1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7438-J081-206 (EZH-206)
Study Protocol Title:	A Phase 2 Study of Tazemetostat in Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma with EZH2 Gene Mutation
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:	2
Approval Date:	V1.0 27 Dec 2017 (original protocol) V2.0 18 Oct 2018 (per Amendment 01) V3.0 15 Nov 2019 (per Amendment 02) V4.0 29 Jan 2021 (per Amendment 03)
GCP Statement:	This study is to be performed in full compliance with all applicable local Good Clinical Practice (GCP) and regulations (Good Post-marketing Study Practice [GPSP] in case of post-marketing study). 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 2 Study of Tazemetostat in Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma with EZH2 Gene Mutation

Investigators

Refer to the Attachment separately provided to each site.

Sites

Study centers: Approximately 30 sites (planned)

Study location: Japan

Study Period and Phase of Development

Study period: 30 months (planned)

Phase of development: Phase 2

(Note: subjects who meet approved indication of E7438 in Japan will continue this study as a post-marketing study.)

Objectives

Primary objective

To assess the efficacy of tazemetostat in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma (NHL) below by objective response rate (ORR).

Cohort 1: Follicular lymphoma (FL) with EZH2 gene mutation

Cohort 2: Diffuse large B-cell lymphoma (DLBCL) with EZH2 gene mutation

Secondary objectives

(1)To assess the efficacy of tazemetostat by the endpoints below.

·Progression-free survival (PFS)

·Duration of response (DOR)

·Time to response (TTR)

(2)To assess the safety of tazemetostat.

Exploratory objectives

(1)To explore the pharmacokinetics (PK) of tazemetostat.

(2)To explore the frequency of EZH2 gene mutation in B-cell NHL.

Study Design

This is a multicenter, open-label, phase 2 study in relapsed or refractory B-cell NHL patients with EZH2 gene mutation, consists with 2 cohorts. The study will assess efficacy and safety of tazemetostat in FL patients with EZH2 gene mutation in cohort 1, and DLBCL (including primary mediastinal B-cell lymphoma and transformed FL) patients with EZH2 gene mutation in cohort 2.

This study will be conducted in the following 3 phases: Pre-treatment Phase, Treatment Phase, and Follow-up Phase.

The Pre-treatment Phase consists of Screening 1, Screening 2, registration, and baseline assessment.

In Screening 1, the EZH2 gene mutation will be confirmed at central laboratory in patients with histologically diagnosed as FL (cohort 1) or DLBCL (cohort 2) who are available to provide archival tumor sample (Inclusion Criteria 1) and not apparent to conflict other eligible criteria to participate in the study. The archival tumor samples will be submitted to the central laboratory, and then this will be reported to the sponsor. If EZH2 gene mutation was confirmed, conduct Screening 2 to confirm the other eligibility for study treatment. Obtain the written informed consent with regards to tumor EZH2 gene mutation test and study treatment respectively, before Screening 1 and Screening 2. Screening 2 will last no longer than 28 days before the start of study treatment. 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 28 days/cycle for tazemetostat 800 mg twice daily (BID) oral administration (1600 mg total daily dose) on a continuous basis and lasts until discontinuation of study drug. Subjects will discontinue study drug at the time of disease progression (site evaluation), 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.
Number of Subjects Cohort 1: FL with EZH2 gene mutation Eight efficacy evaluable patients (planned) Cohort 2: DLBCL with EZH2 gene mutation Thirteen efficacy evaluable patients (planned)

Inclusion Criteria

(1) Patient with histological diagnosis of B-cell NHL as follows, who has provided written consent to submit archival tumor sample to central laboratory to confirm the EZH2 gene mutation status in tumor:
- Cohort 1: Follicular lymphoma (FL)
- Cohort 2: Diffuse large B-cell lymphoma (DLBCL) (including primary mediastinal B-cell lymphoma and transformed FL)

(2) Patient who has confirmed EZH2 gene mutation of tumor in central laboratory

(3) 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

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

(5) Patient who was progressive disease (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

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

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

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

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

(10) 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

(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 a medical need for the continued use of potent inhibitors of CYP3A, or potent 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 the inability to take oral medication, or malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, or vomiting) or medical history (eg, gastrectomy or enterectomy) that might impair the bioavailability of study drug

(8) Patient with significant cardiovascular impairment

1) History of congestive heart failure of ≥ New York Heart Association (NYHA) Class III

2) Uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug

3) Ischemic heart disease, cardiac arrhythmia requiring medical treatment

(9) Patient with prolongation of corrected QT interval using Fridericia's formula (QTcF) to >480 msec

(10) Patient with venous thrombosis or pulmonary embolism within the last 3 months before starting study drug

(11) Patient with complications of hepatic cirrhosis, interstitial pneumonia or pulmonary fibrosis

(12) Patient with active infection requiring systemic therapy

(13) Patient with known hypersensitivity to any component of study drug

(14) Patient who is positive for HIV antibody, HCV antibody, and HCV-RNA, or HBs antigen. Patient who is positive for HBs or HBc antibody and showing DNA more than sensitivity in HBV-DNA assay

(15) 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).

(16) 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 the below note) 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.

(17) Woman who is pregnant or breastfeeding (not eligible even if she discontinues breastfeeding)

(18) Patient who was decided as inappropriate for medical or other reasons to participate in the study by the investigator or sub-investigator

(19) Patient who has a prior history of myeloid malignancy including T-cell lymphoblastic lymphoma, T-cell acute lymphoblastic leukemia or myelodysplastic syndrome

Note: Condom*, contraceptive sponge**, foam**, jelly**, diaphragm*, intrauterine device (IUD)*, or use of oral contraception* from 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 BID (1600 mg total daily dose) will be administered orally by continuous regimen, no less than 8 hours between doses.

Tazemetostat will be provided as 200 mg tablet.

Tazemetostat Dose Reduction and Interruption Instructions

Dose reduction and interruption for subjects who experience tazemetostat-related toxicity will follow the instructions shown in 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, 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.

