle 1/Day 15 (C1D15). Based on the thorough evaluation of the data obtained on C1D15 and all safety data available, the investigator or subinvestigator will determine whether subjects can be treated on an outpatient basis. When subjects are considered to require extended hospitalization to ensure subject safety, they will be hospitalized from C1D15 onwards.
The Extension Phase consists of Cycle 2 of 28 days and later for tazemetostat BID oral administration

on a continuous basis and lasts until discontinuation of study drug.
Subjects will discontinue study drug at the time of disease progression, development of unacceptable toxicity, subject's request to discontinue, withdrawal of consent, or study termination by the sponsor.
Follow-up Phase consists of the evaluation at discontinuation which is performed within 7 days after the discontinuation of the study and a final observation which occurs 30 days (+7 days) after final administration of tazemetostat or initiation of a new anti-tumor therapy, whichever occurs early.
The starting dose of tazemetostat is 800 mg as a single dose (Cycle 0) and 800 mg BID as continuous dosing (Cycle 1 and later). Three subjects will be enrolled and ensure that they are evaluable for dose-limiting toxicities (DLTs) at the end of Cycle 1 of the cohort. When a DLT is observed in 0 or 1 of 3 subjects at a given dose level, 3 additional subjects would be treated at the same dose level. When 2 of 3 subjects at a given dose level experience DLTs, enrollment of additional subjects will be discussed jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor should be also obtained. When additional subjects are to be enrolled, they will be monitored individually. When no DLTs are observed, up to 3 additional subjects will be enrolled. When no additional subjects are accrued or 3 subjects in total experienced DLTs, the enrollment in the cohort will be discontinued and the lower dose level of tazemetostat cohort will be considered jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor can be obtained if needed.
If the subject is regarded as DLT non-evaluable (eg, early discontinuation due to non-DLT, medication compliance with < 75% in Cycle 1 as a result of the reason other than treatment related toxicity), another subject will be added for replacement.

Dose-Limiting Toxicities (DLT)
A DLT is defined as toxicity related to study drug in Table below. The tolerability of tazemetostat will be determined based on the incidence of DLTs in Cycles 0 and 1. If DLTs occurs in 0 or 1 of 6 subjects, this dose level is considered tolerable. If DLTs occur in 2 of 6 subjects, the tolerability of this dose level will be determined jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor should be also obtained. In the case of difficulty of determination of whether a subject should be counted as having experienced a DLT and/or not for tolerability assessment, the final determination will be made jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor can be obtained if needed.

Table Dose-Limiting Toxicities (DLT)

Toxicity Category	Toxicity/CTCAE Grade
Hematological Toxicity	• Grade 4 neutropenia for > 7 days or neutropenia requiring hematopoietic growth factors • ≥ Grade 3 febrile neutropenia • Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with bleeding, or thrombocytopenia requiring platelet transfusion • Grade 4 anemia or anemia requiring erythrocyte transfusion
Non-hematological Toxicity	• ≥ Grade 3 nausea, vomiting, or diarrhea that persists > 7 days despite maximal medical therapy • ≥ Grade 3 non-hematological laboratory abnormalities with clinical symptoms that persists > 7 days • Other Grade 3 toxicity lasting > 7 days or Grade 4 non-hematological toxicity of any duration
Medication compliance	• Failure to administer ≥ 75% (≥ 42/56 doses) of the planned administration number of study drug in Cycle 1 as a result of treatment-related toxicity

Number of Subjects

Six DLT evaluable patients with relapsed or refractory B-cell NHL. Add 6 patients per cohort when additional lower dose level examined.

Inclusion Criteria

(1) Patients with histological diagnosis of B-cell NHL (except transformed lymphoma) as follows:
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma (FL)

(2) Patient who has measurable disease as below.
- Lymph node or ex-nodal disease diagnosed by CT scan.
- Clearly measurable in 2 orthogonal ways by CT scan.
- ≥1.5 cm in long axis or >1.0 cm in short axis, when long axis were <1.5 cm.

(3) Patient who had previous therapy with systemic chemotherapy and/or antibody therapy and for which no standard therapy exists.

(4) Patient who was PD or did not have response (complete response [CR] or partial response [PR]) in previous systemic therapy, or relapsed or progressed after previous systemic therapy.

(5) Patient with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1

(6) Patient with life expectancy of ≥3 months from starting study drug administration.

(7) Patient with adequate renal function:
- Serum creatinine ≤1.5× upper limit of normal (ULN)

(8) Patient with adequate liver function:
- Total bilirubin ≤1.5×ULN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0×ULN

(9) Patient with adequate bone marrow function:
(confirm 2 weeks or later from last administration of granulocyte colony-stimulating factor [G-CSF] and blood transfusion, if these are used)
- Absolute neutrophil count ≥ $1.5\times10^3/\mu L$ ($\geq1.5\times10^9/L$)
- Platelet count ≥ $10.0\times 10^4/\mu L$
- Hemoglobin ≥ 9.0 g/dL

(10) Patient with left ventricular ejection fraction (LVEF) >50% on echocardiography or multiple gate acquisition (MUGA) scan.

(11) Patient with time between prior anti-tumor therapy and first administration of study drug as below:
- Cytotoxic chemotherapy – At least 3 weeks
- Non-cytotoxic chemotherapy (eg, corticosteroids*, small molecule inhibitor) – At least 2weeks
- Monoclonal antibody (ies) – At least 4 weeks
- Radiotherapy
  - -At least 3 weeks from radiation therapy
  - -At least 6 weeks from prior radioisotope therapy
- Autologous hematopoietic stem cell transplantation – At least 6 months

*: Patient may receive no more than 10 mg of prednisolone daily or equivalent corticosteroid when used for treatment of lymphoma-related symptoms.

(12) Patient with no carry-over of ≥ Grade 2 adverse events of the prior treatment that may affect the safety evaluation of the investigational drug.

(13) Male and female patient ≥20 years of age at the time of informed consent.

(14) Patient who has provided written consent to participate in the study

Exclusion Criteria

(1) Patient with prior exposure to EZH2 inhibitor.
(2) Patient with a history or a presence of central nerves invasion.
(3) Patient with malignant pleural effusion, cardiac effusion, or ascites retention.
(4) Patient with allogeneic stem cell transplantation.
(5) Patient with medical need for the continued use of potent or moderate inhibitors of CYP3A or P-gp, or potent or moderate inducer of CYP3A (including St. John's wort). Patient is eligible if 2 weeks or longer have passed since the last use of such agents prior to the first dose of study drug.
(6) Patient unwilling to exclude grapefruit (juice) from the diet for 1 week prior to study drug administration and throughout the study.
(7) Patient with achlorhydria or use of H_2 blockers or proton-pump inhibitors within 2 weeks before study drug administration.
(8) Patient with 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 study drug.
(9) Patient with significant cardiovascular impairment
- History of congestive heart failure ≥ New York Heart Association (NYHA) Class III
- Uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug
- Ischaemic heart disease, cardiac arrhythmia requiring medical treatment

(10) Patient with prolongation of corrected QT interval using Fridericia's formula (QTcF) to > 480 msec.
(11) Patient with venous thrombosis or pulmonary embolism within the last 3 months before starting study drug.
(12) Patient with complications of hepatic cirrhosis, interstitial pneumonia or pulmonary fibrosis.
(13) Patient with active infection requiring systemic therapy.
(14) Patient with known hypersensitivity to any component of study drug.
(15) Patient who is positive for HIV antibody, HCV antibody, or HBs antigen. Patient who is positive for HBs or HBc antibody and showing DNA more than sensitivity in HBV-DNA assay.
(16) Patient with malignancy of activity other than B-cell NHL within 36 months before informed consent (except treated non-invasive melanoma, basal cell carcinoma of the skin or squamous cell carcinoma, intraepithelial carcinoma such as uterine cervix).
(17) Women of childbearing potential or man of impregnate potential who don't agree that both the patient and his/her partner will use a medically effective method for contraception (as below) for periods from before informed consent to during the clinical study and 30 days later (for males 90 days later) from last administration of study drug.
(18) Woman with pregnant or breastfeeding (not eligible even if she discontinues breastfeeding).
(19) Patient who was decided as inappropriate to participate in the study by the investigator or sub-investigator.

Note: Condom*, contraceptive sponge**, foam**, jelly**, diaphragm*, intrauterine device (IUD) *, or use of oral contraception* at least 30 days before starting the study treatment
(*Approved drugs or certified medical devices in Japan, **Non-approved drugs or certified medical devices in Japan)

Study Treatment

Tazemetostat 800 mg will be administered orally by single dose in Cycle 0/Day 1 (C0D1) and continuous BID (1600 mg total daily dose, no less than 8 hours between doses except C1D15 that requires 12 hours or more) in Cycle 1 and later, in a fasted state on C0D1 and at the first administration of C1D15 defined as ≥2 hours before and ≥2 hours after a meal (only water is allowed). Tazemetostat will be provided as 200 mg tablet.

Tazemetostat Dose Reduction and Interruption Instructions

1. Cycles 0 and 1

a. If DLT occurs:
Tazemetostat administration should be interrupted immediately. Treatment may be resumed in Cycle 2 at 600 mg BID (1200 mg total daily dose) if toxicity is resolved to Grade ≤ 1 or baseline and the investigator or subinvestigator decides to continue the study.

b. No DLT
Tazemetostat administration will be interrupted if judged to be clinically needed by investigator or subinvestigator, and may be resumed at the same dose level at appropriate timing.

2. Cycle 2 and later
Dose reduction and interruption for subjects who experience tazemetostat-related toxicity will follow the instructions shown in the Table below. Dose reductions will be based on the previous dose level in order of 600, 400 mg BID (1200 mg, 800 mg total daily dose, respectively). Once the dose is reduced, it cannot be increased at a later date. Any dose adjustment must be discussed with the sponsor or discontinue tazemetostat when toxicities requiring dose reduction occur at the dose of 400 mg BID.

If a subject experiences myeloid malignancy including myelodysplastic syndrome, study treatment should be interrupted and restart (including dose modification)/discontinuation of study treatment should be discussed with the sponsor. If a subject experiences T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia, study treatment should be discontinued and other actions should be discussed with the sponsor.

Study treatment may be interrupted, also if it is required to ensure the safety of a subject experiencing an adverse event that is unrelated to the study drug. In such cases, study treatment should be resumed as soon as possible, at the same dose as had been administered before the interruption.

Table Tazemetostat Dose Reduction and Interruption Instructions

Tazemetostat -related Toxicity		During Therapy[d]	Dose adjustment[d]
Grade 1 and Tolerable Grade 2[a]		Continue tazemetostat	Maintain dose level
Intolerable Grade 2[a] and Grade 3[b]		Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[e]	Dose reduction by one dose level
Grade 3 and Grade 4 neutropenia	ANC $\geq 0.75\times10^9$/L	Continue tazemetostat	Maintain dose level
	ANC $<0.75\times10^9$/L	Interrupt tazemetostat until resolved to ANC$\geq 0.75\times10^9$/L[e]	Dose reduction by one dose level
Grade 4[c]		Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[e]	Discuss with sponsor or discontinue tazemetostat

ANC = absolute neutrophil count.
a: Tolerability of Grade 2 toxicities will be judged by the study investigators.
b: Dose interruption and reduction is not necessary for Grade 3 thrombocytopenia, anemia and Grade 3 or 4 leukopenia, lymphopenia and laboratory abnormalities that are not clinically relevant. Initiate optimal medical management for nausea, vomiting, and/or diarrhea prior to any study treatment interruption or dose reduction.
c: Laboratory abnormalities judged to be non-life threatening, will be managed as Grade 3.
d: Discuss with the sponsor when to consider the dose interruption and adjustment other than instructions.
e: To minimize the duration of interruption, assessment at least every 7 days is recommended. A delay of tazemetostat for more than 28 days due to any toxicity must be discussed with the sponsor before treatment can be resumed.

Duration of Treatment

Treatment will continue until disease progression, development of unacceptable toxicity, subject requests to discontinue, withdrawal of consent, or study termination by the sponsor.

Concomitant Drug/Therapy

The following drugs and therapies are prohibited:

1. From the time of subject enrollment to final study drug administration
   - Anti-tumor therapies (Subjects may receive corticosteroid for local or systemic symptom control prior to and while on study. Subjects may receive no more than 10 mg of prednisolone daily or equivalent corticosteroid when used for treatment of lymphoma related symptoms)
   - Any agent that potently inhibits or induces CYP3A
   - Other investigational agents
2. Cycles 0 and 1
   - To start or change the drugs for prophylactic use to prevent adverse event (AE) occurrence (continuous or treatment use is allowed).
   - Any agent that moderately inhibits or induces CYP3A or inhibits P- gp
   - H_2 blockers, proton-pump inhibitors
   - Any antacids or other drugs known to raise gastric pH (C0D1 and C1D15 only). These drugs should be administered ≥2 hours before study drug administration and 2 hours after study drug administration if used in Cycle 1.

Assessments

Efficacy Assessments:

Tumor assessment will be performed by investigator or subinvestigator using "The Lugano Classification (CT-Based Response)" (Cheson, et al., 2014). Overall response and best overall response (BOR) (best response recorded at the designated visits during the study) will be assessed. Perform CT scans at Screening, every 8 weeks (starting at Cycle 1/Day1) during Cycles 2-6, every 12 weeks starting at Cycle 7 (Cycle 7/Day 1) and beyond, and discontinuation.
A bone marrow aspiration or biopsy will be performed at screening for evaluation of bone marrow infiltration of tumor. After the study drug administration, perform bone marrow aspiration or biopsy if the result of screening was positive or unconfirmed and when to confirm CR as best of response, or if clinically indicated.
Preliminary anti-tumor activity will be objective response rate (ORR) as defined by "The Lugano Classification (CT-Based Response)" (Cheson, et al., 2014). ORR is defined as the proportion of subjects who have a BOR of CR or PR.

Pharmacokinetics Assessments:

Plasma and urine concentrations of tazemetostat and plasma concentrations of its metabolite, ER-897387, and PK parameters.

CCI

Tolerability and Safety Assessments:

Safety assessments will consist of monitoring and recording all AEs, including all grading of Common Terminology Criteria for Adverse Events (CTCAE v4.03), and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; and periodic measurement of vital signs, electrocardiograms (ECGs), echocardiograms/MUGA scans to assess LVEF, ECOG-PS, and physical examinations.

Bioanalytical Methods

Plasma concentrations of tazemetostat and ER-897387 and urine tazemetostat concentrations will be measured by validated methods using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

Statistical Methods

Definitions of Analysis Sets

DLT Analysis Set will include all subjects who have completed treatment Cycles 0 and 1 without major protocol deviations with at least 75% of treatment compliance in Cycle 1 and were assessed for DLT, and subjects who have experienced DLT during Cycles 0 and 1. Subjects with less than 75% treatment compliance in Cycle 1 due to a reason other than toxicity up to Cycle 1/Day 28 will not be included in this analysis set.

Safety/Efficacy Analysis Set will include all subjects who received at least 1 administration of the study drug. This will be the analysis set for all safety and efficacy evaluations, as well as for demographic and baseline characteristics.

Pharmacokinetic Analysis Set will include all subjects who have received at least 1 administration

of the study drug and had sufficient PK data to derive at least 1 PK parameter**.**

Efficacy Analyses

BOR will be summarized in whole or each disease (DLBCL, FL). The assessment of the ORR (CR + PR) in subjects with B cell lymphomas will be based on "The Lugano Classification (CT-Based Response)" (Cheson, et al., 2014) response criteria.

ORR will be presented with corresponding 2-sided Clopper–Pearson exact 95% confidence intervals (CIs). This analysis will be performed on the Efficacy Analysis Set. If applicable, a waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at post-baseline nadir.

Pharmacokinetic Analysis:

The PK Analysis Set will be used for all PK analyses including summaries of plasma and urine concentrations of tazemetostat and plasma concentrations of ER-897387. Plasma concentration-time profiles of tazemetostat and ER-897387 will be plotted. Using non-compartmental analysis methods, plasma concentrations of tazemetostat and ER-897387 will be calculated to determine the PK parameters including C_{max}, t_{max}, AUC at the first administration (Cycle 0/Day 1) and repeated administration (Cycle 1/Day 15).

CCI

Tolerability and Safety Analysis:

All tolerability analyses will be performed on the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated. DLT will also be summarized per type of toxicity. The Safety Analysis Set will be used for all other safety analyses.

The number and percentage of subjects with all AEs and SAEs observed after the first administration of study drug will be summarized and listed by SOC, PT, and severity. Summary statistics will be presented for laboratory test values, vital signs, 12-lead ECG, LVEF parameters, and ECOG-PS. If needed, the changes from baseline will also be summarized.

Sample Size Rationale

The primary objective of this study is to investigate the tolerability of tazemetostat. Hence neither clinical hypothesis nor judgment criteria are set, the sample size is not based on statistical consideration. The sample size of 6 patients is considered adequate for the purpose to evaluate the tolerability of each cohort.

3 TABLE OF CONTENTS

1 TITLE PAGE 1
2 CLINICAL PROTOCOL SYNOPSIS 2
3 TABLE OF CONTENTS 10
4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 15
5 ETHICS 18
5.1 Institutional Review Boards 18
5.2 Ethical Conduct of the Study 18
5.3 Subject Information and Informed Consent 18
6 INVESTIGATORS AND STUDY PERSONNEL 19
7 INTRODUCTION 20
7.1 Diffuse Large B-cell Lymphoma and Follicular Lymphoma and Current Therapeutic Options 20
7.1.1 Malignant Lymphoma 20
7.1.2 Diffuse Large B-Cell Lymphoma 20
7.1.3 Current Therapeutic Options for Diffuse Large B-Cell Lymphoma 20
7.1.4 Follicular Lymphoma (FL) 21
7.1.5 Current Therapeutic Options for Follicular Lymphoma 21
7.2 EZH2 (Enhancer of Zeste Homolog 2) 22
7.3 Tazemetostat (E7438) 23
7.3.1 Physical, Chemical, and Pharmaceutical Properties and Formulations 24
7.3.2 Nonclinical Studies 24
7.3.2.1 Pharmacology 24
7.3.2.1.1 Primary Pharmacodynamics 24
7.3.2.1.2 Secondary Pharmacodynamics 25
7.3.2.2 Safety Pharmacology 25
7.3.2.3 Pharmacokinetics and Drug Metabolism 25
7.3.2.4 Toxicology 26
7.3.3 Clinical Studies 29
7.4 Study Rationale 30
8 STUDY OBJECTIVES 32
8.1 Primary Objective 32
8.2 Secondary Objectives 32
8.3 Exploratory Objectives 32
9 INVESTIGATIONAL PLAN 33
9.1 Overall Study Design and Plan 33
9.1.1 Study Design 33

9.1.1.1 Pre-treatment Phase 33
9.1.1.2 Treatment Phase 34
9.1.1.3 Extension Phase 34
9.1.1.4 Follow-Up Phase 34
9.1.2 Dose-Limiting Toxicities (DLT) 34
9.2 Discussion of Study Design, Including Choice of Control Groups 35
9.3 Selection of Study Population 36
9.3.1 Inclusion Criteria 36
9.3.2 Exclusion Criteria 37
9.3.3 Removal of Subjects From Therapy or Assessment 38
9.3.3.1 Discontinuation Criteria by Subject 38
9.4 Treatment 39
9.4.1 Treatment Administered 39
9.4.1.1 Tazemetostat Dose Reduction and Interruption Instructions 39
9.4.1.1.1 Cycles 0 and 1 39
9.4.1.1.2 Cycle 2 and later 39
9.4.2 Identity of Investigational Product 40
9.4.2.1 Chemical Name, Structural Formula of Tazemetostat 40
9.4.2.2 Comparator Drug 41
9.4.2.3 Labeling for Study Drug 41
9.4.2.4 Storage Conditions 41
9.4.3 Method of Assigning Subjects to Treatment Groups 41
9.4.4 Selection of Doses in the Study 42
9.4.5 Selection and Timing of Dose for Each Subject 42
9.4.6 Blinding 42
9.4.7 Prior and Concomitant Therapy 42
9.4.7.1 Prohibited Concomitant Therapies and Drugs 43
9.4.7.2 Concomitant Drugs to be Used with Caution 43
9.4.8 Prohibitions and Restrictions during Study Period 44
9.4.9 Treatment Compliance 44
9.4.10 Drug Supplies and Accountability 44
9.5 Study Assessments 45
9.5.1 Assessments 45
9.5.1.1 Demography 45
9.5.1.2 Pre-treatment Assessments 45
9.5.1.2.1 Medical History and Current Medical Conditions 45
9.5.1.3 Efficacy Assessments 46

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments 46
9.5.1.4.1 Pharmacokinetic Assessments 46
9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments 47
9.5.1.5 Safety Assessments 49
9.5.1.5.1 Adverse Events and Events Associated with Special Situations 49
9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations 51
9.5.1.5.3 Laboratory Measurements 52
9.5.1.5.4 Vital Signs and Weight Measurements 53
9.5.1.5.5 Physical Examinations 53
9.5.1.5.6 Electrocardiograms 53
9.5.1.5.7 Other Safety Assessments 54
9.5.2 Schedule of Procedures/Assessments 55
9.5.2.1 Schedule of Procedures/Assessments of the Study 55
9.5.3 Appropriateness of Measurements 58
9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations 58
9.5.4.1 Reporting of Serious Adverse Events 58
9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding 59
9.5.4.3 Reporting of Events Associated with Special Situations 59
9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error 59
9.5.4.3.2 Reporting of Study-Specific Events 60
9.5.4.4 Expedited Reporting 60
9.5.4.5 Breaking the Blind 60
9.5.4.6 Regulatory Reporting of Adverse Events 60
9.5.5 Completion/Discontinuation of Subjects 61
9.5.6 Abuse or Diversion of Study Drug 61
9.5.7 Confirmation of Medical Care by Another Physician 61
9.6 Data Quality Assurance 61
9.6.1 Data Collection 61
9.6.2 Clinical Data Management 62
9.7 Statistical Methods 62
9.7.1 Statistical and Analytical Plans 62
9.7.1.1 Study Endpoints 62
9.7.1.1.1 Primary Endpoint 62

9.7.1.1.2 Secondary Endpoints 62
9.7.1.1.3 Exploratory Endpoints 62
9.7.1.2 Definitions of Analysis Sets....63
9.7.1.3 Subject Disposition 63
9.7.1.4 Demographic and Other Baseline Characteristics 63
9.7.1.5 Prior and Concomitant Therapy....63
9.7.1.6 Efficacy Analyses 63
9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses....64
9.7.1.7.1 Pharmacokinetic Analyses 64
9.7.1.7.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses 64
9.7.1.8 Safety Analyses....64
9.7.1.8.1 Extent of Exposure....64
9.7.1.8.2 Dose Limiting Toxicities 64
9.7.1.8.3 Adverse Events 64
9.7.1.8.4 Laboratory Values....65
9.7.1.8.5 Vital Signs....65
9.7.1.8.6 Electrocardiograms 65
9.7.1.8.7 Other Safety Analyses....66
9.7.2 Determination of Sample Size 66
9.7.3 Interim Analysis....66
9.7.4 Other Statistical/Analytical Issues 66
9.7.5 Procedure for Revising the Statistical Analysis Plan....66
10 REFERENCE LIST 67
11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES) 71
11.1 Changes to the Protocol 71
11.2 Adherence to the Protocol....71
11.3 Monitoring Procedures....71
11.4 Recording of Data 72
11.5 Identification of Source Data 72
11.6 Retention of Records....73
11.7 Auditing Procedures and Inspection 73
11.8 Handling of Study Drug....74
11.9 Publication of Results 74
11.10 Disclosure and Confidentiality 74
11.11 Discontinuation of Study 75
11.12 Subject Insurance and Indemnity....75

LIST OF IN-TEXT TABLES

Table 1 Dose-Limiting Toxicities (DLT).....35
Table 2 Tazemetostat Dose Reduction and Interruption Instructions.....40
Table 3 Blood Sampling Schedule for Pharmacokinetic Assessment 47
Table 4 Urine Sampling Schedule for Pharmacokinetic Assessment 47
Table 5 Clinical Laboratory Tests.....53
Table 6 Schedule of Procedures/Assessments in Study E7438-J081-106 (EZH-106) 56

LIST OF IN-TEXT FIGURES

Figure 1 Study Design.....33

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BOR	best overall response
BUN	blood urea nitrogen
C#/D#	Cycle#/Day#
C_{max}	maximum observed concentration
CCI	[redacted]
CR	complete response
CRA	clinical research associate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
EZH2	enhancer of zeste homolog 2
FL	follicular lymphoma
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBc	hepatitis B virus core
HBs	hepatitis B virus surface
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus

Abbreviation	Term
HL	Hodgkin lymphoma
HMT	histone methyltransferase
ICF	informed consent form
INN	International Nonproprietary Name
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDH	lactate dehydrogenase
LLT	lower level term
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin's lymphoma
NYHA	New York Heart Association
ORR	objective response rate
PD	progressive disease
P-gp	P-glycoprotein
PK	pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
R	Rituximab
t_{max}	time at which the highest drug concentration occurs
QOL	quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RP2D	recommended Phase 2 dose

Abbreviation	Term
SD	Sprague Dawley
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
ULN	upper limit of normal
UV	Ultraviolet

5 ETHICS

5.1 Institutional Review Boards

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) constituted and functioning in accordance with Good Clinical Practice (GCP). Any protocol amendment or revision to the ICF will be resubmitted to the IRB for review and approval, except for changes involving only administrative aspects of the study (eg, change in CRAs, change of telephone numbers). Documentation of IRB compliance with the GCP regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB chairman must be sent to the head of the medical institution 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. If the IRB decides to suspend or terminate the study, the head of the medical institution will immediately send the notice of study suspension or termination by the IRB to the sponsor.

Study progress is to be reported to IRBs annually (or as required) by the investigator via the head of the medical institution according to GCP. The investigator or the sponsor will submit, depending on local regulations, periodic reports and inform the investigator and the relevant IRB via the head of the medical institution of any reportable adverse events (AEs) per GCP guidelines and local IRB standards of practice. Upon completion of the study, the investigator will provide the IRB and sponsor via the head of the medical institution with a brief report of the outcome of the study.

5.2 Ethical Conduct of the Study

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

- Principles of the World Medical Association Declaration of Helsinki
- GCP
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceuticals, Medical devices and Other Therapeutic Products Act (Law No. 145, 1960)

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, 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, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study 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 ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB-approved ICF must be prepared by the investigator in accordance with GCP and all applicable local regulations with the cooperation of the sponsor. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the investigator or subinvestigator (and clinical research coordinator, if needed). The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject 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 study. The communication of this information should be documented.

The ICF for genomic test will be prepared separately from the study ICF. Genetic testing will be performed only on subjects who provided their consent to the planned genetic analysis. Subjects can participate in this study even if they do not provide tumor samples or do not agree to undergo genetic test using their tumor samples (see Section 9.5.1.4.2).

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsor at approximately 2 investigational sites in Japan.

The name and telephone and fax numbers of the sponsor are listed in the Attachment separately provided to each site.

7 INTRODUCTION

7.1 Diffuse Large B-cell Lymphoma and Follicular Lymphoma and Current Therapeutic Options

7.1.1 Malignant Lymphoma

The nationwide survey by the Ministry of Labor, Health, and Welfare (2014) has reported that 64,000 people are diagnosed with malignant lymphoma per year in Japan. The survey, "Monitoring of Cancer Incidence in Japan" conducted by the Center for Cancer Control and Information Services at the National Cancer Center (2012) has also reported that malignant lymphoma is prevalent in approximately 26,600 patients per year.

Malignant lymphoma is classified into various subtypes according to the antigen on the tumor cell surface and morphological characteristics, and each subtype has distinct prognosis and therapeutic treatment. Malignant lymphoma is classified into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). The target diseases of this study, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), are subtypes of B-cell NHL.

7.1.2 Diffuse Large B-Cell Lymphoma

DLBCL is a B-cell type of lymphoma that derives from germinal center B-cells and is a diverse set of diseases that have various clinical features, immunophenotypes, genetic and chromosomal abnormalities. The patient survey by the Ministry of Labor, Health, and Welfare (2014) has reported that approximately 10,000 people are categorized as "international classification of disease C833: large cell (diffuse)". This survey also indicates approximately 38,000 people are categorized as "international classification of disease C859: non-Hodgkin's lymphoma, unspecified type" and some of them are thought to be DLBCL. The proportion of DLBCL subtype in Japan was 45.3% among malignant lymphoma according to the survey of the incidence of malignant lymphoma encoded by classification of disease (Chihara, et al., 2014). Based on the information on 7.1.1 Malignant Lymphoma and these reports, it is estimated that approximately 29,000 people are diagnosed with DLBCL and DLBCL is prevalent in approximately 12,000 patients per year.

7.1.3 Current Therapeutic Options for Diffuse Large B-Cell Lymphoma

In Japan, the guideline for management of hematopoietic tumor covering DLBCL is established according to the US NCCN guidelines (general incorporated association, Japanese Society of Hematology, 2013). The standard therapy for advanced-stage primary DLBCL in and outside Japan is the R-CHOP regimen, which is a combination of several chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine, and prednisone) and rituximab (R). The R-CHOP regimen has shown a 5-year event-free survival rate of 47% and a 5-year overall survival rate of 58% (Coiffier, et al., 2002).

The recommended therapy for relapsed or refractory DLBCL is rituximab-based multi-agent salvage chemotherapy. The most common salvage chemotherapies in current use are the R-

DHAP (dexamethasone, cisplatin, and cytosine arabinoside), R-ICE (ifosfamide, carboplatin, and etoposide), and R-GDP (gemcitabine, dexamethasone, and cisplatin) regimens. Comparable results are shown in patients treated with R-DHAP and R-ICE, both with a 3-year event-free survival rate of 31% and a 3-year overall survival rate of 50%. In addition, no differences were identified among the effects of other regimens (Gisselbrecht, et al., 2010). High-dose chemotherapy followed by autologous stem-cell transplantation was an effective therapeutic option before the rituximab era, and this is still an encouraging treatment option for the management of younger patients or other applicable patients (Philip, et al., 1995). As described above, therapeutic options and outcomes, particularly in patients with relapsed or refractory DLBCL are limited, thus a new therapeutic option is anticipated.

7.1.4 Follicular Lymphoma (FL)

FL is the most common type of the indolent B-cell lymphoma, which progress in yearly term. FL has a structure basis that histologically mimics germinal center. The patient survey by the Ministry of Labor, Health, and Welfare (2014) has reported approximately 4,000 people are categorized as “International classification of disease C829: follicular non-Hodgkin's lymphoma, unspecified”. This survey also indicates approximately 38,000 people are categorized as “International classification of disease C859: non-Hodgkin’s lymphoma, unspecified type” and some of them are thought to be FL. The proportion of FL subtype among malignant lymphoma in Japan was 13.5% according to the survey of the incidence of malignant lymphoma encoded by classification of disease (Chihara, et al., 2014). Based on the information on 7.1.1 Malignant Lymphoma and these reports, it is estimated that approximately 8,600 people are diagnosed with FL and FL is prevalent in approximately 3,600 patients per year.

7.1.5 Current Therapeutic Options for Follicular Lymphoma

In Japan, the guideline for management of hematopoietic tumor covering FL is established according to the US NCCN guidelines (general incorporated association, Japanese Society of Hematology, 2013). The standard therapy for advanced-stage primary FL that requires treatment is the R-CHOP regimen or the non-doxorubicin-containing R-CVP regimen. Rituximab monotherapy or chemotherapy alone approach should also be considered based on the patient’s condition. The R-CHOP regimen showed a 3-year time to treatment failure rate of 62% and a 3-year overall survival rate of 95% (Federico, et al., 2013).

The recommended therapy for relapsed or refractory FL is rituximab monotherapy, rituximab in combination with single- or multi-agent chemotherapy, or radioisotope therapy based on the patient’s condition. In Japanese patients with relapsed or refractory indolent B-cell lymphoma, bendamustine monotherapy has demonstrated that the 1-year PFS rate was 70% (Ohmachi, et al., 2010) and a combination of rituximab and fludarabine has demonstrated that the median time to treatment failure was 8.6 months (Tobinai, et al., 2006). While autologous stem-cell transplantation has been considered as consolidation therapy in younger patients who had a positive response, the increased risk of secondary malignancies has been reported (Deconinck, et al., 2005; Ladetto, et al., 2008; Gyan, et al., 2009). As described

above, therapeutic options and outcomes, particularly in patients with relapsed or refractory FL are limited, thus a new therapeutic option is anticipated.

7.2 EZH2 (Enhancer of Zeste Homolog 2)

In epigenetic control of gene expression, post-translational modifications of histones (methylation, acetylation, ubiquitylation, and phosphorylation), the core proteins of chromatin, play an important role in controlling the occurrence of various cancers and malignant alteration. Of these, trimethylation of lysine 27 on histone H3 (H3K27) is enhanced in most of stem cells such as hematopoieticis stem cells and chromatin in tumor cells. H3K27 is also associated with suppression of genes involved in cell differentiation or tumor genes, cell growth-promotion activity (Margueron and Reinberg, 2011; Copeland, 2013).

EZH2 is the specific histone methyltransferase (HMT) that catalyzes the component of H3K27 and the mono-, di-, and trimethylation of H3K27 as subunit of the multi-protein Polycomb Repressive Complex 2 (PRC2). EZH2 gene mutation, amplification and/or overexpression, or increased activity has been observed in several cancer types including DLBCL, FL, malignant rhabdoid tumor (rhabdomyosarcoma), synovial sarcoma, breast cancer, prostate cancer, malignant melanoma or bladder cancer. Therefore, drugs targeting EZH2 may become a new candidate for antitumor therapy (Chase and Cross, 2011; Kim, et al., 2016; Yoo and Hennighausen, 2012; Varambally, et al., 2002; Zingg, et al., 2015; Arisan, et al., 2005).

Mutations in the SET domain of EZH2 (Y646*) associated with DLBCL and FL lead to increased activity of trimethylation of EZH2 and produces hypertrimethylation on H3K27 (H3K27Me3), resulting in tumor proliferation depending on mutant EZH2 (Morin, et al., 2010; Sneeringer, et al., 2010). In addition, germinal center lymphomas are likely to depend on EZH2 activity (Begeulin, et al., 2013). In contrast, subsets of other malignancies such as T-cell acute lymphoblastic leukemia and myeloproliferative disorders show genetic loss of *EZH2* components (Chase and Cross, 2011; Ntziachristos, et al., 2012). Together this suggests that perturbing the correct balance of H3K27Me3 in a given cellular background in either direction can be oncogenic.

In addition to genetic alterations in EZH2 itself, mutations in other chromatin modifying enzymes lead to an imbalance of H3K27 methylation. For instance, mutations in other chromatin modifying enzymes including HMTs (MLL family), histone demethylases (KDM6A), histone acetyltransferases (CREBBP, EP300), and histone deubquitinases (*BAP1*) are found in various tumor types (NHL, multiple myeloma, T-cell acute lymphoblastic leukemia, medulloblastoma, mesothelioma, and others) (Plass 2013, LaFave 2015). These genetic lesions are hypothesized to perturb the methylation state of H3K27, leading to aberrant gene expression. In addition to PRC2 that contains subunit of EZH2, subunits of the SWI/SNF complex play an important role in post-translational modifications of histones and PRC2 and SWI/SNF antagonize each other at many gene loci. Approximately 20% of cancers carry genetic alteration or deletion in subunit of SWI/SNF, such as integrase interactor 1 (*INI1,* also known as *SNF5, SMARCB1*), *SMARCB2*, *SMARCA4*, *ADRID1A*, and

others (Kadoch and Crabtree, 2013, Kadoch, et al., 2016). INI1 or SMARCA4 deficiency promotes inactivation of EZH2 blocks by SWI/SNF (Wilson, et al., 2010; Alimova, et al., 2013). In synovial sarcoma, as gene transcription fuses SS18-SSX1/2 fusion protein, an imbalance in INI1 was observed and led to deregulate EZH2 activity. This is because protease acts easily after SS18-SSX1/2 displaces SS18 from the SWI/SNF complex and INI1 is removed from SWI/SNF complex (Shen, et al., 2016; Kawano, et al., 2016). As shown above, EZH2 gene mutation, INI1 deficiency, SMARCA4 deficiency, and SS18-SSX1/2 fusions drive deregulation of EZH2 activity, which means an imbalance of H3K27 methylation, inducing oncogenesis and malignant alteration.

*Amino acid sequence mutation is based on Genbank database EZH2 NM_004456.3. This mutation is known as Y641.

7.3 Tazemetostat (E7438)

Tazemetostat (E7438) is a selective, reversible, small molecule inhibitor of EZH2, a histone methyltransferase (HMT). EZH2 is a catalytic subunit of the polycomb repressive complex 2 (PRC2) and is responsible for methylation of histone H3 lysine 27 (H3K27). EZH2 plays a role in epigenetic regulation on various genes.

Cell-free biochemical assays showed that tazemetostat inhibited wild-type and mutant EZH2 in SET domain with IC_{50} values ranging from 2 to 38 nmol/L. The compound showed 36-fold selectivity over the closely related HMT, EZH1, and greater than 3000-fold selectivity over other HMTs. Tazemetostat specifically inhibited histone H3K27 methylation across different cell lines. Incubation with tazemetostat inhibited the proliferation of cancer cells, such as DLBCL lines bearing *EZH2* mutations, INI1-negative MRT cell lines, and INI-deficient synovial sarcoma cell lines (Knutson, et al., 2013; Knutson, et al., 2014). Tazemetostat-mediated cell death occurred through G1 cell cycle arrest and the subsequent induction of apoptosis. G1 arrest was observed as of Day 3 to Day 7 and consistent with elimination of intracellular H3K27Me3. Tazemetostat incubation in INI1-negative MRT cell lines induced changes in gene expression together with the expression of the neuronal differentiation markers. An oral administration of tazemetostat to human xenograft models in mice including DLBCL cell lines with *EZH2* mutations induces significant antitumor effects, ranging from tumor growth inhibition to complete and durable tumor regressions. Tazemetostat exposure led to dose- and time-dependent decreases in intracellular H3K27Me3 in both tumor and selected non-tumor tissues. An oral administration of tazemetostat demonstrated significant antitumor activity against 4 of 6 xenograft models of INI-deficient tumors.