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 the sponsor or discontinue tazemetostat

ANC = absolute neutrophil count.

a: Tolerability of Grade 2 toxicities will be judged by the investigator or subinvestigator.

b: Dose interruption and reduction are 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 and follow the dose reduction and interruption instructions when it cannot be controlled.

c: Laboratory abnormalities judged to be non-life threatening, will be excluded and managed as Grade 3.

d: Discuss with the sponsor when to consider the dose interruption and adjustment other than the 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 that is related to the study treatment must be discussed with the sponsor before treatment can be resumed.

Duration of Treatment

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

[Subjects who meet approved indication of tazemetostat in Japan]

As per regulatory requirements in Japan, from the time tazemetostat is approved by the regulatory authority, these subjects will continue this study as a post-marketing study. Treatment will continue until tazemetostat is commercially available for individual subjects at each study site, at which time the subjects will be switched to commercial tazemetostat.

Concomitant Drug/Therapy

The following drugs and therapies are prohibited 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. Starting study drug treatment however, 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

Assessments

Efficacy Assessments

Efficacy assessment will be performed by investigator or subinvestigator based on "Revised response criteria for malignant lymphoma (IWG-2007)" (Cheson, et al., 2007). Overall response and best overall response (BOR) (best response recorded at the designated visits during the study) will be assessed. Perform the assessment below for tumor assessment.

CT scans will be performed at Screening 2, every 8 weeks from study drug administration up to first 32 weeks, then every 12 weeks and at discontinuation.

PET scans will be performed at Screening 2. If positive, perform when it is required to confirm CR as soon as possible or when clinically indicated.

If gastrointestinal disease is suspected, endoscopic examination will be performed at Screening 2. If exists, perform when it is requested to confirm CR as soon as possible or when clinically indicated.

To evaluate bone marrow infiltration, a bone marrow aspiration or biopsy will be performed at Screening 2. If positive or indeterminate, perform when it is requested to confirm CR as soon as possible or when clinically indicated.

Also, central review will be conducted by the Imaging Review Committee for CT and PET assessment which is obtained within 24 months after the last subject's enrollment (cut-off date: 02 Dec 2020). In addition, Efficacy and Safety Evaluation Committee (ESEC) will conduct central evaluation based on the review of Imaging Review Committee and other assessment / bone marrow infiltration evaluated by the investigator or subinvestigator, to determine the overall responses and the best overall response.

The primary endpoint and the secondary endpoint with regard to efficacy are defined as below, and will be evaluated by the result of ESEC review.

- ORR:
  The rate of subjects whose BOR is CR or PR.

- PFS:
  Defined as the term between the date of administration of the first dose of the study drug and the date of the first event (PD or death whichever occurs first). The detail of the censoring rule for PFS will be described in the statistical analysis plan (SAP).
- DOR:
  Defined as the term between the date of confirmation of the first response and the date of confirmation of the PD. The detail of the censoring rule for DOR will be described in the SAP.
- TTR:
  Defined as the term between the date of administration of the first dose of the study drug and the date of confirmation of the first response.

Pharmacokinetics Assessments

To measure plasma trough concentrations of tazemetostat.

Biomarker Assessments

At Screening 1, archival tumor samples (formalin-fixed paraffin-embedded: FFPE) will be submitted to the central laboratory for detection of EZH2 gene mutation status in patients with written informed consent for tumor EZH2 gene mutation test.

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); periodic clinical laboratory assessment; measurement of vital signs, 12-lead electrocardiograms (ECGs), ECOG-PS, and physical examinations. Severity will be evaluated by grading of Common Terminology Criteria for Adverse Events (CTCAE v4.03).

Bioanalytical Methods

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

Statistical Methods

Definitions of Analysis Sets

Efficacy Analysis Set will include efficacy evaluable subjects who received at least 1 administration of the study drug and who has at least 1 appropriate tumor assessment data of Screening 2 and post-baseline.

Pharmacokinetic Analysis Set will include subjects who received at least 1 administration of the study drug and had at least 1 concentration data of tazemetostat.

Biomarker Analysis Set will include subjects who have conducted EZH2 gene mutation assessment at Screening 1.

Safety Analysis Set will include subjects who received at least 1 administration of the study drug.

Efficacy Analyses

This analysis will be performed on the Efficacy Analysis Set. All summary of efficacy will be conducted for each disease (cohort).

Primary Endpoint Analyses

BOR will be summarized. The rate of subjects whose BOR is CR or PR is calculated as ORR, and its corresponding 2-sided exact 90% confidence intervals (CIs) using the method of Clopper–Pearson will also be calculated. 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.

Secondary Endpoint Analyses

- Analysis of PFS
  PFS will be summarized by Kaplan-Meier method using median with 95%CI.
- Analysis of DOR
  DOR will be summarized by Kaplan-Meier method in responders.
- Analysis of TTR
  TTR will be summarized by descriptive statistics in responders.

Pharmacokinetic Analyses

This analysis will be performed on the Pharmacokinetic Analysis Set. The plasma concentrations of tazemetostat will be summarized by timepoint.

Biomarker Analysis

This analysis will be performed on the Biomarker Analysis Set. The rate of the tumor EZH2 gene mutation will be calculated in each disease.

Safety Analyses

This analysis will be performed on the Safety Analysis Set. The number and percentage of subjects with all AEs and SAEs observed after first administration of study drug will be summarized and listed by system organ class (SOC), preferred term (PT), and severity in whole or each disease (cohort). Summary statistics will be presented for laboratory test values, vital signs, 12-lead ECG, and ECOG-PS. If needed, the changes from baseline will also be summarized.

Sample Size Rationale

In cohort 1, 8 efficacy evaluable FL patients with EZH2 mutation are required to detect lower limit of the 90% CI that exceed the 10% threshold in ORR, which is the primary endpoint of the study, with the expected ORR of 50% with power of approximately 80%.