Therefore, based on the above results, a Phase 1/2 study of tazemetostat in patients with advanced solid tumors including INI1 or SMARCA4-negative tumors (including synovial sarcoma, malignant rhabdoid tumor, epithelioid sarcoma, and other INI1 or SMARCA4-negative tumors) or with B cell lymphomas including DLBCL and FL (E7438-G000-101) has been conducted outside Japan from Nov 2012. Phase 1 data were reviewed by an Independent Data Monitoring Committee on 12 Nov 2014. The committee agreed that the

recommended Phase 2 dose be 800 mg BID based on evaluation of safety, pharmacokinetics (PK), biomarker, antitumor activity.

Tazemetostat is currently under investigation for the treatment of DLBCL, FL, and INI1- or SMARCA4-negative tumors outside Japan.

7.3.1 Physical, Chemical, and Pharmaceutical Properties and Formulations

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) is an organonitrogen compound with molecular weight of 653.65. Drug product of tazemetostat is a red, film-coated tablet with a diameter of 10.1 mm. Tazemetostat tablets contain 200 mg of drug substance as the free base. Tazemetostat film-coated tablets should be stored at room temperature.

7.3.2 Nonclinical Studies

7.3.2.1 Pharmacology

7.3.2.1.1 PRIMARY PHARMACODYNAMICS

Cell-free biochemical assays showed that E7438 inhibited wild-type and mutant EZH2 in SET domain with IC_{50} values ranging from 2 to 38 nmol/L. The compound showed 36-fold selectivity over the closely related HMT, EZH1, and greater than 3000-fold selectivity over other HMTs. E7438 specifically inhibited histone H3K27 methylation across different cell lines. This result indicates E7438 also specifically inhibit EZH2 in cell lines. Incubation with E7438 inhibited the proliferation of cancer cells, such as DLBCL lines bearing *EZH2* mutations, INI1-negative MRT cell lines, and INI-deficient synovial sarcoma cell lines. E7438-mediated cell death occurred through G1 cell cycle arrest and the subsequent induction of apoptosis. G1 arrest was observed as of Day 3 to Day 7 and consistent with elimination of intracellular H3K27Me3. E7438 incubation in INI1-negative MRT cell lines induced changes in gene expression together with the expression of the neuronal differentiation markers. E7438-induced cell death occurring through G1 cell cycle arrest and genetic alterations occurred Day 3 of culture or later, consistent with elimination of intracellular H3K27Me3 requiring 3 days.

An oral administration of E7438 to human xenograft models in mice including DLBCL cell lines with *EZH2* mutations (WSU-DLCL2, KARPAS-422, and Pfeiffer) induces significant antitumor effects, ranging from tumor growth inhibition to complete and durable tumor regressions. E7438 exposure led to dose- and time-dependent decreases in intracellular H3K27Me3 in both tumor and selected non-tumor tissues. An oral administration of E7438 demonstrated significant antitumor activity against 4 of 6 xenograft models of INI-deficient tumors (INI1-negative G401 MRT cell line, INI1 levels reduced Fuji synovial sarcoma cell line, patient-derived CTG-0331 and CTG-0771).

7.3.2.1.2 SECONDARY PHARMACODYNAMICS

E7438 dose-dependently inhibited H3K27Me3 in skin in mice and peripheral blood mononuclear cells, bone marrow, spleen, and skin in rats and cynomolgus monkeys. Bone marrow showed the highest degree of H3K27Me3 inhibition. While H3K27Me3 changes in skin in rats are observed after 7 days of dosing, longer dosing periods (22–28 days) are necessary to detect H3K27Me3 significant reduction.

E7438 did not significantly inhibit a panel of G-protein-coupled receptors, transporters, and ion channels, and had no effect on the activity of 40 kinases.

7.3.2.2 Safety Pharmacology

The effects of E7438 on the cardiovascular system were examined in in vitro electrophysiology study assessing effects on the human ether-à-go-go related gene (hERG) in human embryonic kidney cells (HEK293), ex vivo rabbit ventricular wedge evaluations, and an oral-dose safety study in conscious, telemetered cynomolgus monkeys. The effects on the central nervous system and respiratory systems were evaluated in neurological examinations and respiratory function tests performed in the repeated-dose oral toxicity study in cynomolgus monkey.

E7438 inhibited hERG potassium current by 15.1% at 10 μmol/L in cell lines expressing hERG channels. While E7438 had no effects on QRS duration at concentrations up to 20 μmol/L, E7438 decreased QRS duration at 20 μmol/L and $T_{p\text{-}e}$ interval at 7 and 20 μmol/L, however, E7438 did not cause any pro-arrhythmic events. Additionally, E7438 had no effects on cardiovascular parameters in conscious, telemetered cynomolgus monkeys at single oral doses up to 1000 mg/kg. Neurological examination was conducted in the repeated-dose oral toxicity study in cynomolgus monkeys. Monkeys showed a decrease in muscle tone in both legs at 1000 mg/kg/day. No abnormality in neuromuscular function was observed at lower doses (≤ 300 mg/kg). E7438 did not affect respiratory function at up to 1000 mg/kg/day in cynomolgus monkeys. Based on the above results, no notable cardiovascular, central nervous system, or respiratory risks were identified.

7.3.2.3 Pharmacokinetics and Drug Metabolism

The plasma PK following E7438 administration to Sprague-Dawley (SD) rats and cynomolgus monkeys was characterized by high-to-moderate clearance (3.5 and 1.4 L/h/kg respectively), moderate-to-large volume of distribution (1.8 and 2.0 L/kg respectively), and a short half-life ($t_{1/2}$) (0.4 and 1.6 hours, respectively). The absolute bioavailability of tazemetostat was < 4% at a dose of 5 mg/kg in rats and monkeys, and approximately 40% at a dose of 10 mg/kg in mice.

[^{14}C] E7438-derived radioactivity was rapidly absorbed and widely distributed in SD rats following a single oral administration of [^{14}C] E7438 (50 mg/kg). Elimination of the radioactivity was completed in the majority of tissues up to 168 hours postdose. The primary route of elimination of radioactivity after a single oral dose of [^{14}C] E7438 in rats was in the feces (86% of the dose), with low renal excretion (8% of the dose). The primary route of

elimination of radioactivity in bile duct cannulated rats was in the bile (54% of the dose). [^{14}C] E7438-derived radioactivity was widely distributed in Long-Evans (LE) rats similar to SD rats following a single oral administration of [^{14}C]E7438 (50 mg/kg). Radioactivity concentrations observed in melanin-containing tissues in LE rats were notably higher than those in SD rats, which indicated that there was a specific association of [^{14}C] E7438-derived radioactivity with melanin. Association with melanin was considered to be reversible.

Protein binding of tazemetostat at a concentration of 1000 ng/mL was 96.4%, 88.3%, 85.6%, 81.8%, and 83.4% in mouse, rat, dog, monkey, and human plasma, respectively. There was minimal difference among species (mouse, rat, monkey, and human) or concentrations (50–50000 ng/mL) in the blood/plasma concentration ratios (RB) (ratios between 0.53 and 1.06).

In vitro, cytochrome P450 (CYP) 3A was the predominant enzyme responsible for the hepatic metabolism of E7438. ER-897387-00, the N-desethylated metabolite (EPZ-6930; M5), was the major metabolite formed in vitro and there was no metabolite observed unique to humans.

E7438 directly inhibited CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A activities in vitro with IC_{50} values of 4 to 19 µmol/L. E7438 showed time-dependent inhibition of CYP3A. E7438 induced CYP3A4 messenger ribonucleic acid (mRNA) in vitro, with a potency similar to the positive control, 10 µmol/L of rifampicin.

Results from in vitro studies demonstrated that E7438 was a substrate for P-glycoprotein (P-gp), but not a substrate for breast cancer resistance protein (BCRP). E7438 inhibited P-gp and BCRP with IC_{50} values of 5.9 and 34.1 µmol/L, respectively. E7438 was not a substrate for organic anion transporting polypeptiden (OATP), 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2. E7438 inhibited OATPB1, OATP1B3, OCT2, and OAT3 with IC_{50} values of 19.7, 14.4, 14.7, and 10.0 µmol/L, respectively. E7438 hardly inhibited OAT1 with IC_{50} values of >100 µmol/L. E7438 inhibited bile salt export pump (BSEP) with IC_{50} values of 20.0 µmol/L (for reference purpose only).

7.3.2.4 Toxicology

Single oral administration of E7438 up to 1000 mg/kg was tolerated in SD rats and cynomolgus monkeys.

In a 4-week repeated-dose toxicity study in rats, a number of animals were found dead possibly due to the gastrointestinal tract toxicity at a dose of 1000 mg/kg/day between Day 7 and Day 21. Pathological changes were found in these animals in the gastrointestinal tract (glandular stomach mucosa erosion/ulceration and glandular stomach and gastrointestinal epithelia degeneration/necrosis) and other organs such as kidney (eosinophilic droplets and necrosis in epithelial cells), bone marrow (slight-to-moderate hypocellularity), lymphoid tissues (lymphoid depletion), and new trabecular bone formation in the medullary cavity of the sternum and femur. In some rats at 1000 mg/kg/day, there were secondary clinical laboratory changes or changes possibly due to general deterioration. Reversibility or recovery trend of all adverse findings observed at 1000 mg/kg/day was demonstrated after a

2-week off-dose period subsequent to cessation of dosing in surviving animals at 1000 mg/kg/day on Day 21 or later. While a drop of urinary sediment was observed at doses of 100 and 300 mg/kg, no pathological changes were found in the urinary system. In the 13-week repeated-dose toxicity study, there was an occurrence of lymphoblastic lymphoma originated from the thymus in the 300 mg/kg group or higher doses. Lymphoma was the cause of death or moribundity after Day 65. A total of 3/20 males and 8/20 females at 300 mg/kg, and 1/20 male and 0/20 female at 600 mg/kg developed lymphoblastic lymphoma in the study. Metastases to various tissues and organs included. At 600 mg/kg, findings other than lymphoma were lymphoid depletion, shortening of the lower incisor, trabecular formation in the femur and sternum, erosion/ulcer and regenerative changes in the upper gastrointestinal tract, and granular materials in the renal pelvis. Changes at 300 mg/kg/day were similar to but less severe than those observed at 600 mg/kg/day. At 100 mg/kg/day, there were no significant changes except for labial abscess observed at 300 mg/kg/day or higher doses in one male rat. For the recovery evaluation, primary non-neoplastic changes were generally reversible with the exception of splenic lymphoid depletion and changes in the bone and incisors after the 4-week recovery period.

In a 4-week repeated-dose toxicity study in cynomolgus monkeys, the 1000-mg/kg dose was discontinued on Day 8 or Day 9 of dosing due to adverse clinical observations, which resulted in the euthanasia of 3 moribund animals. On Day 11 or Day 12, dosing was re-initiated at a lower dose of 600 mg/kg/day for surviving animals. During the dosing period, 1000 mg/kg/day caused infrequent and intermittent emesis on Day 6 after the morning dose only. There were no test article-related effects on heart rate or electrocardiograms (ECGs) observed in this study. In moribund animals at 1000 mg/kg/day, there were adverse clinical signs and associated decreased muscle tone on Day 7, clinical pathology abnormalities, and changes in the gastrointestinal tract and liver, however, the cause of morbidity in these animals was not clearly identified. In both the moribund animals at 1000 mg/kg and the remaining high-dose animals that had their dose reduced to 600 mg/kg, there were test article-related changes in the liver and kidney as well as an increase in alanine aminotransferase (ALT) and triglycerides. At 300 mg/kg and above, lymphoid depletion, that was dose-dependent in incidence and severity was observed. Reversibility or a trend towards reversibility for toxicity was demonstrated in one 1000-mg/kg/day animal after a 21-day recovery period. In the 13-week cynomolgus monkey study, the principal clinical and necropsy findings in the 13-week monkey study were similar to those observed in a 4-week study, although more pronounced. Moribundity occurred in a single female animal at 600 mg/kg/day on Day 83 following severe clinical signs (decreased activity, cold to touch, hunched posture, and shivering/tremor). While the cause of moribundity was not clearly explained by histopathology, E7438-related significant changes in this animal were similar to those observed in terminal sacrificed animals as below. E7438-related clinical observations included emesis and abnormal feces. The incidence of emesis and/or fecal changes was sporadic in all tazemetostat-treated groups; however, the incidence of emesis was dose related. At 300 mg/kg/day and above there was a mild shortening of the RR interval, which was not statistically significant. Dose-dependent lymphoid depletion in the spleen, lymph nodes, and thymus, increases in ALT and AST, hepatocyte hypertrophy, Kupffer cell hypertrophy/pigmentation, and bile duct hyperplasia in the liver were observed. At 600 mg/kg/day there were increases in ALP and glomerulopathy and tubular pigmentation in

the kidney. No toxicologically significant changes were observed at 100 mg/kg/day. After a 4-week recovery, there was a trend toward reversibility in most parameters; however, the 4-week recovery period was not sufficient for complete assessment of reversibility for some changes.

E7438 was not genotoxic in an in vitro bacterial reverse mutation assay, in vitro micronuclei assay, and in vivo rat micronuclei studies.

In a repeated-dose, range-finding study in juvenile SD rats, E7438 was initiated at Post-Natal Day 7 and repeatedly administered for 4 weeks. All male and female animals treated at 500 and 1000 mg/kg euthanized following clinical signs of hypoactivity and a cool and/or pale body after first or second dosing. Histopathological changes were limited to the stomach, hematopoietic and lymphoid tissues, and kidney. The gastric toxicity was considered to be the cause of moribundity. No toxicologically significant changes were found at 50 and 150 mg/kg/day.

The ultraviolet (UV) absorption spectrum of E7438 showed absorption maxima at 302 nm and 265 nm was observed. Thus, an in vitro phototoxicity study of E7438 in 3T3 cells was performed. E7438 showed phototoxic potential because Mean Photo Effect, known as phototoxicity index, was more than the criterion for phototoxic, 0.15 (0.270 and 0.347) when examined up to the solubility limit of 100 μg/mL.

In a 13-week repeated-dose rat toxicity study with a 4-week recovery period, there was an occurrence of lymphoblastic lymphoma originated from the thymus. To investigate further the mechanism of lymphomagenesis noted in this study, additional 13-week rat studies were completed using two structurally similar, but chemically distinct EZH2 inhibitors, EPZ-10961 and EPZ011989. They have similar specificity and mechanism of inhibition and inhibit cellular H3K27Me3 with 3 to 4-fold higher potency than E7438. Non-dose dependent incidence of lymphoma was observed in studies for EPZ-10961 and EPZ011989 in approximately the same time frame that it was seen in the 13-week rat study with E7438 (after 8-10 weeks of dosing). Immunophenotyping of cells isolated from the thymus, bone marrow, and spleen samples showed higher percentages of CD8+ T-cells and αβ TCR+T-cells and lower percentage of CD4+ T-cells and γδ TCR+ T-cells in thymus derived samples. In contrast, immunophenotyping of cells isolated from the thymus, bone marrow, and spleen samples from rats without lymphoma showed lower percentages of αβ TCR+ T-cells and concurrent higher percentage of γδ TCR+ T-cells. The similar results were obtained with EPZ-10961. Notch-mediated transcription was studied in thymus samples from E7438 or the EPZ011989 study. The mechanism of lymphomagenesis in these rats does not appear to be related to E7438-mediated alterations in the Notch signaling pathway or effects on retroviral reintegration of the Rat Leukemia virus (RaLV). Gene expression and whole transcriptome analysis from thymus tissue isolated during studies with EPZ011989 revealed elevated expression of *Myc* in rats with lymphoma, but otherwise, no similarities to genetic and transcriptional abnormalities related to mechanism of occurrence and immunophenotyping in human T-cell acute lymphoblastic leukemia were seen.

An additional 4-week oral study in rats was performed with E7438 to assess the toxicologic impact of the presence of new impurities in the lot to be used in the clinical study of

tazemetostat in tablet form. No notable changes attributable to new impurities were observed.

7.3.3 Clinical Studies

As of the cutoff date of 15 Jan 2016, the following 3 studies are ongoing outside Japan.

- Study E7438-G000-101, "An Open-Label, Multicenter, Phase 1/2 Study of E7438 (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects with Advanced Solid Tumors or with B-cell Lymphomas"
- Study EZH-102 "A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with Relapsed or Refractory INI1-Negative Tumors or Synovial Sarcoma"
- Study EZH-202 "A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma"

Eighty-eight subjects had been enrolled in Study E7438-G000-101 and 1 subject in study EZH-202, all of whom, a total of 89 subjects, had been exposed to tazemetostat.

Seventy-eight of 89 (87.6%) subjects experienced at least 1 AE and 51 of 89 (57.3%) subjects experienced AEs that were considered related to tazemetostat by the investigator. AEs occurring in ≥ 5% of subjects and in descending order of frequency were asthenia (34.8%), nausea (15.7%), thrombocytopenia (14.6%), decreased appetite (13.5%), anemia (12.4%), constipation (12.4%), dysgeusia (7.9%), vomiting (7.9%), diarrhea (6.7%), dry skin (6.7%), dyspnea (6.7%), muscle spasms (6.7%), abdominal pain (5.6%), and neutropenia (5.6%). Of the subjects who experienced related AEs, the majority reported Grade 1 or 2 events. Seven subjects (7.9%) experienced Grade 3 or 4 AEs and 5 subjects (5.6%) discontinued study drug due to AEs.

One subject experienced Grade 4 thrombocytopenia during the dose-escalation group of Study E7438-G000-101 at the dose level of 1600 mg BID; this event was also considered to be a DLT. The protocol-defined MTD was not reached. No other DLTs were observed.

Twenty-two of 89 subjects experienced 31 serious adverse events (SAEs). Of these, 4 SAEs occurring in 3 subjects were considered possibly related to study drug (anemia, thrombocytopenia, and 2 events of neutropenia). In Study E7438-G000-101, 11 subjects died. For 9 subjects, the cause of death was progressive disease, 1 was due to an AE, and 1 was noted as being not due to progressive disease (no further information was available at the time of data cutoff [15 Jan 2016]).

The clinical PK characteristics of tazemetostat are derived from Study E7438-G000-101 in which tazemetostat was administered at doses of 100 mg BID as a suspension or tablet formulation and 200, 400, 800, and 1600 mg BID as a tablet formulation. Tazemetostat was rapidly absorbed with a time to the maximum plasma concentration (t_{max}) of approximately 1 to 2 hours postdose and a mean $t_{1/2}$ of approximately 3 to 5 hours. After multiple dosing, there was a dose-dependent decrease in tazemetostat systemic exposure relative to Day1. However, no further reduction in systemic exposure was observed beyond Day 15.