In cohort 2, 13 efficacy evaluable DLBCL patients with EZH2 mutation are required to detect lower limit of the 90% CI that exceed the 10% threshold in ORR, which is the primary endpoint of the study, with the expected ORR of 40% with power of approximately 80%.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BUN	blood urea nitrogen
C#D#	Cycle# Day#
CI	confidence interval
COO	cell-of-origin
CR	complete response
CRA	clinical research associate
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
ESEC	Efficacy and Safety Evaluation Committee
EZH2	enhancer of zeste homolog 2
FFPE	formalin-fixed paraffin-embedded
FL	follicular lymphoma
GCB	germinal center B-cell-like
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor

Abbreviation	Term
GPSP	Good Post-marketing Study Practice
HBc	hepatitis B virus core
HBs	hepatitis B virus surface
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HMT	histone methyltransferase
ICF	informed consent form
ICML	International Congress of Malignant Lymphoma
IDMC	Independent Data Monitoring Committee
INN	International Nonproprietary Name
INR	international normalized ratio
IUD	intrauterine device
IxRS	interactive voice/web response system
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDH	lactate dehydrogenase
LLT	lower level term
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRT	malignant rhabdoid tumor
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin's lymphoma
NYHA	New York Heart Association
ORR	objective response rate
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics

Abbreviation	Term
PK/PD	pharmacokinetic/pharmacodynamic
PR	partial response
PRC2	polycomb repressive complex 2
PS	performance status
PT	preferred term
QOL	quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
R	rituximab
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TTR	time to response
ULN	upper limit of normal
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

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 clinical research associates [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, the head of the medical institution, 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 the sponsor via the head of the medical institution with a brief report of the outcome of the study, if required.

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

In addition, after tazemetostat is approved by the Japanese regulatory authority, the study will be conducted as a post-marketing study as per regulatory requirements of GPSP.

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 in accordance with GCP and all applicable local regulations. 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 written informed consent with regard to tumor EZH2 gene mutation test will be obtained from all patients who will participate in the study, followed by obtaining the written informed consent with regard to study treatment. EZH2 gene mutation status will be detected using archival tumor samples in patients with written informed consent for tumor EZH2 gene mutation test.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsor at approximately 30 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 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 the stem cells such as hematopoietic 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 a 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 follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), 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 FL and DLBCL lead to increased activity of trimethylation of EZH2 and produces hypertrimethylation on H3K27 (H3K27Me3), resulting 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 (T-ALL) 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 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-ALL, medulloblastoma, mesothelioma, and others) (Plass, et al., 2013; LaFave, et al., 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 on 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 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.

7.2 Epidemiology and Current Therapeutic Options of Follicular Lymphoma and Diffuse Large B-cell Lymphoma

7.2.1 Epidemiology of Malignant Lymphoma

The nationwide survey by the Ministry of Labor, Health, and Welfare (2014) has reported that approximately 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, FL and DLBCL, are subtypes of B-cell NHL.

7.2.2 Epidemiology of Follicular Lymphoma

FL is the most common type of the indolent B-cell lymphoma, which progresses in yearly term. FL has structure basis that histologically mimics germinal center. Outside Japan, gain-of-function mutation of EZH2 is reported in 7% to 27% of FL (Morin, et al., 2010; Bödör, et al., 2013). 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 Section 7.2.1 Epidemiology of Malignant Lymphoma and these reports, it is estimated that approximately 600 to 2,300 people are diagnosed as FL with EZH2 gene mutation and FL with EZH2 gene mutation is prevalent in approximately 250 to 970 patients per year.

7.2.3 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). In and outside Japan, the standard therapy for advanced-stage primary FL that requires treatment is the R-CHOP regimen, which is a combination of several chemotherapy drugs (cyclophosphamide, doxorubicin, vincristine, and prednisone) and rituximab (R), or the non-doxorubicin-containing R-CVP regimen. Rituximab monotherapy or chemotherapy alone approach should also be considered based on the patient 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 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.

7.2.4 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. DLBCL is classified to germinal center B-cell like (GCB) type and the others (non-GCB type including activated B-cell like type) based on gene expression profile, in approximately a half of proportion respectively (Lenz, et al., 2008). Outside Japan, gain-of-function mutation of EZH2 is reported in 22% of GCB type while no activating mutation of EZH2 is reported in non-GCB type (Morin, et al., 2010). 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 Section 7.2.1 Epidemiology of Malignant Lymphoma and these reports, it is estimated that approximately 3,200 people are diagnosed as DLBCL with EZH2 gene mutation and DLBCL with EZH2 gene mutation is prevalent in approximately 1,300 patients per year.

7.2.5 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. 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 chemotherapy in current use are the R-DHAP (dexamethasone, cisplatin, and cytarabine), 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.

7.3 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 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 November 2012. Phase 1 data were reviewed by an Independent Data Monitoring Committee on 12 November 2014. The committee agreed that the recommended Phase 2 dose be 800 mg BID based on the evaluation of safety, pharmacokinetics (PK), biomarker, and antitumor activity.

Tazemetostat is currently under investigation for the treatment of FL, DLBCL, and INI1- or SMARCA4-negative tumors outside Japan. In Japan, a Phase 1 study (E7438-J081-106) is ongoing in patients with B-cell non-Hodgkin's lymphomas (NHLs) including FL and DLBCL.

7.4 Clinical Studies

7.4.1 Clinical Studies Conducted Outside Japan

7.4.1.1 Overview of Phase 1 Study Conducted Outside Japan

As of 15 January 2017, a total of 64 subjects have received treatment with tazemetostat in a Phase 1 study (E7438-G000-101 [Phase 1 part]). This study enrolled subjects with B-cell NHLs including FL and DLBCL, and solid tumors including INI1-negative tumors and synovial sarcoma. Tazemetostat was administered as monotherapy at doses ranging from 100 mg to 1600 mg BID.