Administration of tazemetostat with a high-fat meal decreased geometric mean $AUC_{(0\text{-inf})}$ and C_{max} values approximately 7% and 28%, respectively, relative to administration in the fasted state. Administration of tazemetostat with a high-fat meal also resulted in a 4-fold increase in median t_{max} relative to administration in the fasted state. All individual C_{max} and $AUC_{(0\text{-inf})}$ values observed after administration of tazemetostat following a high-fat meal were within the range of the respective values observed after administration in the fasted state. The decrease in systemic exposure is not clinically significant, and therefore tazemetostat can be taken without regard to meals.

Tazemetostat antitumor activity has been evaluated in Phase 1 part of Study E7438-G000-101. As of 07 Nov 2015, tazemetostat has demonstrated antitumor activity in subjects with B-cell lymphomas and INI1- and SMRCA4-negative cancers. Objective responses (2 CRs and 7 PRs) have been observed in 9 of 16 response evaluable subjects (DLBCL [5 of 12]; FL [3 of 4]; and marginal zone lymphoma [1 of 1]). Objective responses (1 CR and 3 PRs) were also observed in 4 of 11 response evaluable subjects with INI1- and SMARCA4-negative cancers (MRT) [2 of 5]; epithelioid sarcoma (ES) [1 of 3]; malignant rhabdoid tumor of the ovary (MRTO) [1 of 2]).

Phase 1 data were reviewed by an Independent Data Monitoring Committee on 12 Nov 2014. The committee agreed that the recommended Phase 2 dose be 800 mg BID based on evaluation of safety, PK, biomarker, and antitumor activity.

7.4 Study Rationale

This study is the Japan Phase 1 study to investigate the tolerability, safety, PK, and preliminary antitumor activity of tazemetostat in patients with relapsed or refractory B-cell NHL. The tolerability and safety of tazemetostat in Japanese patients has not yet been investigated; therefore, this study was planned.

Tazemetostat 800 mg will be administered orally by single dose in Cycle 0 and by continuous 800 mg BID in Cycle 1 and later in 28-day cycles. Tazemetostat treatment will continue until disease progression, development of unacceptable toxicity, subject requests to discontinue, withdrawal of consent, or study termination by the sponsor.

In the Phase 1 part of the Study E7438-G000-101, a Phase 1/2 study currently ongoing outside Japan, the recommended dose of tazemetostat has been determined to be 800 mg BID. The Phase 2 part of the study is ongoing at this dose level. Safety and tolerability of tazemetostat for subjects enrolled in Study E7438-G000-101 was assessed as of 15 Jan 2016. Tazemetostat was administered twice daily in 6 subjects for100 mg, 3 subjects for 200 mg, 16 subjects for 400 mg, 46 subjects for 800 mg (including 1 subject from Study EZH-202), and 18 subjects for 1600 mg. One subject experienced treatment-related Grade 4 thrombocytopenia at the dose level of 1600 mg BID; this event was also considered to be a DLT. The protocol-defined MTD was not reached. Treatment-related Grade 3 or 4 AEs observed at 800 mg BID were thrombocytopenia (2 subjects, 4.3%) and Grade 3 hepatocellular injury and Grade 3 hypertension (1 subject each, 2.2%) while no treatment-related Grade 3 or 4 AEs occurred at the dose level of 400 mg BID or lower doses. Based on

the current clinical data, the starting dose of 800 mg, half of the maximum single dose of 1600 mg established outside Japan, was considered as suitable for this study whereas clinical data in Japanese subjects are not available.

Tazemetostat has demonstrated antitumor activity in subjects with B-cell lymphomas in Study E7438-G000-101. As of 07 Nov 2015, objective responses (2 CRs and 7 PRs) have been observed in 9 of 16 response evaluable subjects. Therefore, the target population of this study is considered to be relapsed or refractory B-cell NHL, in which preliminary efficacy is expected.

With these reasons, the Phase 1 study was designed to investigate the tolerability, safety, PK, and preliminary anti-tumor activity of tazemetostat in Japanese patients with relapsed or refractory B-cell NHL, and the current study is rationalized.

8 STUDY OBJECTIVES

8.1 Primary Objective

To assess the tolerability of tazemetostat in patients with B-cell non-Hodgkin's lymphoma (NHL).

8.2 Secondary Objectives

(1)To assess the safety of tazemetostat.
(2)To assess the PK profile of tazemetostat.
(3)To assess the preliminary anti-tumor activity of tazemetostat.

8.3 Exploratory Objectives

CCI

[redacted]

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, single-arm, phase 1 study to assess the tolerability, safety, PK and preliminary anti-tumor activity of tazemetostat in patients with relapsed or refractory B-cell NHL.

9.1.1 Study Design

The study design of this study is presented in Figure 1. This study will be conducted in the following 4 phases: Pre-treatment Phase, Treatment Phase, Extension Phase, and Follow-up Phase.

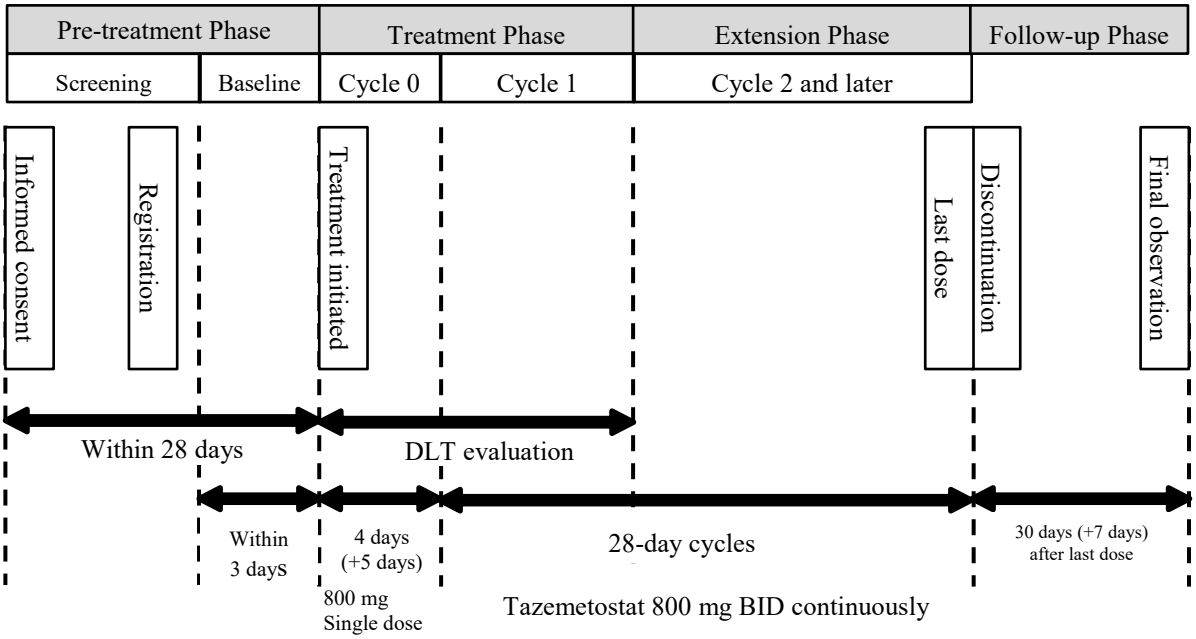


Figure 1 Study Design

BID = twice daily, DLT = dose limiting toxicity.

9.1.1.1 Pre-treatment Phase

The Pre-treatment Phase will last no longer than 28 days and include a period to obtain informed consent, screening, enrollment, and a baseline assessment. 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. After screening assessments, the patient who meets the inclusion criteria and does not meet the exclusion criteria will be enrolled. The baseline assessment will be conducted within 3 days before the treatment in order to confirm

that the patient continues to meet the inclusion criteria and does not meet the exclusion criteria before moving to the Treatment Phase.

The CRF must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.2 Treatment Phase

The Treatment Phase consists of Cycle 0 (4 days) for tazemetostat single-dose oral administration and Cycle 1 of 28 days for tazemetostat twice daily (BID) oral administration on a continuous basis. The subject who discontinues study drug during the Treatment Phase will have a discontinuation visit of the Follow-up Phase. The subject who completes the Treatment Phase will enter the Extension Phase.

Considering visit schedule and safety, subjects will be hospitalized from Cycle 0/Day 1 (C0D1) to Cycle 1/Day 15 (C1D15). Based on the thorough evaluation of the data obtained on C1D15 and all safety data available, the investigator or subinvestigator will determine whether subjects can be treated on an outpatient basis. When subjects are considered to require extended hospitalization to ensure subject safety, they will be hospitalized from C1D15 onwards.

9.1.1.3 Extension Phase

The Extension Phase consists of Cycle 2 of 28 days and later for tazemetostat BID oral administration on a continuous basis and lasts until discontinuation of study drug. Informed consent should be obtained before initiating the study or before entering the Extension Phase when Cycle 2 or later administrations will be continued. Subjects will discontinue study drug at the time of disease progression, development of unacceptable toxicity, subject's request to discontinue, withdrawal of consent, or study termination by the sponsor. The subject who discontinues study drug during the Extension Phase will have a discontinuation visit of the Follow-up Phase.

9.1.1.4 Follow-Up Phase

The Follow-up Phase consists of the evaluation at discontinuation which is performed within 7 days after the discontinuation of the study and a final observation which occurs 30 days (+7 days) after final administration of tazemetostat or initiation of a new anti-tumor therapy, whichever occurs early.

9.1.2 Dose-Limiting Toxicities (DLT)

The starting dose of tazemetostat is 800 mg as a single dose (Cycle 0) and 800 mg BID as continuous dosing (Cycle 1 and later). Three subjects will be enrolled and ensure that they are evaluable for dose-limiting toxicities (DLTs) at the end of Cycle 1 of the cohort. When a DLT is observed in 0 or 1 of 3 subjects at a given dose level, 3 additional subjects would be treated at the same dose level. When 2 of 3 subjects at a given dose level experience DLTs, enrollment of additional subjects will be discussed jointly by the investigator and sponsor.

The opinion of Independent Data Monitoring Advisor should be also obtained. When additional subjects are to be enrolled, they will be monitored individually. When no DLTs are observed, up to 3 additional subjects will be enrolled. When no additional subjects are accrued or 3 subjects in total experienced DLTs, the enrollment in the cohort will be discontinued and the lower dose level of tazemetostat cohort will be considered jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor can be obtained if needed.

If the subject is regarded as DLT non-evaluable (eg, early discontinuation due to non-DLT, medication compliance with <75% in Cycle 1 as a result of the reason other than treatment related toxicity), another subject will be added for replacement.

A DLT is defined as toxicity related to study drug in Table 1 below. The tolerability of tazemetostat will be determined based on the incidence of DLTs in Cycles 0 and 1. If DLTs occur in 0 or 1 of 6 subjects, this dose level is considered tolerable. If DLTs occurs in 2 of 6 subjects, the tolerability of this dose level will be determined jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor should be also obtained. In the case of difficulty of determination of whether a subject should be counted as having experienced a DLT and/or not for tolerability assessment, the final determination will be made jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor can be obtained if needed.

Table 1 Dose-Limiting Toxicities (DLT)

Toxicity Category	Toxicity/CTCAE Grade
Hematological Toxicity	• Grade 4 neutropenia for > 7 days or neutropenia requiring hematopoietic growth factors • ≥ Grade 3 febrile neutropenia • Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with bleeding, or thrombocytopenia requiring platelet transfusion • Grade 4 anemia or anemia requiring erythrocyte transfusion
Non-hematological Toxicity	• ≥ Grade 3 nausea, vomiting, or diarrhea that persists > 7 days despite maximal medical therapy • ≥ Grade 3 non-hematological laboratory abnormalities with clinical symptoms that persists > 7 days • Other Grade 3 toxicity lasting > 7 days or Grade 4 non-hematological toxicity of any duration
Medication compliance	• Failure to administer ≥ 75% (≥ 42/56 doses) of the planned administration number of study drug in Cycle 1 as a result of treatment-related toxicity

9.2 Discussion of Study Design, Including Choice of Control Groups

This study was designed according to "The Guidelines for Clinical Evaluation of Anti-Cancer Drugs in Japan (Notification No. 1101001 issued on 01 Nov, 2005)."

9.3 Selection of Study Population

Approximately 6 subjects will be enrolled at approximately 2 sites in Japan. 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.

9.3.1 Inclusion Criteria

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

(1)Patients with histological diagnosis of B-cell NHL (except transformed lymphoma) as follows:
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma (FL)

(2)Patient who has measurable disease as below.
- Lymph node or ex-nodal disease diagnosed by CT scan.
- Clearly measurable in 2 orthogonal ways by CT scan.
- ≥1.5 cm in long axis or >1.0 cm in short axis, when long axis were <1.5 cm.

(3)Patient who had previous therapy with systemic chemotherapy and/or antibody therapy and for which no standard therapy exists.

(4)Patient who was PD or did not have response (complete response [CR] or partial response [PR]) in previous systemic therapy, or relapsed or progressed after previous systemic therapy.

(5)Patient with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1

(6)Patient with life expectancy of ≥3 months from starting study drug administration.

(7)Patient with adequate renal function:
- Serum creatinine ≤1.5× upper limit of normal (ULN)

(8)Patient with adequate liver function:
- Total bilirubin ≤1.5×ULN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0×ULN

(9)Patient with adequate bone marrow function:
(confirm 2 weeks or later from last administration of granulocyte colony-stimulating factor [G-CSF] and blood transfusion, if these are used)
- Absolute neutrophil count ≥1.5×10^3/μL (≥1.5×10^9/L)
- Platelet count ≥10.0×10^4/μL
- Hemoglobin ≥9.0 g/dL

(10)Patient with left ventricular ejection fraction (LVEF) >50% on echocardiography or multiple gate acquisition (MUGA) scan.

(11)Patient with time between prior anti-tumor therapy and first administration of study drug as below:
- Cytotoxic chemotherapy – At least 3 weeks
- Non-cytotoxic chemotherapy (eg, corticosteroids*, small molecule inhibitor) – At least 2weeks
- Monoclonal antibody (ies) – At least 4 weeks

· Radiotherapy
  -At least 3 weeks from radiation therapy
  -At least 6 weeks from prior radioisotope therapy
· Autologous hematopoietic stem cell transplantation – At least 6 months
  *: Patient may receive no more than 10 mg of prednisolone daily or equivalent corticosteroid when used for treatment of lymphoma-related symptoms.

(12)Patient with no carry-over of ≥ Grade 2 adverse events of the prior treatment that may affect the safety evaluation of the investigational drug.
(13)Male and female patient ≥20 years of age at the time of informed consent.
(14)Patient who has provided written consent to participate in the study

9.3.2 Exclusion Criteria

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

(1)Patient with prior exposure to EZH2 inhibitor.
(2)Patient with a history or a presence of central nerves invasion.
(3)Patient with malignant pleural effusion, cardiac effusion, or ascites retention.
(4)Patient with allogeneic stem cell transplantation.
(5)Patient with medical need for the continued use of potent or moderate inhibitors of CYP3A or P-gp, or potent or moderate inducer of CYP3A (including St. John's wort). Patient is eligible if 2 weeks or longer have passed since the last use of such agents prior to the first dose of study drug.
(6)Patient unwilling to exclude grapefruit (juice) from the diet for 1 week prior to study drug administration and throughout the study.
(7)Patient with achlorhydria or use of H_2 blockers or proton-pump inhibitors within 2 weeks before study drug administration.
(8)Patient with 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 study drug.
(9)Patient with significant cardiovascular impairment
· History of congestive heart failure ≥ New York Heart Association (NYHA) Class III
· Uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug
· Ischaemic heart disease, cardiac arrhythmia requiring medical treatment

(10)Patient with prolongation of corrected QT interval using Fridericia's formula (QTcF) to > 480 msec.
(11)Patient with venous thrombosis or pulmonary embolism within the last 3 months before starting study drug.
(12)Patient with complications of hepatic cirrhosis, interstitial pneumonia or pulmonary fibrosis.
(13)Patient with active infection requiring systemic therapy.
(14)Patient with known hypersensitivity to any component of study drug.
(15)Patient who is positive for HIV antibody, HCV antibody, or HBs antigen. Patient who is positive for HBs or HBc antibody and showing DNA more than sensitivity in HBV-DNA assay.

(16)Patient with malignancy of activity other than B-cell NHL within 36 months before informed consent (except treated non-invasive melanoma, basal cell carcinoma of the skin or squamous cell carcinoma, intraepithelial carcinoma such as uterine cervix).
(17)Women of childbearing potential or man of impregnate potential who don't agree that both the patient and his/her partner will use a medically effective method for contraception (as below) for periods from before informed consent to during the clinical study and 30 days later (for males 90 days later) from last administration of study drug.
(18)Woman with pregnant or breastfeeding (not eligible even if she discontinues breastfeeding).
(19)Patient who was decided as inappropriate to participate in the study by the investigator or subinvestigator.

Note: Condom*, contraceptive sponge**, foam**, jelly**, diaphragm*, intrauterine device (IUD) *, or use of oral contraception* at least 30 days before starting the study treatment

(*Approved drugs or certified medical devices in Japan, **Non-approved drugs or certified medical devices in Japan)

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator or subinvestigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. If a subject discontinues study treatment, the subject will enter the Follow-up Phase and complete protocol-specified off-treatment visits and procedures unless the subject withdraws consent. If a subject withdraws consent, the date will be documented in the source documents. The CRF will be completed indicating the primary reason for discontinuation. In addition, the date of last dose of study drug will be documented on the CRF.

9.3.3.1 Discontinuation Criteria by Subject

If a subject meet any of the following criteria, the investigator or subinvestigator will discontinue treating the subject with study treatment. If a subject experiences myeloid malignancy including myelodysplastic syndrome, study treatment should be interrupted and restart (including dose modification)/discontinuation of study treatment should be discussed with the sponsor. If a subject experiences T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia, study treatment should be discontinued and other actions should be discussed with the sponsor.

(1) Withdrawal of consent or proposal to refuse continuation of participation by the subject
(2) Major violation of inclusion or exclusion criteria are found.
(3) Presence of adverse event that is judged by the investigator or subinvestigator to prohibit continuation with therapy
(4) Pregnancy
(5) Evidence of disease progression. Subjects will be allowed to be treated with study drug

if the investigator judges that the administration of the study drug is clinically beneficial for the subject.

(6) Subject is turned to be non-compliant with the protocol and ineligible in view of safety issue.

(7) Study discontinuation is appropriate judged by the investigator or subinvestigator.

(8) Subject experiences T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia.

9.4 Treatment

9.4.1 Treatment Administered

Tazemetostat 800 mg will be administered orally by single dose in Cycle 0/Day 1 (C0D1) and continuous BID (1600 mg total daily dose, no less than 8 hours between doses except C1D15 that requires 12 hours or more) in Cycle 1 and later, in a fasted state on C0D1 and at the first administration of C1D15 defined as either ≥2 hours before and ≥2 hours after a meal (only water is allowed).

9.4.1.1 Tazemetostat Dose Reduction and Interruption Instructions

9.4.1.1.1 CYCLES 0 AND 1

If DLT occurs:

Tazemetostat administration should be interrupted immediately. Treatment may be resumed in Cycle 2 at 600 mg BID (1200 mg total daily dose) if toxicity is resolved to Grade ≤ 1 or baseline and the investigator or subinvestigator decides to continue the study.

No DLT:

Tazemetostat administration will be interrupted if judged to be clinically needed by investigator or subinvestigator, and may be resumed at the same dose level at appropriate timing.

9.4.1.1.2 CYCLE 2 AND LATER

Dose reduction and interruption for subjects who experience tazemetostat-related toxicity will follow the instructions shown in Table 2. Dose reductions will be based on the previous dose level in order of 600, 400 mg BID (1200 mg, 800 mg total daily dose, respectively). Once the dose is reduced, it cannot be increased at a later date. Any dose adjustment must be discussed with the sponsor or discontinue tazemetostat when toxicities requiring dose reduction occur at the dose of 400 mg BID.

If a subject experiences myeloid malignancy including myelodysplastic syndrome, study treatment should be interrupted and restart (including dose modification)/discontinuation of study treatment should be discussed with the sponsor. If a subject experiences T-cell

lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia, study treatment should be discontinued and other actions should be discussed with the sponsor.

Study treatment may be interrupted, also if it is required to ensure the safety of a subject experiencing an adverse event that is unrelated to the study drug. In such cases, study treatment should be resumed as soon as possible, at the same dose as had been administered before the interruption.

Table 2 Tazemetostat Dose Reduction and Interruption Instructions

Tazemetostat -related Toxicity		**During Therapy[d]**	**Dose adjustment[d]**
Grade 1 and Tolerable Grade 2[a]		Continue tazemetostat	Maintain dose level
Intolerable Grade 2[a] and Grade 3[b]		Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[e]	Dose reduction by one dose level
Grade 3 and Grade 4 neutropenia	ANC $\geq 0.75\times10^9$/L	Continue tazemetostat	Maintain dose level
	ANC $<0.75\times10^9$/L	Interrupt tazemetostat until resolved to ANC$\geq 0.75\times10^9$/L[e]	Dose reduction by one dose level
Grade 4[c]		Interrupt tazemetostat until resolved to Grade ≤ 1 or baseline[e]	Discuss with sponsor or discontinue tazemetostat

ANC = absolute neutrophil count.
a: Tolerability of Grade 2 toxicities will be judged by the study investigators.
b: Dose interruption and reduction is not necessary for Grade 3 thrombocytopenia, anemia and Grade 3 or 4 leukopenia, lymphopenia and laboratory abnormalities that are not clinically relevant. Initiate optimal medical management for nausea, vomiting, and/or diarrhea prior to any study treatment interruption or dose reduction.
c: Laboratory abnormalities judged to be non-life threatening, will be managed as Grade 3.
d: Discuss with the sponsor when to consider the dose interruption and adjustment other than instructions.
e: To minimize the duration of interruption, assessment at least every 7 days is recommended. A delay of tazemetostat for more than 28 days due to any toxicity must be discussed with the sponsor before treatment can be resumed.

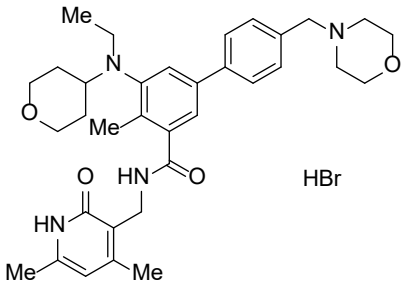
9.4.2 Identity of Investigational Product

Tazemetostat will be provided as 200 mg tablet by the sponsor. Tazemetostat tablets contain 200 mg of drug substance as the free base.

9.4.2.1 Chemical Name, Structural Formula of Tazemetostat

- Test drug code: E7438
- Generic name: tazemetostat (INN)
- 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: $C_{34}H_{44}N_4O_4Br$

- Molecular weight: 653.65
- Structural formula:



9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

The following information is provided on the study drug labeling. Details on labeling and package are shown in the Attachment separately provided to each site.

- For clinical study use only
- Name and address of the sponsor
- Drug identifier
- Lot number/batch number
- Storage conditions

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. The assigned pharmacist or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study, that the study drug is maintained within an established temperature range, and that records are maintained; the temperature should be monitored continuously by using either an in-house data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent and satisfy all eligibility requirements (see Section 9.3) will receive study drug. There is no randomization in this study.

(1)The investigator, subinvestigator, or clinical research coordinator will issue the Subject ID Number to individual subjects who provide signed informed consent for study entry and record it in “Subject Screening Log.”
(2)The investigator, subinvestigator, or clinical research coordinator will screen the subjects

and determine subject eligibility based on the inclusion and exclusion criteria. The investigator, subinvestigator, or clinical research coordinator will record the decision on the subject eligibility in the "Subject Screening Log."

(3) The investigator, subinvestigator, or clinical research coordinator will notify the sponsor of date of informed consent, date of screening initiation, and eligibility decision by email or fax immediately after the investigator or subinvestigator determines the subject eligibility.

(4) After the sponsor confirms the subject eligibility, the investigator or subinvestigator will be informed of the date of registration and dose to be administered by email or fax (subject registration).

(5) The investigator or subinvestigator will confirm the subject registration and then confirm the subject eligibility based on the results of screening according to the inclusion and exclusion criteria. The investigator or subinvestigator will record the subject eligibility in medical charts and initiate study drug administration.

9.4.4 Selection of Doses in the Study

In the Phase 1 part of the Study E7438-G000-101, a Phase 1/2 study currently ongoing outside Japan, the recommended dose of tazemetostat has been determined to be 800 mg BID. The Phase 2 part of the study is ongoing at this dose level. Safety and tolerability of tazemetostat for subjects enrolled in Study E7438-G000-101 was assessed as of 15 Jan 2016. Tazemetostat was administered twice daily in 6 subjects for 100 mg, 3 subjects for 200 mg, 16 subjects for 400 mg, 46 subjects for 800 mg (including 1 subject from Study EZH-202), and 18 subjects for 1600 mg. One subject experienced Grade 4 thrombocytopenia at the dose level of 1600 mg BID; this event was also considered to be a DLT. The protocol-defined MTD was not reached. Treatment-related Grade 3 or 4 AEs observed at 800 mg BID were thrombocytopenia (2 subjects, 4.3%) and Grade 3 hepatocellular injury and Grade 3 hypertension (1 subject each, 2.2%) while no treatment-related Grade 3 or 4 AEs occurred at the dose level of 400 mg BID or lower doses. Based on the current clinical data, the starting dose of 800 mg, half of the maximum single dose of 1600 mg established outside Japan, was considered as suitable for this study whereas clinical data in Japanese subjects are not available.

9.4.5 Selection and Timing of Dose for Each Subject

The selection and timing of the dose for each subject are provided in Section 9.4.1 Treatment Administered.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent until the final observation)

will be recorded on the CRF. For all drugs, the name, treatment start dates (or timing of starting treatment), treatment end dates, and reason for use will be recorded on the CRF. Concomitant drugs such as premedication, diagnostic agents, solutions, or fluid transfusions provided for surgery, medical examinations, or administrations will be excepted. For concomitant therapy, the name, treatment start dates (or timing of starting treatment), treatment end dates, and reason for use will be recorded on the CRF.

Treatment of complications or AEs, or therapy to ameliorate symptoms (including G-CSF, blood products, blood transfusions, fluid transfusions, antibiotics, steroids, antidiarrheal drugs, or tranquilizers) other than prohibited therapies and drugs may be given at the discretion of the investigator or subinvestigator but these therapies or drugs should be used in caution.

9.4.7.1 Prohibited Concomitant Therapies and Drugs

The following drugs and therapies are prohibited:

(1)From the time of subject enrollment to final study drug administration
- Anti-tumor therapies (Subjects may receive corticosteroid for local or systemic symptom control prior to and while on study. Subjects may receive no more than 10 mg of prednisolone daily or equivalent corticosteroid when used for treatment of lymphoma related symptoms)
- Any agent that potently inhibits or induces CYP3A (see the Attachment separately provided to each site)
- Other investigational agents

(2)Cycles 0 and 1
- To start or change the drugs for prophylactic use to prevent AE occurrence (continuous or treatment use is allowed).
- Any agent that moderately inhibits or induces CYP3A or inhibits P- gp
- H_2 blockers, proton-pump inhibitors
- Any antacids or other drugs known to raise gastric pH (C0D1 and C1D15 only). These drugs should be administered ≥2 hours before study drug administration and ≥2 hours after study drug administration if used in Cycle 1.

When anti-tumor therapies are implemented, study drug administration should be discontinued and protocol-specified off-treatment visits and procedures will be completed.

9.4.7.2 Concomitant Drugs to be Used with Caution

Medications that are substrates of CYP3A, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 and have a narrow therapeutic range (as shown in the Attachment separately provided to each site) should be avoided if possible.

9.4.8 Prohibitions and Restrictions during Study Period

Grapefruit and grapefruit juice-containing products are not permitted for 1 week prior to dosing and throughout the study.

Phototoxic Potential: There are nonclinical data supporting a potential for phototoxicity, which has not been observed in clinical studies. Skin-related AEs include dry skin, pruritus, rash, and eczema. Based on the current limited clinical data, subjects should be instructed to take measures to avoid prolonged exposure to sunlight such as wearing sun screen and sun glasses, wearing protective clothing.

9.4.9 Treatment Compliance

The investigator, subinvestigator, or clinical research coordinator will instruct subjects to follow appropriate use of study drug and record the treatment compliance. The CRA will review the treatment compliance during site visits and at the completion of the study.

Treatment compliance (date of administration, dose, time of administration [at second administration on the day before the PK sampling day, first administration on the PK sampling day, and second administration on C1D15] as shown in Table 6) and meal time before and after the first administration on C0D1 and C1D15 will be collected and recorded on the CRF.

9.4.10 Drug Supplies and Accountability

The assigned pharmacist (or the designee) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator or subinvestigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The assigned pharmacist (or the designee) must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, unused study drugs that are returned by the subjects (unused study drug-1), unused study drugs that are shipped to site but not dispensed to subjects (unused study drug-2), and return of reconciled study drugs to the sponsor or (a sum of unused study drugs 1 and 2). This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) documentation of returns to the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a CRA or a representative of a health authority. Upon completion of unused drug accountability procedures and documentation of study drugs dispensing/return reconciliation log and documentation of returns to the sponsor by the assigned pharmacist (or designee), all unused study drugs and empty bottles are to be returned to the sponsor. Unused study drugs

that are returned from the site are hand-delivered to CRAs and to be returned to the sponsor's designated depot.

Drug accountability will be reviewed by the CRA during site visits and at the completion of the study, and throughout the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at Screening. Demography information includes Subject ID Number, date of written informed consent, date of birth (or age), sex, race, and ethnicity.

9.5.1.2 Pre-treatment Assessments

9.5.1.2.1 Medical History and Current Medical Conditions

Medical and surgical history and current medical conditions will be recorded at Screening. All medical history that is considered to have effects on safety, efficacy, or PK by the investigator or subinvestigator, and medical conditions that are identified at Screening must be noted on the CRF.

The following information on primary disease and its prior therapies will be collected at Screening and noted on the CRF.

(1)Primary disease
- Date of diagnosis
- Diagnosis
- Clinical staging at Screening (Ann Arbor staging) (Carbone, et al., 1971)
- B symptoms (unexplained fever more than 38 °C, drenching night sweats, unexplained weight loss of more than 10% of usual body weight over 6 months)
- CCI
-

(2)Prior therapies for primary disease
1)Chemotherapy (type of therapy, best overall response, name of therapy/drug, start dates, end dates)
2)Radiotherapy (site of radiation, deterioration after radiotherapy, first date of radiation, last date of radiation)
3)Autologous stem cell transplantation (with or without autologous stem cell transplantation, date of transplantation)

9.5.1.3 Efficacy Assessments

Tumor assessment will be performed by investigator or subinvestigator using "The Lugano Classification (CT-Based Response)" (Cheson, et al., 2014). Overall response and best overall response (BOR) (best response recorded at the designated visits during the study) will be assessed. Perform CT scans at Screening, every 8 weeks (starting at Cycle 1/Day 1) during Cycles 2-6, every 12 weeks starting at Cycle 7 (Cycle 7/Day 1) and beyond, and discontinuation.

A bone marrow aspiration or biopsy will be performed at screening for evaluation of bone marrow infiltration of tumor. After the study drug administration, perform bone marrow aspiration or biopsy if the result of screening was positive or unconfirmed and when to confirm CR as best of response or if clinically indicated.

Preliminary anti-tumor activity will be objective response rate (ORR) as defined by "The Lugano Classification (CT-Based Response)" (Cheson, et al., 2014). ORR is defined as the proportion of subjects who have a BOR of CR or PR.

Details of procedure of efficacy assessments will be provided in the Attachment "Overall response evaluation criteria" separately provided to each site.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

The sampling schedule of PK, pharmacogenomics, and other biomarker assessments of tazemetostat is shown in Table 6 and below.

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Plasma and urine concentrations of tazemetostat and plasma concentrations of its metabolite, ER–897387 will be measured to evaluate pharmacokinetics in all of the registered subjects. Blood samples and urine samples will be collected at the time points designated in Table 6. Detailed blood and urine sampling schedules for PK assessment are shown in Table 3 and Table 4, respectively. Procedures for collection, handling, and shipping for PK samples will be provided in a separate manual.

Plasma concentrations of tazemetostat and ER-897387 and urine tazemetostat concentrations will be measured by validated methods using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

For PK assessment, actual time and date of PK blood samplings, starting time of urine collection (defined as the time of first administration of study drug), ending time of urine collection, urine volume, and tween80 volume will be recorded in the CRF.

Table 3 Blood Sampling Schedule for Pharmacokinetic Assessment

Tazemetostat and ER-897387

Day	Sampling Time	Allowance (as a Target)
C0D1	Predose	Within 180 minutes before dosing
	0.5 hours postdose	±10 minutes
	1 hour postdose	±10 minutes
	2 hours postdose	±10 minutes
	4 hours postdose	±10 minutes
	6 hours postdose	±10 minutes
	8 hours postdose	±10 minutes
	10 hours postdose	±10 minutes
	12 hours postdose	±10 minutes
C0D2	24 hours postdose	±60 minutes
C0D3	48 hours postdose	±60 minutes
C0D4	72 hours postdose	±60 minutes
C1D3	Predose of first administration	Within 120 minutes before dosing
C1D8	Predose of first administration	Within 120 minutes before dosing
C1D15 (Blood sampling after first administration of study drug should be performed before second administration)	Predose of first administration	Within 60 minutes before dosing
	0.5 hours postdose of first administration	±10 minutes
	1 hour postdose of first administration	±10 minutes
	2 hours postdose of first administration	±10 minutes
	4 hours postdose of first administration	±10 minutes
	6 hours postdose of first administration	±10 minutes
	8 hours postdose of first administration	±10 minutes
	10 hours postdose of first administration	±10 minutes
	12 hours postdose of first administration	±10 minutes
C1D22	Predose of first administration	Within 120 minutes before dosing
C2D1	Predose of first administration	Within 120 minutes before dosing

C#D# = Cycle #/Day #.

Table 4 Urine Sampling Schedule for Pharmacokinetic Assessment

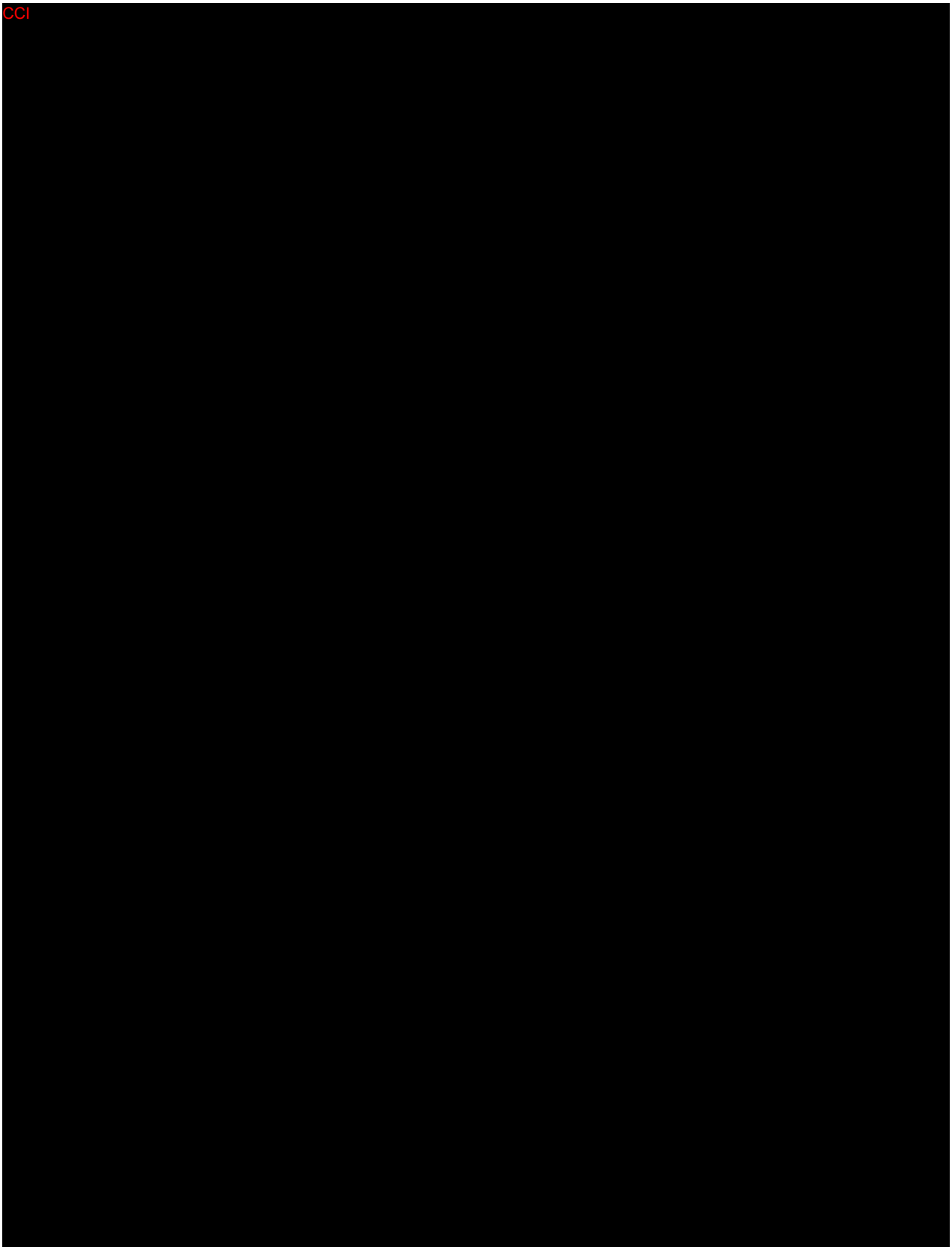
Tazemetostat

Day	Sampling Time	Allowance (as a Target)
C0D1	Predose (urine sampling)	From the time of wake-up to just before dosing
C0D2	0–24 hours postdose (urine collection)	–
C0D3	24–48 hours postdose (urine collection)	–
C0D4	48–72 hours postdose (urine collection)	–
C1D15	0–12 hours postdose of first administration (urine collection) (should be ended before second administration)	–

C#D# = Cycle #/Day #.