Study E7438-G000-101 (Phase 1 Part)

Study E7438-G000-101 is a multicenter, open-label, first-in-human, Phase 1/2 study. The Phase 1 part of this study enrolled subjects with advanced or metastatic solid tumors or B-cell NHLs that have progressed after treatment with approved therapies or for which there are no standard therapies available. The objectives of the Phase 1 part are to determine the recommended Phase 2 dose (RP2D) of tazemetostat as a single agent administered orally twice daily (BID) continuously in 28-day cycles and to assess the preliminary anti-tumor activity of tazemetostat. Additionally, in separate 2 cohorts in Phase 1 of this study, clinical pharmacologic assessments were performed.

The first subject was enrolled in June 2013, and subjects in all cohorts (dose escalation, food effect, drug-drug interaction [DDI]) have been enrolled in the Phase 1 part of this study. Tazemetostat 100, 200, 400, 800, and 1600 mg BID were administered in the Phase 1 dose escalation. One dose-limiting toxicity (DLT) of Grade 4 thrombocytopenia was observed at the dose level of 1600 mg BID; thus, the protocol-defined maximum tolerated dose (MTD) was not reached. Based on the safety, PK, biomarker, and antitumor activity observed, the RP2D of tazemetostat monotherapy was determined to be 800 mg BID. The study of the

effect of food on the bioavailability of tazemetostat showed that the decrease in systemic exposure observed when tazemetostat was administered with a high-fat meal was not clinically significant. Tazemetostat is moderately or weakly inhibitory to CYP3A activities and induced CYP3A messenger ribonucleic acid (mRNA) in human hepatocytes in vitro. The results from the DDI cohort demonstrated that tazemetostat is a net weak inducer of CYP3A-mediated metabolism.

7.4.1.2 Overview of Phase 2 Study Conducted Outside Japan

As of 15 January 2017, a total of 266 subjects with FL, DLBCL, INI1-negative tumor, SMARCA4-negative tumor, synovial sarcoma, or malignant mesothelioma have received tazemetostat 800 mg BID in 3 ongoing Phase 2 studies (E7438-G000-101 [Phase 2 part], EZH-202, EZH-203).

Study E7438-G000-101 (Phase 2 part)

The Phase 2 part of this study is designed to assess the objective response rate of tazemetostat in patients with 1) EZH2 gene mutation-positive FL, 2) EZH2 gene mutation-negative (wild-type) FL, 3) EZH2 gene mutation-positive DLBCL of germinal center origin subtype, 4) EZH2 gene mutation-negative (wild-type) DLBCL of germinal center origin subtype, or 5) DLBCL of non-germinal center origin subtype. The primary objective of the Phase 2 part is to determine the objective response rate of tazemetostat. The secondary objectives are to assess the effect of tazemetostat on duration of response (DOR), progression-free survival (PFS), and durable stable disease; the safety and tolerability of tazemetostat; and PK profile of tazemetostat. The exploratory objectives are to explore the PK and pharmacodynamic (PD) relationship of tazemetostat; biomarkers and their correlation with biological activity for tazemetostat; the effects of tazemetostat on histone H3K27 methylation, target gene expression, and phenotypic markers including those for differentiation, apoptosis, and cell proliferation; the role of DNA sequence variability on absorption, metabolism, excretion and susceptibility to adverse events (AEs) of tazemetostat.

Upon review of the data available as of 06 September 2016, the Independent Data Monitoring Committee (IDMC) concluded that the futility hurdles have been surpassed in the last of all planned (5) monotherapy cohorts and that the safety profile of tazemetostat continued to be acceptable; therefore, the IDMC determined that enrollment should continue. A total of 151 subjects have been enrolled and the study is ongoing.

Study EZH-202

This study is enrolling subjects with histologically and/or cytologically confirmed advanced or metastatic INI1-deficient or SMARCA4-negative tumors, and is a multicenter, open-label, Phase 2 study, which has been conducted since December 2015. Subjects aged more than 16 years have been enrolled into disease-specific 5 cohorts which comprise of 1) malignant rhabdoid tumors, 2) synovial sarcoma, 3) other INI1-negative tumors, 4) renal medullary carcinoma, or 5) epithelioid sarcoma, and have received 800 mg BID tazemetostat.

The primary objective for Cohorts 1, 3, and 4 is to assess the objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) in patients with malignant rhabdoid tumors, other INI1-negative tumors, or renal medullary carcinoma. The primary objective for Cohort 2 is to assess progression-free survival at Week 16 (as assessed by RECIST 1.1) in patients with synovial sarcoma. The primary objective of Cohort 5 is to assess the disease control rate (complete response [CR] or partial response [PR] of any duration, or stable disease of >32 weeks' duration) in patients with epithelioid sarcoma.

Upon review of the data available on 04 October 2016, the IDMC concluded that futility hurdles in Cohorts 2 and 5 had been surpassed and that study should continue, as there were no safety concerns. IDMC review of other cohorts will convene in the future based on enrollment and data maturation. As of 15 January 2017, a total of 102 subjects have been enrolled and the study is ongoing.

Study EZH-203

This Phase 2 study is enrolling adult subjects with relapsed or refractory malignant mesothelioma and consists of Part 1 and Part 2. The primary objective of Part 1 was to assess the PK and safety of tazemetostat administered orally in 400 mg tablet form at a total dose of 800 mg BID. Part 2 uses a 2-stage design and is enrolling subjects with BAP1 loss of function. The primary objective of Part 2 is to assess the disease control rate at 12 weeks.

Thirteen subjects were enrolled in Part 1, irrespective of BAP1 status at data cut-off.

7.4.1.3 Summary of Safety in Clinical Studies Conducted Outside Japan

As of 15 January 2017, 63 subjects (98%) enrolled in the Phase 1 part of E7438-G000-101 (n=64) had experienced at least 1 treatment-emergent adverse event (TEAE) and 49 subjects (77%) experienced at least 1 TEAE that was considered by the investigator to be possibly related to tazemetostat. TEAEs of Grade 3 or 4 severity were reported in 36% of subjects, and 9% of subjects experienced at least 1 Grade 3 or Grade 4 TEAE that was considered to be related to study drug.