9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

CCI [redacted]


CCI

9.5.1.5 Safety Assessments

Safety assessments are shown in Table 6 (Schedule of Procedures/Assessments) and below.

Safety assessments include monitoring and recording all AEs, including all grading of Common Terminology Criteria for Adverse Events (CTCAE) v4.03, and SAEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; and periodic measurement of vital signs, ECGs, echocardiograms/MUGA scans to assess LVEF, ECOG-PS, and physical examinations.

9.5.1.5.1 Adverse Events and Events Associated with Special Situations

An AE is any untoward medical occurrence in a subject. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is tazemetostat.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease found after the time of informed consent, whether or not considered

related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)

- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the final observation visit. SAEs will be collected until the final observation visit. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure and its seriousness reported on the CRF.

Any laboratory abnormality considered to constitute an AE should be reported on the CRF. 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. It is the responsibility of the investigator or subinvestigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

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 more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator or subinvestigator considers as an AE should be reported as such.

All AEs must be followed until last visit for final observation or until resolution, whichever comes first. However, if other anticancer treatments should be implemented as soon as possible considering the deterioration of subject's physical condition, the last visit will be allowed within 30 days after the last dose (ie, before the start of other anticancer treatments). All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator or subinvestigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v 4.03. Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Assessing Relationship to Study Treatment

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

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

Classification of Causality

Yes (related)	A causal relationship between the study drug and the AE is a reasonable possibility.
No (not related)	A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An 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 adverse event 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
- 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 one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, occurrence of T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia or myeloid malignancy including myelodysplastic syndrome will be considered AEs of interest for this study. These events should be reported to the sponsor by completed SAE report (see Section 9.5.4.3.2) and considered as serious only if events meet the serious criteria. These AEs should be entered on the CRF even if the events do not meet serious criteria.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error (see Section 9.5.4.2 and 9.5.4.3). These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

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

The following hospitalizations are not considered to be SAEs because there is no "adverse event" 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 after 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

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 5. The Schedule of Procedures/Assessments (Table 6) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study. Clinical laboratory tests will be performed at each site.

Table 5 Clinical Laboratory Tests

Category	Parameters
Hematology	WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), RBC count, hemoglobin, hematocrit, and platelets Peripheral blood smear morphology assessment[a]
Chemistry	
Liver function tests	AST, ALT, ALP, total bilirubin, direct bilirubin
Renal function tests	Creatinine, BUN
Other	Total protein, albumin, globulin, LDH, creatine phosphokinase, amylase, uric acid, glucose, triglycerides, cholesterol, INR, sodium, chloride, potassium, calcium, phosphorus
Urinalysis	Protein (qualitative), glucose (qualitative), occult blood

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, INR = international normalized ratio, LDH = lactate dehydrogenase.

a: On Day 15 of each cycle, peripheral blood smear morphology assessment can be omitted at the discretion of the investigator or subinvestigator, if there was no concern for safety of the subject. If peripheral blood smear morphology assessment is confirmed to be abnormal (eg, blood cell dysplasia, appearance of blast cells) and myeloid malignancy including myelodysplastic syndrome is suspected, then conduct bone marrow aspirate with cytogenic testing (eg, G-banding).

For the management of clinically significant laboratory abnormalities, refer to the Tazemetostat Dose Reduction and Interruption Instructions in Table 2. A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the CRF.

9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic blood pressure [mmHg], pulse [beats per minute], temperature [in centigrade]), body weight (kg), and height (cm) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 6) by a validated method. Blood pressure and pulse will be measured after the subject has rested.

9.5.1.5.5 Physical Examinations

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 6). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the CRF.

9.5.1.5.6 Electrocardiograms

ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 6). Standardized, 12-lead ECG 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 are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. ECGs will be obtained after the subject has rested.

ECG parameters (heart rate, PR interval, QRS interval, QRS axis, QT interval, QTcF interval, RR Interval) will be recorded on the CRF. ECG findings (normal, abnormal not clinically significant, abnormal clinically significant) will also be recorded. QTc will be corrected using Fridericia method (QTcF).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the ECG abnormality will be recorded on the CRF.

9.5.1.5.7 Other Safety Assessments

9.5.1.5.7.1 Echocardiograms and MUGA scan

An echocardiogram or a MUGA scan (using technetium-99m-pertechnetate) to assess LVEF will be performed as designated in the Schedule of Procedures/Assessments (Table 6). Echocardiograms or MUGA scans and should be performed locally in accordance with the institution's standard practice. Either an echocardiogram or a MUGA scan which is used for an individual subject at baseline should be repeated for all subsequent LVEF assessments for that subject. LVEFs as assessed by the institution will be entered into the CRF.

9.5.1.5.7.2 ECOG PS

An ECOG performance status (ECOG-PS) should be done at each visit as designated in the Schedule of Procedures/Assessments (Table 6).

9.5.1.5.7.3 Pregnancy Test

An hCG or β-hCG test will be performed for women of childbearing potential. A serum or urine sample will be taken at visits as designated in the Schedule of Procedures/Assessments (Table 6).

All females will be considered to be of childbearing potential unless:

- Postmenopausal (amenorrheic for at least 12 consecutive months without other known or suspected cause)
- Sterilized surgically (bilateral tubal ligation at least 1 month before dosing, total hysterectomy, or bilateral oophorectomy at least 1 month before dosing).

9.5.1.5.7.4 Viral Tests

Hepatitis B surface (HBs) antigen, HBs antibody, hepatitis B virus core (HBc) antibody, hepatitis C virus (HCV) antibody, and HIV antibody tests will be performed at Screening. When subjects have HBs antibody or HBc antibody positive results, HBV-DNA tests will be performed.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments of the Study

Table 6 presents the schedule of procedures/assessments for the study.

Table 6 Schedule of Procedures/Assessments in Study E7438-J081-106 (EZH-106)

Phase	Pre-treatment		Treatment						Extension		Follow-up	
Period	Screening[a]	Baseline	Cycle 0	Cycle 1					Cycle 2 and later		Discontinuation	Final observation
Day	Within 28 days before administration	Within 3 days before administration	1	1[b]	3	8 (±1)	15 (±1)	22 (±1)	1 (±3)[c]	15 (±3)[n]	(+7)	30 days after last dosing (+7)[d]
Informed Consent	X								[X][m]			
Demographic data	X											
Inclusion/exclusion Criteria	X	X										
Medical history/Current medical condition	X											
Previous therapy	X											
Height	X											
Body weight	X	X		X		X	X	X	X	X	X	
Physical examination	X	X	X	X		X	X	X	X	X	X	X
Vital signs	X		X	X		X	X	X	X	X	X	X
ECOG-PS	X	X		X					X		X	
12-lead ECGs[e]	X		X	X			X		X	X	X	
Echocardiogram or MUGA scan[f]	X								[X]			
Pregnancy test (if applicable)	X										X	
Virus test	X											
Hematology[o]	X	X		X		X	X	X	X	X	X	X
Blood chemistry	X	X		X		X	X	X	X	X	X	X
Urinalysis	X	X		X		X	X	X	X	X	X	X
PK (blood)[g]			X		X	X	X	X	[X]			
PK (urine)[h]			X				X					
Tumor assessments (CT)[i]	X								[X]		X	
Bone marrow aspiration or biopsy[j]	X								[X]			
Tazemetostat administration[k]			X	Continuous 28-day cycle of tazemetostat twice daily.								
Archival tumor sample submission[l]	X											
Adverse events	From informed consent to final observation											

Concomitant drug/therapies	From informed consent to final observation

Note, [X]: In case to perform.

C#/D# = Cycle #/Day #, CR = complete response, CT = computed tomography, ECG = electrocardiogram, ECOG-PS = Eastern Cooperative Oncology Group-Performance Status, MUGA = multigated acquisition, PK = pharmacokinetics.

a: Screening assessments may be used as baseline assessments if performed within 3 days of the first administration of study drug.

b: To start C1D1 on Cycle 0 Days 4-9.

c: +1 day for C2D1.

d: When subject needs to receive other anti-tumor therapy due to deterioration of the disease within 30 days after the final study drug administration, final observation must be conducted before initiation of other anti-tumor therapy and the data within 7 days before next anti-tumor therapy can be used for final observation. .

e: 12-Lead ECGs on C0D1, C1D1, and C2D1 will be collected at pre-dose and 0.5-2 hours post dose of first administration.

f: Echocardiogram or MUGA scan will be performed at screening, every 16 weeks (ie, Day 1 of every 4 cycles [± 1 week]) from C2D1. Additional assessments may be performed if clinically indicated.

g: Blood samples for PK analyses of tazemetostat and metabolites will be collected in C0D1 at predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 hours postdose; C1D3 and C1D8 at predose of first administration; C1D15 at predose of first administration, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdose (postdose blood samples should be collected before the second administration of study drug); C1D22 and C2D1 predose of first administration.

h: Urine samples for PK analyses of tazemetostat will be collected in C0D1 at predose, 0-24, 24-48 and 48-72 hours postdose; C1D15 at 0-12 hours postdose of first administration.

i: The data of tumor assessments before informed consent within 28 days from study drug administration can be used as screening data if it meets the requirement of the protocol. Perform tumor assessment at screening, every 8 weeks [±1 week] (starting at Cycle 1 Day 1) during Cycles 2-6, every 12 weeks [± 1 week] starting at Cycle 7 and beyond, and discontinuation. The data within 28 days can be used as discontinuation data.

j: The data of bone marrow aspiration or biopsy before informed consent within 42 days from study drug administration can be used as screening data if it meets the requirement of the protocol. After the study drug dosing, perform bone marrow aspiration or biopsy if the result of screening was positive or unconfirmed and when to confirm CR as best of response or if clinically indicated.

k: Subjects should not take study drug before evaluations are performed (except tumor assessments and peripheral blood smear morphology assessment), unless specified.

l: Submit pre-study drug treated tumor sample to central laboratory before final observation, as far as possible.

m: Informed consent should be obtained before initiating the study or before entering the Extension Phase when Cycle 2 or later administrations will be continued.

n: In Cycle 13 or later, visits and assessments on Day 15 can be omitted at the discretion of the investigator or subinvestigator, if there was no concern for safety of the subject.

o: On Day 15 of each cycle, peripheral blood smear morphology assessment can be omitted at the discretion of the investigator or subinvestigator, if there was no concern for safety of the subject.

9.5.3 Appropriateness of Measurements

All clinical assessments were standard measurements commonly used in studies of malignant lymphoma.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, vital signs, body weight, ECGs, echocardiograms/MUGA scans, ECOG-PS, physical examinations, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

The investigator must report SAEs to the sponsor according to the following procedure:

(1)Initial report (when the investigator becomes aware of the event)
All SAEs regardless of the causal relationship to the study drug must be reported to the sponsor by telephone, fax, or email within 24 hours after obtaining the information. However, the following events must be reported immediately by telephone or other means:

- "Unexpected fatal events" (ie, treatment-related events are not listed in the investigator brochure or periodic safety report)
- The terms of treatment-related "unexpected fatal events" that are already reported are changed to the new term of "unexpected fatal events."

(2)Completed SAE report
SAE reports will be sent to the sponsor directly or by fax within 3 business days for fatal or life-threatening AEs and within 5 business days for other SAEs. The faxed report should be followed up by the original SAE report.

SAEs, regardless of causality assessment, must be collected through the final observation visit. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator or subinvestigator to be related to the study drug or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Attachment separately provided to each site.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator or subinvestigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded from the investigator to the sponsor 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.

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment, any partner's pregnancy of male subjects in which the estimated date of conception is either before the last visit or within 90 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment, 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 treatment.

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 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy or breastfeeding. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Attachment separately provided to each site. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported to the sponsor as soon as possible but no 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.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

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

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol

Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the CRF.

9.5.4.3.2 Reporting of Study-Specific Events

The occurrence of T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia or myeloid malignancy including myelodysplastic syndrome will be considered events of interest for this study. These events should be reported to the sponsor as soon as possible (no later than 1 business day) after obtaining the information. In addition, these events should be directly reported to the sponsor or by fax with completed SAE report promptly. The faxed report should be followed up by the original SAE report. Events of interest for this study must be followed to resolution or, if resolution is unlikely, to stabilization. Any event of interest to be related to the study drug or any protocol-required procedure judged by the investigator or subinvestigator should be reported to the sponsor regardless of the length of time that has passed since study completion. Events of interest should be considered as serious only if the events meet the serious criteria. These events should be entered on the CRF even if the events do not meet serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators, 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 the investigator or subinvestigator provides complete SAE information in the manner described above (Section 9.5.4.1).

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by 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.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 6).

The investigator or subinvestigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of primary reasons. Study disposition information will be collected on the CRF.

If the subject is regarded as DLT non-evaluable, he/she is not considered as DLT evaluable subjects. The sponsor can enroll additional subjects.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator, subinvestigator, or clinical research coordinator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator, subinvestigator, or clinical research coordinator will ask the subject whether he/she has received medical care by another physician 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 or subinvestigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's qualified compliance auditing team, which is an independent function from the study team responsible for the conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs. As defined by GCP, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection 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 data entered on the CRF. The investigator must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of the sponsor and should not be made available in any form to third parties without written permission from the sponsor, except for authorized representatives of the sponsor or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed after the study is completed and the database is locked. 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).

9.7.1 Statistical and Analytical Plans

The statistical analyses of the study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

- DLTs

9.7.1.1.2 SECONDARY ENDPOINTS

- Safety assessments (AEs, clinical laboratory tests, vital signs, body weight, 12-lead ECGs, echocardiograms/MUGA scans to assess LVEF, ECOG-PS, and physical examinations)
- PK parameters
- ORR of BOR

9.7.1.1.3 EXPLORATORY ENDPOINTS

CCI

[redacted]

9.7.1.2 Definitions of Analysis Sets

DLT Analysis Set will include all subjects who have completed treatment Cycles 0 and 1 without major protocol deviations with at least 75% of treatment compliance in Cycle 1 and were assessed for DLT, and subjects who have experienced DLT during Cycles 0 and 1. Subjects with less than 75% treatment compliance in Cycle 1 due to a reason other than toxicity up to Cycle 1/Day 28 will not be included in this analysis set.

Safety/Efficacy Analysis Set will include all subjects who received at least 1 administration of the study drug. This will be the analysis set for all safety and efficacy evaluations, as well as for demographic and baseline characteristics.

Pharmacokinetic Analysis Set will include all subjects who have received at least 1 administration of the study drug and had sufficient PK data to derive at least 1 PK parameter.

9.7.1.3 Subject Disposition

Subjects who signed informed consent, were registered in the study, and failed screening and the reason for screen failures will be presented. Subjects who were treated, were not treated, were ongoing, and discontinued from study treatment and the reason for discontinuation will be presented.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety/Efficacy Analysis Set will be summarized in whole or each disease (DLBCL, FL). Continuous demographic and baseline variables include age, height, and body weight; categorical variables include sex, age group, race, ethnics, ECOG-PS, and prior therapies for primary disease (chemotherapy, radiotherapy, and other therapies).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) preferred name. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started before the first dose of study drug and were continuing at the time of the first dose of study drug, or started on or after the date of the first dose of study drug up to the final observation. All prior and concomitant medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

BOR will be summarized in whole or each disease (DLBCL, FL). The assessment of the ORR (CR + PR) in subjects with B cell lymphomas will be based on "The Lugano Classification (CT-Based Response)" (Cheson, et al., 2014) response criteria.

ORR will be presented with corresponding 2-sided Clopper–Pearson exact 95% confidence intervals (CIs). This analysis will be performed on the Efficacy Analysis Set. If applicable,

a waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at post-baseline nadir.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The PK Analysis Set will be used for all PK analyses including summaries of plasma and urine concentrations of tazemetostat and plasma concentrations of ER-897387. Plasma concentration-time profiles of tazemetostat and ER-897387 will be plotted. Using non-compartmental analysis methods, plasma concentrations of tazemetostat and ER-897387 will be calculated to determine the PK parameters including C_{max}, t_{max}, AUC at the first administration (Cycle 0/Day 1) and repeated administration (Cycle 1/Day 15).

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

CCI

[redacted]

9.7.1.8 Safety Analyses

All tolerability analyses will be performed on the DLT Analysis Set. The Safety Analysis Set will be used for all other safety analyses.

9.7.1.8.1 EXTENT OF EXPOSURE

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

9.7.1.8.2 DOSE LIMITING TOXICITIES

The number and percentage of subjects with DLT will be calculated. DLT will also be summarized per type of toxicity.

9.7.1.8.3 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 lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- 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 are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized. The number (percentage) of subjects with TEAEs will be summarized 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 highest CTCAE grade.

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by highest CTCAE grade.

The number (percentage) of subjects with SAEs and TEAEs leading to death, discontinuation from study drug, study drug dose reduction or interruption will be summarized by SOC and PT. Subject data listings of all SAEs and AEs leading to death, discontinuation from study drug, study drug dose reduction or interruption will be provided.

9.7.1.8.4 Laboratory Values

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the last observation will be summarized by visit using descriptive statistics. Qualitative parameters will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and the last observation will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

CTCAE v4.03 will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). The details of TEMAV definitions will be provided in the SAP. TEMAVs will be summarized for overall visits.

9.7.1.8.5 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic blood pressure, pulse rate, body temperature) and body weight and changes from baseline will be presented by visit.

9.7.1.8.6 Electrocardiograms

ECG assessments will be performed at each visit. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit.

Shift tables will present changes from baseline in ECG parameters.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

9.7.1.8.7 OTHER SAFETY ANALYSES

Descriptive statistics for LVEF and LVEF changes from baseline using MUGA scans or echocardiograms will be calculated.

ECOG-PS will be summarized by the scale at each visit and by highest postbaseline scale.

9.7.2 Determination of Sample Size

The primary objective of this study is to investigate the tolerability of tazemetostat. Hence neither clinical hypothesis nor judgment criteria are set, the sample size is not based on statistical consideration. The sample size of 6 patients is considered adequate for the purpose to evaluate the tolerability of each cohort.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

10 REFERENCE LIST

Alimova I, Birks DK, Harris PS, Knipstein JA, Venkataraman S, Marquez VE, et al. Inhibition of EZH2 suppresses self-renewal and induces radiation sensitivity in atypical rhabdoid teratoid tumor cells. Neuro Oncol. 2013 Feb;15(2):149-60.