The most frequently reported treatment-related TEAEs that occurred in more than 5% of the subjects were asthenia (33%), nausea (20%), anemia, muscle spasms, and thrombocytopenia (14% each), dry skin (11%), vomiting (9%), dysgeusia (8%), decreased appetite, diarrhea, neutropenia, and night sweats (6% each), and abdominal pain (5%). There were no Grade 3 or Grade 4 treatment-related TEAEs that occurred in ≥5% of subjects. Two subjects experienced Grade 4 treatment-related TEAEs, neutropenia and thrombocytopenia. An event of Grade 4 thrombocytopenia occurred in a subject who experienced *E. coli* sepsis related to underlying disease with concurrent anemia and was considered a DLT. Only 1 DLT (Grade 4 thrombocytopenia) was observed at the dose level of 1600 mg BID; but, the protocol-defined MTD was not reached.

No clear pattern of dose-related increase in toxicity (AEs of all grades and Grade 3 and 4 AEs) was identified in the dose-escalation part of Study E7438-G000-101.

As of 15 January 2017, of the 266 subjects enrolled in Phase 2 studies, 237 subjects (89%) experienced at least 1 TEAE and 157 subjects (59%) experienced a treatment-related TEAE. Grade 3 or Grade 4 events, regardless of causality, occurred in 40% of subjects, and 14% of subjects experienced a Grade 3 or Grade 4 TEAE deemed related to study treatment.

The most frequently reported treatment-related TEAEs that occurred in more than 5% of subjects were nausea (14%), fatigue (13%), asthenia (8%), thrombocytopenia (7%), and anemia, diarrhea, and decreased appetite (6% each). The only TEAE of Grade 3 or higher severity, regardless of assessed causality, to occur in ≥ 5% of subjects treated with tazemetostat monotherapy in the Phase 2 studies was anemia (17 subjects; 6%). The reported Grade 4 treatment-related TEAEs were neutropenia (4 subjects, 2%), thrombocytopenia (2 subjects; 1%), pancytopenia and dyspnea (1 subject each; <1%).

Table 1 presents the incidence of TEAEs determined to be related to study drug that occurred in ≥5% of subjects who received 800 mg BID tazemetostat monotherapy in the Phase 2 studies.

Table 1 Summary of Treatment-Related Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects in Phase 2 Studies with Tazemetostat

MedDRA Preferred Term	B-cell NHL N=151 n (%)	Solid Tumors N=115 n (%)	Overall N=266 n (%)
Subjects with at least 1 TEAE	85 (56)	72 (63)	157 (59)
Nausea	20 (13)	18 (16)	38 (14)
Fatigue	11 (7)	24 (21)	35 (13)
Asthenia	14 (9)	7 (6)	21 (8)
Thrombocytopenia	19 (13)	0 (0)	19 (7)
Anemia	7 (5)	10 (9)	17 (6)
Diarrhea	11 (7)	5 (4)	16 (6)
Decreased appetite	6 (4)	9 (8)	15 (6)

NHL=non Hodgkin lymphoma, TEAE=treatment-emergent adverse event.

In the Phase 1 part of Study E7438-G000-101 (n=64), 19 subjects (30%) experienced at least 1 treatment-emergent serious adverse event (SAE) of any assessed causality. A total of 2 subjects (3%) experienced an SAE that was assessed as possibly related to study drug; these SAEs included anemia and thrombocytopenia in 1 subject and neutropenia in 1 subject.

SAEs of any causality occurred in 82 subjects (31%) in the Phase 2 studies (n=266); 18 subjects (7%) experienced an SAE that was assessed as related to study drug. SAEs assessed as related to tazemetostat that were experienced by more than 1 subject included neutropenia (3 subjects) and thrombocytopenia and constipation (2 subjects each). All other

treatment-related SAEs occurred in no more than 1 subject (anemia, histiocytosis hematophagic, abdominal pain, gastric ulcer perforation, esophageal candidiasis, pneumonia, soft tissue infection, malaise, hyperbilirubinemia, hyponatremia, hemoptysis, and melaena).

7.4.1.4 Summary of Efficacy in Clinical Studies Conducted Outside Japan

As of 01 June 2017, the efficacy of tazemetostat was reported as interim result of ongoing Phase 2 study (Study E7438-G000-101 [n=203]). The ORR (primary endpoint) was 92% (12/13 subjects) in EZH2 gene mutation-positive FL, 26% (14/54 subjects) in EZH2 gene mutation-negative (wild-type) FL, 29% (5/17 subjects) in EZH2 gene mutation-positive DLBCL of germinal center origin subtype, and 15% (18/119 subjects) in EZH2 gene mutation-negative (wild-type) DLBCL of either germinal center origin or non-germinal center origin subtype. Tazemetostat showed high efficacy in subjects with EZH2 gene mutation compared to subjects with wild type (Morschhauser, et al., 2017).

7.4.2 Clinical Study Conducted in Japan

7.4.2.1 Overview of Phase 1 Study Conducted in Japan

As of 31 July 2017, a total of 7 subjects have received treatment with tazemetostat in a Phase 1 study (E7438-J081-106). This study enrolled subjects with B-cell NHLs including FL and DLBCL, and the study is ongoing.

Study E7438-J081-106

This study is a multicenter, single-arm, Phase 1 study in Japan to assess the tolerability, safety, PK profile, and preliminary anti-tumor activity of tazemetostat in patients with relapsed or refractory B-cell NHL. Tazemetostat 800 mg has been administered orally by single dose in Cycle 0 Day 1 and then continuous BID (1600 mg total daily dose).