Arisan S, Buyuktuncer ED, Palavan-Unsal N, Caşkurlu T, Cakir OO, Ergenekon E. Increased expression of EZH2, a polycomb group protein, in bladder carcinoma. Urol Int. 2005;75(3):252-7.

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.

Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res. 1971 Nov;31(11):1860-1.

Chase A, Cross NC. Aberrations of EZH2 in cancer. Clin Cancer Res. 2011 May 1;17(9):2613-8.

Chihara D, Ito H, Matsuda T, Shibata A, Katsumi A, Nakamura S, et al. Differences in incidence and trends of haematological malignancies in Japan and the United States. Br J Haematol. 2014 Feb;164(4):536-45.

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.

Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002 Jan 24;346(4):235-42.

Copeland RA. Molecular pathways: protein methyltransferases in cancer. Clin Cancer Res. 2013 Dec 1;19(23):6344-50.

Deconinck E, Foussard C, Milpied N, Bertrand P, Michenet P, Cornillet-LeFebvre P, et al. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. Blood. 2005 May 15;105(10):3817-23.

Federico M, Luminari S, Dondi A, Tucci A, Vitolo U, Rigacci L, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. J Clin Oncol. 2013 Apr 20;31(12):1506-13.

Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010 Sep 20;28(27):4184-90.

Gyan E, Foussard C, Bertrand P, Michenet P, Le Gouill S, Berthou C, et al. High-dose therapy followed by autologous purged stem cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by the GOELAMS with final results after a median follow-up of 9 years. Blood. 2009 Jan 29;113(5):995-1001.

Kadoch C, Crabtree GR. Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. Cell. 2013 Mar 28;153(1):71-85.

Kadoch C, Copeland RA, Keilhack H. PRC2 and SWI/SNF Chromatin Remodeling Complexes in Health and Disease. Biochemistry. 2016 Mar 22;55(11):1600-14.

Kawano S, Grassian AR, Tsuda M, Knutson SK, Warholic NM, Kuznetsov G, et al. Preclinical Evidence of Anti-Tumor Activity Induced by EZH2 Inhibition in Human Models of Synovial Sarcoma. PLoS One. 2016 Jul 8;11(7):e0158888.

Kim KH, Roberts CW, Targeting EZH2 in cancer. Nat Med. 2016 Feb;22(2):128-34.

Knutson SK, Warholic NM, Wigle TJ, Klaus CR, Allain CJ, Raimondi A, et al. Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. Proc Natl Acad Sci U S A. 2013 May 7;110(19):7922-7.

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.

Ladetto M, De Marco F, Benedetti F, Vitolo U, Patti C, Rambaldi A, et al. Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. Blood. 2008 Apr 15;111(8):4004-13.

LaFave LM, Béguelin W, Koche R, Teater M, Spitzer B, Chramiec A, et al. Loss of BAP1 function leads to EZH2-dependent transformation. Nat Med. 2015 Nov;21(11):1344-9.

Margueron R, Reinberg D. The Polycomb complex PRC2 and its mark in life. Nature. 2011 Jan 20;469(7330):343-9.

Morin RD, Johnson NA, Severson TM, Mungall AJ, An J, Goya R, et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. Nat Genet. 2010 Feb;42(2):181-5.

Ntziachristos P, Tsirigos A, Van Vlierberghe P, Nedjic J, Trimarchi T, Flaherty MS, et al. Genetic inactivation of the polycomb repressive complex 2 in T cell acute lymphoblastic leukemia. Nat Med. 2012 Feb 6;18(2):298-301.

Ohmachi K, Ando K, Ogura M, Uchida T, Itoh K, Kubota N, et al. Multicenter phase II study of bendamustine for relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma. Cancer Sci. 2010 Sep;101(9):2059-64.

Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995 Dec 7;333(23):1540-5.

Plass C, Pfister SM, Lindroth AM, Bogatyrova O, Claus R, Lichter P. Mutations in regulators of the epigenome and their connections to global chromatin patterns in cancer. Nat Rev Genet. 2013 Nov;14(11):765-80.

Shen JK, Cote GM, Gao Y, Choy E, Mankin HJ, Hornicek FJ, et al. Targeting EZH2-mediated methylation of H3K27 inhibits proliferation and migration of Synovial Sarcoma in vitro. Sci Rep. 2016 Apr 29;6:25239.

Sneeringer CJ, Scott MP, Kuntz KW, Knutson SK, Pollock RM, Richon VM, Copeland RA. Coordinated activities of wild-type plus mutant EZH2 drive tumor-associated hypertrimethylation of lysine 27 on histone H3 (H3K27) in human B-cell lymphomas. Proc Natl Acad Sci U S A. 2010 Dec 7;107(49):20980-5.

Tobinai K, Watanabe T, Ogura M, Morishima Y, Ogawa Y, Ishizawa K, et al. Phase II study of oral fludarabine phosphate in relapsed indolent B-Cell non-Hodgkin's lymphoma. J Clin Oncol. 2006 Jan 1;24(1):174-80.

Varambally S, Dhanasekaran SM, Zhou M, Barrette TR, Kumar-Sinha C, Sanda MG, et al. The polycomb group protein EZH2 is involved in progression of prostate cancer. Nature. 2002 Oct 10;419(6907):624-9.

Wilson BG, Wang X, Shen X, McKenna ES, Lemieux ME, Cho YJ, et al. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. Cancer Cell. 2010 Oct 19;18(4):316-28.

Yoo KH, Hennighausen L. EZH2 methyltransferase and H3K27 methylation in breast cancer. Int J Biol Sci. 2012;8(1):59-65.

Zingg D, Debbache J, Schaefer SM, Tuncer E, Frommel SC, Cheng P, et al. The epigenetic modifier EZH2 controls melanoma growth and metastasis through silencing of distinct tumour suppressors. Nat Commun. 2015 Jan 22;6:6051.

General incorporated association, The Japanese Society of Hematology. Guideline for management of hematopoietic tumor, 2013.

CTCAE Reference

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_2010-06-1 4_QuickReference_8.5x11.pdf.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs. 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 the investigator or subinvestigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor and the IRB for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to the IRB. In these cases, the sponsor may be required to send a letter to the head of the medical institution detailing such changes.

11.2 Adherence to the Protocol

The investigator or subinvestigator will conduct the study in strict accordance with the protocol.

11.3 Monitoring Procedures

The CRA will maintain contact with the investigator or subinvestigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The head of the medical institution will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP 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 study protocol and data accuracy in accordance with GCP. All records at the site are subject to inspection by the local auditing agency and to IRB review.

In accordance with GCP, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, EEGs, pulmonary function tests, microfiche and photographic negatives) regardless of how these images are stored, including microfiche and photographic negatives

- Pain, quality of life, or 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 and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For items other than the following items from 1 to 8, the data on medical records will be source data, but they can also be considered source data if appropriate records are available:

(1)For items from below, the data recorded directly on the CRF are source data:

- Demography–race, ethnicity
- Study drug administration (reason for treatment discontinuation, reason for dose modification, or others)
- Reasons and dates for prior and concomitant therapy (including medications and therapies)
- Discontinuation (reason for discontinuation, or others)
- Sampling date and time for PK analysis, administration date and time, meal date and time
- Sampling date for clinical laboratory tests
- AEs (grade, relationship to study drug, outcome or others)
- Tumor assessment (target lesions, non-target lesions, sites, tumor diameter, new lesions)

- Comments

(2)Source data of informed consent

- Signed ICF

(3)Source data of relevant tests

- Clinical laboratory test chart including electronic data

(4)Source data of histopathology

- Histopathology chart, patient referral document including electronic data

(5)Source data of tumor assessment

- Films including electronic data
- Note that findings and measurement recorded on the CRF are source data.

(6)Source data of ECGs

- ECG charts including electronic data
- Normal or abnormal findings recorded on the CRF

(7)Record of sample shipment to external vender

- Sample shipment slip

(8)Source data of subject registration (subject eligibility determination)

- Subject eligibility correspondence, email of subject registration correspondence (including printed email) or facsimile form

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator, the head of the medical institution or the designated representative is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, ICFs, and IRB correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 3 years after the approval of a marketing application and until there are no pending or contemplated marketing applications or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product, whichever occurs later.

It is requested that at the completion of the required retention period the medical institution contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 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 SOPs to evaluate compliance with the GCP and all applicable local regulations. Government regulatory authority may request an inspection during the study or after its completion.

11.8 Handling of Study Drug

All study drug will be supplied to the assigned pharmacist (or designee) 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 labels. The assigned pharmacist (or designee) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The assigned pharmacist (or designee) 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 study, the assigned pharmacist (or designee) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor, if required.

11.9 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 head of the medical institution and the sponsor.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator’s staff, and the IRB 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 used 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 either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor and the head of the medical institution.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor and the head of the medical institution.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigator/the head of the medical institution and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided 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 study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/the head of medical institution should promptly inform the sponsor and the IRB and provide a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

Protocol Amendment

Study Protocol Title: A Phase 1 Study of Tazemetostat in Patients With Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma

Study Protocol Number: E7438-J081-106 (EZH-106)

Protocol Pages	Protocol V1.0, 20 Sep 2016	Protocol V2.0, 21 Oct 2016	Rationale
Footer in all pages	Date: 20 Sep 2016	Date: 21 Oct 2016	Changed with the protocol updated.
1	**Approval Date:** V1.0, 20 Sep 2016	**Approval Date:** V2.0, 21 Oct 2016	Changed with the protocol updated.
2 26	**9.1.1.2 Treatment Phase** Considering visit schedule and safety, subjects will be hospitalized from Cycle 0 Day 1 (C0D1) to Cycle 1 Day 15 (C1D15), in principle.	**9.1.1.2 Treatment Phase** Considering visit schedule and safety, subjects will be hospitalized from Cycle 0/Day 1 (C0D1) to Cycle 1/Day 15 (C1D15). Based on the thorough evaluation of the data obtained on C1D15 and all safety data available, the investigator or subinvestigator will determine whether subjects can be treated on an outpatient basis. When subjects are considered to require extended hospitalization to ensure subject safety, they will be hospitalized from C1D15 onwards.	To allow subjects to continue hospitalization after C1D15, considering the safety of subjects.
27	**9.1.1.3 Extension Phase** The Extension Phase consists of Cycle 2 of 28 days and later for tazemetostat BID oral administration on a	**9.1.1.3 Extension Phase** The Extension Phase consists of Cycle 2 of 28 days and later for tazemetostat BID oral administration on a	To clarify that informed consent should be

Protocol Pages	Protocol V1.0, 20 Sep 2016	Protocol V2.0, 21 Oct 2016	Rationale
	continuous basis and lasts until discontinuation of study drug.	continuous basis and lasts until discontinuation of study drug. Informed consent should be obtained before initiating the study or before entering the Extension Phase when Cycle 2 or later administrations will be continued.	obtained when Cycle 2 or later administrations will be continued.
3 27	**9.1.2 Dose-Limiting Toxicities (DLT)** Three subjects will be enrolled and ensure that they are evaluable for dose-limiting toxicities (DLTs) at the end of Cycle 1 of the cohort. When a DLT is observed in 0 to 2 of 3 subjects at a given dose level, 3 additional subjects would be treated at the same dose level. When 3 subjects at a given dose level experience DLTs, the enrollment in the cohort will be discontinued and the lower dose level of tazemetostat cohort will be considered jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor can be obtained if needed.	**9.1.2 Dose-Limiting Toxicities (DLT)** Three subjects will be enrolled and ensure that they are evaluable for dose-limiting toxicities (DLTs) at the end of Cycle 1 of the cohort. When a DLT is observed in 0 or 1 of 3 subjects at a given dose level, 3 additional subjects would be treated at the same dose level. When 2 of 3 subjects at a given dose level experience DLTs, enrollment of additional subjects will be discussed jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor should be also obtained. When additional subjects are to be enrolled, they will be monitored individually. When no DLTs are observed, up to 3 additional subjects will be enrolled. When no additional subjects are accrued or 3 subjects in total experienced DLTs, the enrollment in the cohort will be discontinued and the lower dose level of tazemetostat cohort will be considered jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor can be obtained if needed.	To clarify the procedure of enrollment of additional subjects to avoid more than 3 subjects to have DLTs when 2 of 3 subjects at a given dose level experience DLTs.

<table>
<tr><th>Protocol Pages</th><th>Protocol V1.0, 20 Sep 2016</th><th>Protocol V2.0, 21 Oct 2016</th><th>Rationale</th></tr>
<tr><td>3
27</td><td>9.1.2 Dose-Limiting Toxicities (DLT)
The tolerability of tazemetostat will be determined based on the incidence of DLTs in Cycles 0 and 1. If DLTs occur in 0 to 2 of 6 subjects, this dose level is considered tolerable.</td><td>9.1.2 Dose-Limiting Toxicities (DLT)
The tolerability of tazemetostat will be determined based on the incidence of DLTs in Cycles 0 and 1. If DLTs occur in 0 or 1 of 6 subjects, this dose level is considered tolerable. If DLTs occurs in 2 of 6 subjects, the tolerability of this dose level will be determined jointly by the investigator and sponsor. The opinion of Independent Data Monitoring Advisor should be also obtained.</td><td>To clarify that the tolerability of the dose level will be determined with discussion if DLTs occurs in 2 of 6 subjects.</td></tr>
<tr><td>3
27</td><td>9.1.2 Dose-Limiting Toxicities (DLT)
Table 1 Dose-Limiting Toxicities (DLT)
<table>
<tr><th>Toxicity Category</th><th>Toxicity/CTCAE Grade</th></tr>
<tr><td>Hematological Toxicity</td><td>• Grade 4 neutropenia for > 7 days
• ≥ Grade 3 febrile neutropenia
• Grade 4 thrombocytopenia
• Grade 3 thrombocytopenia with bleeding or requiring platelet transfusion</td></tr>
<tr><td>Non-hematological Toxicity</td><td>• ≥ Grade 3 nausea, vomiting, or diarrhea that persists > 7 days despite maximal medical therapy
• ≥ Grade 3 non-hematological laboratory abnormalities with clinical symptoms that persists > 7 days
• Other Grade 3 toxicity lasting > 7 days or Grade 4 non-hematological toxicity of any duration</td></tr>
<tr><td>Medication compliance</td><td>• Failure to administer ≥ 75% (≥ 42/56 doses) of the planned administration number of study drug in Cycle 1 as a result of treatment-related toxicity</td></tr>
</table></td><td>9.1.2 Dose-Limiting Toxicities (DLT)
Table 1 Dose-Limiting Toxicities (DLT)
<table>
<tr><th>Toxicity Category</th><th>Toxicity/CTCAE Grade</th></tr>
<tr><td>Hematological Toxicity</td><td>• Grade 4 neutropenia for > 7 days or neutropenia requiring hematopoietic growth factors
• ≥ Grade 3 febrile neutropenia
• Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with bleeding, or thrombocytopenia requiring platelet transfusion
• Grade 4 anemia or anemia requiring erythrocyte transfusion</td></tr>
<tr><td>Non-hematological Toxicity</td><td>• ≥ Grade 3 nausea, vomiting, or diarrhea that persists > 7 days despite maximal medical therapy
• ≥ Grade 3 non-hematological laboratory abnormalities with clinical symptoms that persists > 7 days
• Other Grade 3 toxicity lasting > 7 days or Grade 4 non-hematological toxicity of any duration</td></tr>
<tr><td>Medication compliance</td><td>• Failure to administer ≥ 75% (≥ 42/56 doses) of the planned administration number of study drug in Cycle 1 as a result of treatment-related toxicity</td></tr>
</table></td><td>Added DLTs.</td></tr>
</table>

Protocol Pages	Protocol V1.0, 20 Sep 2016	Protocol V2.0, 21 Oct 2016	Rationale
4 28	**9.3.1 Inclusion Criteria** (3)Patient who had previous therapy with systemic chemotherapy and/or antibody therapy.	**9.3.1 Inclusion Criteria** (3)Patient who had previous therapy with systemic chemotherapy and/or antibody therapy and for which no standard therapy exists.	To clarify that the patients for which no standard therapy exists should be enrolled.
5 29	**9.3.2 Exclusion Criteria** (17)Women of childbearing potential or man of impregnate potential who don't agree that both the patient and his/her partner will use a medically effective method for contraception (as below) for periods from before informed consent to during the clinical study and 30 days later (for males 90 days later) from last administration of study drug. Note: Condom, contraceptive sponge, foam, jelly, diaphragm, intrauterine device (IUD), or use of oral, transdermal, or transvaginal contraception at least 30 days before starting the study treatment (*Approved drugs or certified medical devices in Japan, **Non-approved drugs or certified medical devices in Japan)	**9.3.2 Exclusion Criteria** (17)Women of childbearing potential or man of impregnate potential who don't agree that both the patient and his/her partner will use a medically effective method for contraception (as below) for periods from before informed consent to during the clinical study and 30 days later (for males 90 days later) from last administration of study drug. Note: Condom*, contraceptive sponge**, foam**, jelly**, diaphragm*, intrauterine device (IUD)*, or use of oral contraception* at least 30 days before starting the study treatment (*Approved drugs or certified medical devices in Japan, **Non-approved drugs or certified medical devices in Japan)	To clarify whether the medically effective methods for contraception are approved or certified.

<table>
<tr><th>Protocol Pages</th><th>Protocol V1.0, 20 Sep 2016</th><th>Protocol V2.0, 21 Oct 2016</th><th>Rationale</th></tr>
<tr><td>36</td><td>

9.5.1.4.1 Pharmacokinetic Assessments

Table 3 Blood Sampling Schedule for Pharmacokinetic Assessment
Tazemetostat and ER-897387

Day	Sampling Time	Allowance (as a Target)
C0D1	Predose	Within 60 minutes before dosing
	0.5 hours postdose	±10 minutes
	1 hour postdose	±10 minutes
	2 hours postdose	±10 minutes
	4 hours postdose	±10 minutes
	6 hours postdose	±10 minutes
	8 hours postdose	±10 minutes
	10 hours postdose	±10 minutes
	12 hours postdose	±10 minutes
C0D2	24 hours postdose	±60 minutes
C0D3	48 hours postdose	±60 minutes
C0D4	72 hours postdose	±60 minutes
C1D3	Predose of first administration	Within 60 minutes before dosing
C1D8	Predose of first administration	Within 60 minutes before dosing
C1D15	Predose of first administration	Within 60 minutes before dosing
(Blood sampling after first administration should be performed before second administration)	0.5 hours postdose of first administration	±10 minutes
	1 hour postdose of first administration	±10 minutes
	2 hours postdose of first administration	±10 minutes
	4 hours postdose of first administration	±10 minutes
	6 hours postdose of first administration	±10 minutes
	8 hours postdose of first administration	±10 minutes
	10 hours postdose of first administration	±10 minutes
	12 hours postdose of first administration	±10 minutes
C1D22	Predose of first administration	Within 60 minutes before dosing
C2D1	Predose of first administration	Within 60 minutes before dosing

C#D# = Cycle #/Day #.