A total of 7 subjects have received tazemetostat, and 1 subject was excluded from DLT evaluation due to early disease progression. No DLT was observed in 6 subjects; therefore, tazemetostat 800 mg BID, which is RP2D outside Japan, was confirmed to be well tolerated in Japanese subjects.

7.4.2.2 Summary of Safety in Clinical Study Conducted in Japan

As of 31 July 2017, tazemetostat 800 mg has been administered orally by single dose in Cycle 0 Day 1 and then continuous BID to 7 subjects enrolled in the Japanese Phase 1 study. The most frequently reported treatment-related TEAEs were thrombocytopenia (3 subjects; 43%), anemia, dry skin, rash, and dysgeusia (2 subjects each; 29%), constipation, fatigue, gastritis, hypoalbuminemia, insomnia, leukopenia, muscle spasms, nausea, neutropenia, and stomatitis (1 subject each; 14%). The treatment-related TEAEs of Grade 3 or higher were thrombocytopenia (2 subjects; 29%) and anemia (1 subject; 14%). There were no SAEs related to study drug.

7.5 Study Rationale

In the Phase 1 part of the Study E7438-G000-101 conducted outside Japan, the recommended Phase 2 dose of tazemetostat has been determined to be 800 mg BID. As interim result of ongoing Phase 2 part of the study, encouraging efficacy of tazemetostat was reported in relapsed or refractory FL and DLBCL with EZH2 gene mutation.

In the Phase 1 study of the Study E7438-J081-106 conducted in Japan, no DLT was observed in tazemetostat 800 mg BID by continuous regimen; therefore, tazemetostat 800 mg BID, which is RP2D outside Japan, was confirmed to be well tolerated in Japanese subjects. Also, the favorable safety profile of tazemetostat has been shown in Japanese and non-Japanese subjects.

Based on above, the Phase 2 study (E7438-J081-206) was planned to evaluate the efficacy and safety of tazemetostat in Japanese patients with relapsed or refractory B-cell NHL (FL and DLBCL) with EZH2 gene mutation.

In this study, tazemetostat 800 mg BID (1600 mg total daily dose) will be administered orally in continuous cycles of 28 days each, and the treatment will continue until disease progression, development of unacceptable toxicity, subject's requests to discontinue, withdrawal of consent, or study termination by the sponsor.

As the patients eligible to this study are extremely few and standard therapy/treatment to prolong the overall survival for relapsed or refractory B-cell NHL has not been established yet, the response itself is considered to be clinically meaningful. Therefore, the primary endpoint of the study was set as ORR, by referring the interim result of ongoing E7438-G000-101 study outside of Japan. Regarding sample size of this study, in cohort 1, 8 efficacy evaluable FL patients with EZH2 mutation are required to detect lower limit of the 90% CI that exceed the 10% threshold in ORR, which is the primary endpoint of the study, with the expected ORR of 50% with power of approximately 80%. In cohort 2, 13 efficacy evaluable DLBCL patients with EZH2 mutation are required to detect lower limit of the 90% CI that exceed the 10% threshold in ORR, which is the primary endpoint of the study, with the expected ORR of 40% with power of approximately 80%.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to assess the efficacy of tazemetostat in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma (NHL) below by objective response rate (ORR).

Cohort 1: Follicular lymphoma (FL) with EZH2 gene mutation

Cohort 2: Diffuse large B-cell lymphoma (DLBCL) with EZH2 gene mutation

8.2 Secondary Objectives

(1)To assess the efficacy of tazemetostat by the endpoints below.

·Progression-free survival (PFS)

·Duration of response (DOR)

·Time to response (TTR)

(2)To assess the safety of tazemetostat.

8.3 Exploratory Objectives

(1)To explore the pharmacokinetics (PK) of tazemetostat.

(2)To explore the frequency of EZH2 gene mutation in B-cell NHL.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, open-label, phase 2 study in relapsed or refractory B-cell NHL patients with EZH2 gene mutation, and consists with 2 cohorts. The study will assess efficacy and safety of tazemetostat in FL patients with EZH2 gene mutation in cohort 1, and DLBCL (including primary mediastinal B-cell lymphoma and transformed FL) patients with EZH2 gene mutation in cohort 2.

Note: As per regulatory requirements in Japan, from the time tazemetostat is approved by the regulatory authority, subjects who meet approved indication of tazemetostat will continue this study as a post-marketing study (clinical study shall be deemed to post-marketing study in this protocol) until tazemetostat is commercially available for individual subjects at each study site. For these subjects, the end of the study will be the date of the last study treatment or evaluation at discontinuation, whichever comes later.

9.1.1 Study Design

The study design of this study is presented in Figure 1. This study will be conducted in the following 3 phases: Pre-treatment Phase, Treatment Phase, and Follow-up Phase.

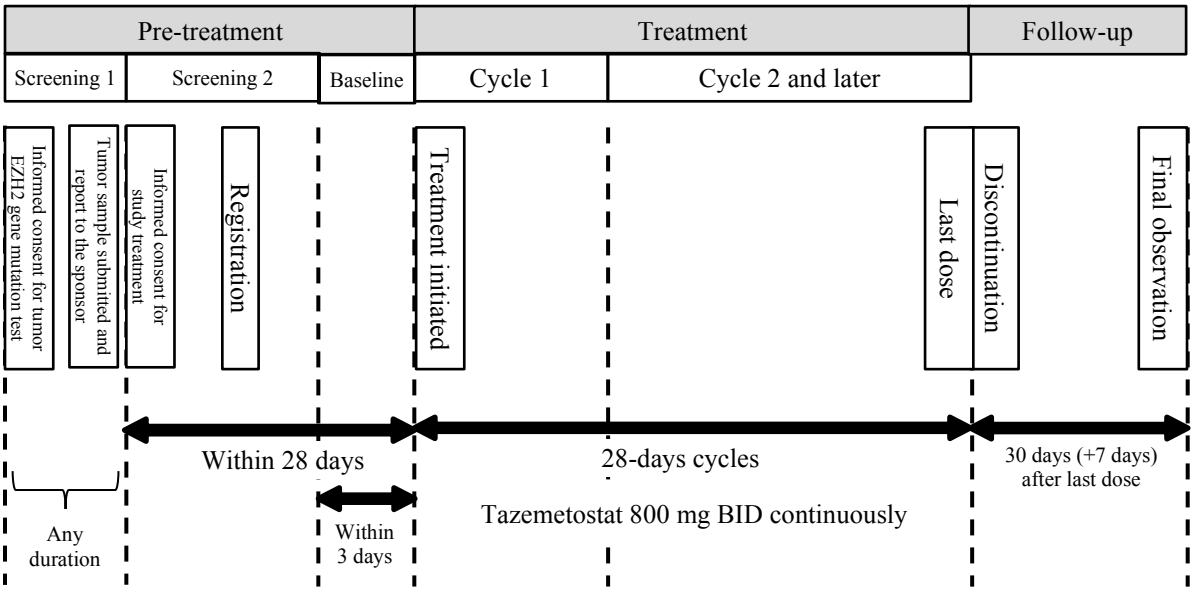

Figure 1 Study Design

BID = twice daily.

9.1.1.1 Pre-treatment Phase

The Pre-treatment Phase consists of Screening 1, Screening 2, registration, and baseline assessment. In Screening 1, the EZH2 gene mutation will be confirmed at central laboratory in patients with histologically diagnosed as FL (cohort 1) or DLBCL (cohort 2) who are available to provide archival tumor sample (Inclusion Criteria 1) and not apparent to conflict other eligible criteria to participate in the study. The archival tumor samples will be submitted to the central laboratory, and then this will be reported to the sponsor. If EZH2 gene mutation was confirmed, conduct Screening 2 to confirm the other eligibility for study treatment. Obtain the written informed consent with regards to tumor EZH2 gene mutation test and study treatment respectively, before Screening 1 and Screening 2. Screening 2 will last no longer than 28 days before the start of study treatment. 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.

9.1.1.2 Treatment Phase

The Treatment Phase consists of 28 days/cycle for tazemetostat 800 mg twice daily (BID) oral administration (1600 mg total daily dose) on a continuous basis and lasts until discontinuation of study drug. Subjects will discontinue study drug at the time of disease progression (site evaluation), 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 Treatment Phase will have a discontinuation visit of the Follow-up Phase.

9.1.1.3 Follow-up Phase

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. Final observation is unnecessary for subjects who withdraw from the study and continuously take commercial tazemetostat.

9.2 Discussion of Study Design, Including Choice of Control Groups

Control groups are not set in this study. This study was designed according to "The Guidelines for Clinical Evaluation of Anti-Cancer Drugs in Japan (Notification No. 1101001 issued on 01 November, 2005)."

9.3 Selection of Study Population

Eight efficacy evaluable FL patients with EZH2 mutation and 13 efficacy evaluable DLBCL patients with EZH2 mutation will be enrolled in cohort 1 and cohort 2, respectively, at approximately 30 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) Patient with histological diagnosis of B-cell NHL as follows, who has provided written consent to submit archival tumor sample to central laboratory to confirm the EZH2 gene mutation status in tumor:
- Cohort 1: Follicular lymphoma (FL)
- Cohort 2: Diffuse large B-cell lymphoma (DLBCL) (including primary mediastinal B-cell lymphoma and transformed FL)

(2) Patient who has confirmed EZH2 gene mutation of tumor in central laboratory

(3) 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

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

(5) Patient who was progressive disease (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

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

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

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

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

(10) 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

(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 a medical need for the continued use of potent inhibitors of CYP3A, or potent 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 the inability to take oral medication, or malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, or vomiting) or medical history (eg, gastrectomy or enterectomy) that might impair the bioavailability of study drug
(8) Patient with significant cardiovascular impairment
  1)History of congestive heart failure of ≥ New York Heart Association (NYHA) Class III
  2)Uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug
  3)Ischemic heart disease, cardiac arrhythmia requiring medical treatment
(9) Patient with prolongation of corrected QT interval using Fridericia's formula (QTcF) to >480 msec
(10) Patient with venous thrombosis or pulmonary embolism within the last 3 months before starting study drug
(11) Patient with complications of hepatic cirrhosis, interstitial pneumonia or pulmonary fibrosis
(12) Patient with active infection requiring systemic therapy
(13) Patient with known hypersensitivity to any component of study drug

(14) Patient who is positive for HIV antibody, HCV antibody, and HCV-RNA, or HBs antigen. Patient who is positive for HBs or HBc antibody and showing DNA more than sensitivity in HBV-DNA assay

(15) 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).

(16) 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 the below note) 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.

(17) Woman who is pregnant or breastfeeding (not eligible even if she discontinues breastfeeding)

(18) Patient who was decided as inappropriate for medical or other reasons to participate in the study by the investigator or sub-investigator

(19) Patient who has a prior history of myeloid malignancy including T-cell lymphoblastic lymphoma, T-cell acute lymphoblastic leukemia or myelodysplastic syndrome

Note: Condom*, contraceptive sponge**, foam**, jelly**, diaphragm*, intrauterine device (IUD)*, or use of oral contraception* from 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.

9.3.3.1 Discontinuation Criteria by Subject

If a subject meets 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 subject

(2) Major violation of inclusion or exclusion criteria are found.

(3) Presence of adverse event that investigator or subinvestigator judged it is difficult to continue with therapy
(4) Pregnancy
(5) Evidence of disease progression. Subjects will be allowed to be treated with study drug if the investigator or subinvestigator judges that 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 BID (1600 mg total daily dose) will be administered orally by continuous regimen, no less than 8 hours between doses.

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

9.4.1.1 Tazemetostat Dose Reduction and Interruption Instructions

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, 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.