</td><td>

9.5.1.4.1 Pharmacokinetic Assessments

Table 3 Blood Sampling Schedule for Pharmacokinetic Assessment
Tazemetostat and ER-897387

Day	Sampling Time	Allowance (as a Target)
C0D1	Predose	Within 180 minutes before dosing
	0.5 hours postdose	±10 minutes
	1 hour postdose	±10 minutes
	2 hours postdose	±10 minutes
	4 hours postdose	±10 minutes
	6 hours postdose	±10 minutes
	8 hours postdose	±10 minutes
	10 hours postdose	±10 minutes
	12 hours postdose	±10 minutes
C0D2	24 hours postdose	±60 minutes
C0D3	48 hours postdose	±60 minutes
C0D4	72 hours postdose	±60 minutes
C1D3	Predose of first administration	Within 120 minutes before dosing
C1D8	Predose of first administration	Within 120 minutes before dosing
C1D15	Predose of first administration	Within 60 minutes before dosing
(Blood sampling after first administration should be performed before second administration)	0.5 hours postdose of first administration	±10 minutes
	1 hour postdose of first administration	±10 minutes
	2 hours postdose of first administration	±10 minutes
	4 hours postdose of first administration	±10 minutes
	6 hours postdose of first administration	±10 minutes
	8 hours postdose of first administration	±10 minutes
	10 hours postdose of first administration	±10 minutes
	12 hours postdose of first administration	±10 minutes
C1D22	Predose of first administration	Within 120 minutes before dosing
C2D1	Predose of first administration	Within 120 minutes before dosing

C#D# = Cycle #/Day #.

</td><td>To extend allowance of sampling time considering feasibility of the blood sampling schedule.</td></tr>
</table>

Protocol Pages	Protocol V1.0, 20 Sep 2016	Protocol V2.0, 21 Oct 2016	Rationale
37	**9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, And Other Biomarker Assessments** Details of sample collection, handling, and shipping will be provided in a separate manual. Sample security, use, retention and subject privacy are provided below. **Security of the Samples, Use of the Samples, Retention of the Samples** Sample processing, for example DNA extraction, 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. 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 destroyed at the finalization of the analytical report at the central laboratory.	**9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, And Other Biomarker Assessments** Sample collection, timing, storage, security, use, retention and subject privacy are provided below. Details of sample collection, handling, and shipping will be provided in a separate manual. **Sample Collection, Timing and Storage** Five FFPE slides (5 µm) from the pre-study preserved tumor sample will be obtained according to the handling procedure at the site. The slides should be stored at room temperature until the sponsor's designated vender collects for sample shipping. **Security of the Samples, Use of the Samples, Retention of the Samples** Sample processing, for example DNA extraction, 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. 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.	To clarify the sample collection, timing, and storage method and period.

Protocol Pages	Protocol V1.0, 20 Sep 2016	Protocol V2.0, 21 Oct 2016	Rationale
		Samples will be stored until the finalization of the analytical report at the central laboratory. At the end of the storage period, samples will be destroyed.	
42	**9.5.1.5.7.3 Pregnancy Test** An hCG or β-hCG test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. A serum or urine sample will be taken at visits as designated in the Schedule of Procedures/Assessments (Table 6).	**9.5.1.5.7.3 Pregnancy Test** An hCG or β-hCG test will be performed for women of childbearing potential. A serum or urine sample will be taken at visits as designated in the Schedule of Procedures/Assessments (Table 6). All females will be considered to be of childbearing potential unless: - Postmenopausal (amenorrheic for at least 12 consecutive months without other known or suspected cause) - Sterilized surgically (bilateral tubal ligation at least 1 month before dosing, total hysterectomy, or bilateral oophorectomy at least 1 month before dosing).	To clarify the definition of women of childbearing potential and postmenopausal women.

<table>
<tr><th>Protocol Pages</th><th>Protocol V1.0, 20 Sep 2016</th><th>Protocol V2.0, 21 Oct 2016</th><th>Rationale</th></tr>
<tr><td>43</td><td>

9.5.2.1 Schedule of Procedures/Assessments of the Study

Table 6 Schedule of Procedures/Assessments in Study E7438-J081-106 (EZH-106)

<table>
<tr><th>Phase</th><th colspan="2">Pre-treatment</th><th colspan="7">Treatment</th><th colspan="2">Extension</th><th colspan="2">Follow-up</th></tr>
<tr><th>Period</th><th>Screening[a]</th><th>Baseline</th><th>Cycle 0</th><th colspan="5">Cycle 1</th><th colspan="2">Cycle 2 and later</th><th>Discontinuation</th><th>Final observation</th></tr>
<tr><th>Day</th><td>Within 28 days before admin.</td><td>Within 3 days before admin.</td><td>1</td><td>1[b]</td><td>3</td><td>8 (±1)</td><td>15 (±1)</td><td>22 (±1)</td><td>1 (±3)[c]</td><td>15 (±3)</td><td>(+7)</td><td>30 days after last dosing (+7)[d]</td></tr>
<tr><td>Informed Consent</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

</td><td>

9.5.2.1 Schedule of Procedures/Assessments of the Study

Table 6 Schedule of Procedures/Assessments in Study E7438-J081-106 (EZH-106)

<table>
<tr><th>Phase</th><th colspan="2">Pre-treatment</th><th colspan="7">Treatment</th><th colspan="2">Extension</th><th colspan="2">Follow-up</th></tr>
<tr><th>Period</th><th>Screening[a]</th><th>Baseline</th><th>Cycle 0</th><th colspan="5">Cycle 1</th><th colspan="2">Cycle 2 and later</th><th>Discontinuation</th><th>Final observation</th></tr>
<tr><th>Day</th><td>Within 28 days before admin.</td><td>Within 3 days before admin.</td><td>1</td><td>1[b]</td><td>3</td><td>8 (±1)</td><td>15 (±1)</td><td>22 (±1)</td><td>1 (±3)[c]</td><td>15 (±3)</td><td>(+7)</td><td>30 days after last dosing (+7)[d]</td></tr>
<tr><td>Informed Consent</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>[X][m]</td><td></td><td></td><td></td></tr>
</table>

m: Informed consent should be obtained before initiating the study or before entering the Extension Phase when Cycle 2 or later administrations will be continued.

</td><td>To stipulate that informed consent for entering the Extension Phase will be obtained if subjects enter the Extension Phase.</td></tr>
</table>

Protocol Pages	Protocol V1.0, 20 Sep 2016	Protocol V2.0, 21 Oct 2016	Rationale
45	**9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations** **9.5.4.1 Reporting of Serious Adverse Events** The investigator must report SAEs to the sponsor according to the following procedure: (1)Initial report (when the investigator becomes aware of the event) All SAEs regardless of the causal relationship to the study drug must be reported to the sponsor by telephone, fax, or email as soon as possible but no later than 1 business day after obtaining the information. However, the following events must be reported within 24 hours (no later than 1 calendar day) by telephone or other means: • "Unexpected fatal events" (ie, treatment-related events are not listed in the investigator brochure or periodic safety report) • The terms of treatment-related "unexpected fatal events" that are already reported are changed to the new term of "unexpected fatal events."	**9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations** **9.5.4.1 Reporting of Serious Adverse Events** The investigator must report SAEs to the sponsor according to the following procedure: (1)Initial report (when the investigator becomes aware of the event) All SAEs regardless of the causal relationship to the study drug must be reported to the sponsor by telephone, fax, or email within 24 hours after obtaining the information. However, the following events must be reported immediately by telephone or other means: • "Unexpected fatal events" (ie, treatment-related events are not listed in the investigator brochure or periodic safety report) • The terms of treatment-related "unexpected fatal events" that are already reported are changed to the new term of "unexpected fatal events."	To stipulate that all SAEs must be reported within 24 hours after obtaining the information.

Protocol Amendment

Study Protocol Title: A Phase 1 Study of Tazemetostat in Patients With Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma

Study Protocol Number: E7438-J081-106 (EZH-106)

Protocol Pages	Protocol V2.0, 21 Oct 2016	Protocol V3.0, 15 Dec 2016	Rationale
Footer in all pages	Date: 21 Oct 2016	Date: 15 Dec 2016	Changed with the protocol updated.
1	**Approval Date:** V2.0, 21 Oct 2016	**Approval Date:** V3.0, 15 Dec 2016	Changed with the protocol updated.
3 27	**9.1.1.4 Follow-Up Phase** The Follow-up Phase consists of the evaluation at discontinuation which is performed within 7 days after final administration of tazemetostat and a final observation which occurs 30 days (+7 days) after final administration or initiation of a new anti-tumor therapy, whichever occurs early.	**9.1.1.4 Follow-Up Phase** The Follow-up Phase consists of the evaluation at discontinuation which is performed within 7 days after the discontinuation of the study and a final observation which occurs 30 days (+7 days) after final administration of tazemetostat or initiation of a new anti-tumor therapy, whichever occurs early.	Revised the timing of the evaluation at discontinuation to be performed appropriately.

Protocol Pages	Protocol V2.0, 21 Oct 2016	Protocol V3.0, 15 Dec 2016	Rationale
6 31	**9.4.1 Treatment Administered** Tazemetostat 800 mg will be administered orally by single dose in Cycle 0/Day 1 (C0D1) and continuous BID (1600 mg total daily dose, no less than 8 hours between doses except C1D15 that requires 12 hours or more) in Cycle 1 and later, in a fasted state on C0D1 and at the first administration of C1D15 defined as either ≥2 hours before or ≥2 hours after a meal (only water is allowed).	**9.4.1 Treatment Administered** Tazemetostat 800 mg will be administered orally by single dose in Cycle 0/Day 1 (C0D1) and continuous BID (1600 mg total daily dose, no less than 8 hours between doses except C1D15 that requires 12 hours or more) in Cycle 1 and later, in a fasted state on C0D1 and at the first administration of C1D15 defined as ≥2 hours before and ≥2 hours after a meal (only water is allowed).	Revised the definition of fasted state appropriately.
7 35	**9.4.7.1 Prohibited Concomitant Therapies and Drugs** (2)Cycles 0 and 1 • Any antacids or other drugs known to raise gastric pH (C0D1 and C1D15 only). These drugs should be administered ≥2 hours before study drug administration or ≥2 hours after study drug administration if used in Cycle 1.	**9.4.7.1 Prohibited Concomitant Therapies and Drugs** (2)Cycles 0 and 1 • Any antacids or other drugs known to raise gastric pH (C0D1 and C1D15 only). These drugs should be administered ≥2 hours before study drug administration and ≥2 hours after study drug administration if used in Cycle 1.	Revised appropriately the available timing of receiving the concomitant drug.

Protocol Amendment

Study Protocol Title: A Phase 1 Study of Tazemetostat in Patients With Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma

Study Protocol Number: E7438-J081-106 (EZH-106)

Protocol Pages	Protocol V3.0, 15 Dec 2016	Protocol V4.0, 23 Mar 2018	Rationale
Footer in all pages	Date: 15 Dec 2016	Date: 23 Mar 2018	Changed with the protocol updated.
1	**Approval Date:** V3.0, 15 Dec 2016	**Approval Date:** V4.0, 23 Mar 2018	Changed with the protocol updated.
2	**Investigators** To be determined.	**Investigators** See the Attachment separately provided to each site.	Updated the reference of the investigators.
45 46	**9.5.2.1 Schedule of Procedures/Assessments of the Study** **Table 6, Cycle 2 and later, Day 15 (±3)** Footnote: (Not included)	**9.5.2.1 Schedule of Procedures/Assessments of the Study** **Table 6, Cycle 2 and later, Day 15 (±3)[n]** Footnote: n: In Cycle 13 or later, visits and assessments on Day 15 can be omitted at the discretion of the investigator or subinvestigator, if there was no concern for safety of the subject.	To reduce the burden on subjects.

Protocol Amendment

Study Protocol Title: A Phase 1 Study of Tazemetostat in Patients With Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma

Study Protocol Number: E7438-J081-106 (EZH-106)

Protocol Pages	Protocol V4.0, 23 Mar 2018	Protocol V5.0, 18 Oct 2018	Rationale
Footer in all pages	Date: 23 Mar 2018	Date: 18 Oct 2018	Changed with the protocol updated.
1	**Approval Date:** V4.0, 23 Mar 2018	**Approval Date:** V5.0, 18 Oct 2018	Changed with the protocol updated.
6	**Tazemetostat Dose Reduction and Interruption Instructions** (Not included)	**Tazemetostat Dose Reduction and Interruption Instructions** If a subject experiences myeloid malignancy including myelodysplastic syndrome, study treatment should be interrupted and restart (including dose modification)/discontinuation of study treatment should be discussed with the sponsor. If a subject experiences T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia, study treatment should be discontinued and other actions should be discussed with the sponsor.	Updated based on the latest protocol text provided by Epizyme to ensure the safety of subjects.

Protocol Pages	Protocol V4.0, 23 Mar 2018	Protocol V5.0, 18 Oct 2018	Rationale
14	**4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS** T-ALL: T-cell acute lymphoblastic leukemia	**4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS** (Deleted)	–
32	**9.3.3.1 Discontinuation Criteria by Subject** If a subject meet any of the following criteria, the investigator or subinvestigator will discontinue treating the subject with study treatment.	**9.3.3.1 Discontinuation Criteria by Subject** If a subject meet any of the following criteria, the investigator or subinvestigator will discontinue treating the subject with study treatment. If a subject experiences myeloid malignancy including myelodysplastic syndrome, study treatment should be interrupted and restart (including dose modification)/discontinuation of study treatment should be discussed with the sponsor. If a subject experiences T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia, study treatment should be discontinued and other actions should be discussed with the sponsor. (8)Subject experiences T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia.	Updated based on the latest protocol text provided by Epizyme to ensure the safety of subjects.
33	**9.4.1.1 Tazemetostat Dose Reduction and Interruption Instructions** **9.4.1.1.2 Cycle 2 And Later** (Not included)	**9.4.1.1 Tazemetostat Dose Reduction and Interruption Instructions** **9.4.1.1.2 Cycle 2 And Later** If a subject experiences myeloid malignancy including myelodysplastic syndrome, study treatment should be interrupted and restart (including dose modification)/discontinuation of study treatment should be discussed with the sponsor. If a subject	Updated based on the latest protocol text provided by Epizyme to ensure the safety of subjects.

Protocol Pages	Protocol V4.0, 23 Mar 2018	Protocol V5.0, 18 Oct 2018	Rationale
		experiences T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia, study treatment should be discontinued and other actions should be discussed with the sponsor.	
43	**9.5.1.5.2 Serious Adverse Events And Events Associated With Special Situations** For this study, occurrence of lymphoblastic lymphoma/T-ALL and abnormal bone formation* will be considered AEs of interest for this study. These events should be reported to the sponsor by completed SAE report (see Section 9.5.4.3.2) and considered as serious only if events meet the serious criteria. These AEs should be entered on the CRF even if the events do not meet serious criteria. *Definition of signs and symptoms for abnormal bone formation: unexplained localized bone pain, neuropathy, nerve compression and symptomatic skeletal events. Symptomatic skeletal events are defined as pathological fracture not related to metastases, spinal cord compression, or external beam radiotherapy or surgery to the bone.	**9.5.1.5.2 Serious Adverse Events And Events Associated With Special Situations** For this study, occurrence of T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia or myeloid malignancy including myelodysplastic syndrome will be considered AEs of interest for this study. These events should be reported to the sponsor by completed SAE report (see Section 9.5.4.3.2) and considered as serious only if events meet the serious criteria. These AEs should be entered on the CRF even if the events do not meet serious criteria.	Updated based on the latest protocol text provided by Epizyme to ensure the safety of subjects.

Protocol Pages	Protocol V4.0, 23 Mar 2018	Protocol V5.0, 18 Oct 2018	Rationale
44	**9.5.1.5.3 Laboratory Measurements** **Table 5 Clinical Laboratory Tests** Hematology: (Not included)	**9.5.1.5.3 Laboratory Measurements** **Table 5 Clinical Laboratory Tests** Hematology: Peripheral blood smear morphology assessment[a] a: On Day 15 of each cycle, peripheral blood smear morphology assessment can be omitted at the discretion of the investigator or subinvestigator, if there was no concern for safety of the subject. If peripheral blood smear morphology assessment is confirmed to be abnormal (eg, blood cell dysplasia, appearance of blast cells) and myeloid malignancy including myelodysplastic syndrome is suspected, then conduct bone marrow aspirate with cytogenic testing (eg, G-banding).	Updated based on the latest protocol text provided by Epizyme to ensure the safety of subjects.
46 47	**9.5.2.1 Schedule of Procedures/Assessments of the Study** **Table 6 Schedule of Procedures/Assessments in Study E7438-J081-106 (EZH-106)** Hematology k: Subjects should not take study drug before evaluations are performed (except tumor assessments), unless specified.	**9.5.2.1 Schedule of Procedures/Assessments of the Study** **Table 6 Schedule of Procedures/Assessments in Study E7438-J081-106 (EZH-106)** Hematology[o] k: Subjects should not take study drug before evaluations are performed (except tumor assessments and peripheral blood smear morphology assessment), unless specified. o: On Day 15 of each cycle, peripheral blood smear morphology assessment can be omitted at the discretion of the investigator or subinvestigator, if there was no concern for safety of the subject.	Updated based on the latest protocol text provided by Epizyme to ensure the safety of subjects.

Protocol Pages	Protocol V4.0, 23 Mar 2018	Protocol V5.0, 18 Oct 2018	Rationale
49	**9.5.4.3.2 Reporting Of Study-Specific Events** Occurrence of lymphoblastic lymphoma/T-ALL and abnormal bone formation will be considered events of interest for this study. These events should be directly reported to the sponsor or by fax with completed SAE report as soon as the investigator becomes aware of the event. The faxed report should be followed up by the original SAE report. Study-specific events must be followed to resolution or, if resolution is unlikely, to stabilization. Study-specific events should be considered as serious only if the events meet the serious criteria. These events should be entered on the CRF even if the events do not meet serious criteria.	**9.5.4.3.2 Reporting Of Study-Specific Events** The occurrence of T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia or myeloid malignancy including myelodysplastic syndrome will be considered events of interest for this study. These events should be reported to the sponsor as soon as possible (no later than 1 business day) after obtaining the information. In addition, these events should be directly reported to the sponsor or by fax with completed SAE report promptly. The faxed report should be followed up by the original SAE report. Events of interest for this study must be followed to resolution or, if resolution is unlikely, to stabilization. Any event of interest to be related to the study drug or any protocol-required procedure judged by the investigator or subinvestigator should be reported to the sponsor regardless of the length of time that has passed since study completion. Events of interest should be considered as serious only if the events meet the serious criteria. These events should be entered on the CRF even if the events do not meet serious criteria.	Updated based on the latest protocol text provided by Epizyme to ensure the safety of subjects.

Pages 96 to 167 have been removed - non-English text removed.