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 the sponsor or discontinue tazemetostat

ANC = absolute neutrophil count.
a: Tolerability of Grade 2 toxicities will be judged by the investigator or subinvestigator.
b: Dose interruption and reduction are 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 and follow the dose reduction and interruption instructions when it cannot be controlled.
c: Laboratory abnormalities judged to be non-life threatening, will be excluded and 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 that is related to the study treatment 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 and 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: $C_{34}H_{44}N_4O_4 \cdot HBr$
- Molecular weight: 653.65

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.

Screening 1

(1) The investigator, subinvestigator, or clinical research coordinator will issue the Subject ID Number to individual subjects who provide signed informed consent for tumor EZH2 gene mutation test and record the date of informed consent for the test in "Subject Screening Log."
(2) The archival tumor samples will be submitted to the central laboratory.
(3) The sponsor will be notified by fax immediately after the archival tumor samples are submitted.
(4) The result of the tumor EZH2 gene mutation test will be recorded in "Subject Screening Log."

Screening 2

The same Subject ID Number will be used for the same subject in Screening 1 and Screening 2, in principle.

(1) The investigator, subinvestigator, or clinical research coordinator will record the date of

informed consent for study treatment in "Subject Screening Log" for the subjects who were confirmed to have EZH2 gene mutation and have signed the consent.

(2) The investigator or subinvestigator will screen the subjects and determine subject eligibility based on the inclusion and exclusion criteria. The decision on the subject eligibility will be recorded in "Subject Screening Log."

(3) The sponsor will be notified of date of informed consent for study treatment, date of screening initiation, expected treatment start date, and eligibility decision by fax immediately after the investigator or subinvestigator determines the subject eligibility (registration to study).

(4) The investigator or subinvestigator will reconfirm the subject eligibility based on the results of baseline assessment 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 conducted outside Japan, the RP2D of tazemetostat has been determined to be 800 mg BID. As interim result of ongoing Phase 2 part of the study, encouraging efficacy of tazemetostat was reported in relapsed or refractory FL and DLBCL with EZH2 gene mutation.

In the Phase 1 study of the Study E7438-J081-106 conducted in Japan, no DLT was observed in tazemetostat 800 mg BID by continuous regimen; therefore, tazemetostat 800 mg BID, which is RP2D outside Japan, was confirmed to be well tolerated in Japanese subjects. Also, the favorable safety profile of tazemetostat has been shown in Japanese and non-Japanese subjects.

Based on these results, tazemetostat 800 mg BID by continuous regimen was selected in this study, and the efficacy and safety of tazemetostat 800 mg BID will be assessed in patients with relapsed or refractory B-cell NHL (FL and DLBCL).

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 for study treatment and until the final observation) will be recorded on the case report form (CRF). For all drugs, the name, dose/frequency, route, 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 premedications, 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 adverse events (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 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. However, 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

When anti-tumor therapies are implemented, study drug administration should be discontinued and the subject will be moved to the Follow-up Phase.

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. Skin-related AEs including dry skin and rash have been reported in clinical studies. 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 clinical research associate (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] as shown in Table 5) 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 (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 return 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 and noted on the CRF. The information to be collected at Screening 1 includes Subject ID Number, date of written informed consent for tumor EZH2 gene mutation test, date of birth (or age), sex, race, ethnicity, primary disease (date of diagnosis, disease diagnosis [see below]), and EZH2 gene mutation status (including known information of EZH2 gene mutation status, sampling date of tissues). The information to be collected at Screening 2 includes date of written informed consent for study treatment, clinical staging, B symptoms, prior therapies for primary disease.

(1) Primary disease
- Date of diagnosis
- Disease diagnosis (for DLBCL only: Cell-of-origin [COO] and test method)
- 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)

(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)

9.5.1.2 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 2. All medical history that is considered to have effects on efficacy or safety by the investigator or subinvestigator and medical conditions that are identified at Screening 2 must be noted on the CRF.

9.5.1.3 Efficacy Assessments

Efficacy assessment will be performed by investigator or subinvestigator based on “Revised response criteria for malignant lymphoma (IWG-2007)” (Cheson, et al., 2007). Overall response and best overall response (BOR) (best response recorded at the designated visits during the study) will be assessed. Perform the assessment below for tumor assessment.

CT scans will be performed at Screening 2, every 8 weeks from study drug administration up to first 32 weeks, then every 12 weeks and at discontinuation.

PET scans will be performed at Screening 2. If positive, perform when it is required to confirm CR as soon as possible or when clinically indicated.

If gastrointestinal disease is suspected, endoscopic examination will be performed at Screening 2. If exists, perform when it is required to confirm CR as soon as possible or when clinically indicated.

To evaluate bone marrow infiltration, a bone marrow aspiration or biopsy will be performed at Screening 2. If positive or indeterminate, perform when it is required to confirm CR as soon as possible or when clinically indicated.

Also, central review will be conducted by the Imaging Review Committee for CT and PET assessment. In addition, Efficacy and Safety Evaluation Committee (ESEC) will conduct central evaluation based on the review of Imaging Review Committee and other assessment / bone marrow infiltration evaluated by the investigator or subinvestigator, to determine the overall responses and the best overall response.

The primary endpoint and the secondary endpoint with regard to efficacy are defined as below, and will be evaluated by the result of ESEC review.

- ORR:
  The rate of subjects whose BOR is CR or PR.
- PFS:
  Defined as the term between the date of administration of the first dose of the study drug and the date of the first event (PD or death whichever occurs first). The detail of the censoring rule for PFS will be described in the statistical analysis plan (SAP).
- DOR:
  Defined as the term between the date of confirmation of the first response and the date of confirmation of the PD. The detail of the censoring rule for DOR will be described in the SAP.
- TTR:
  Defined as the term between the date of administration of the first dose of the study drug and the date of confirmation of the first response.

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

Storage and provision of data

In order to carry out central review by the Imaging Review Committee, CT/MRI images and PET images taken at Screening 2 and tumor evaluations will be stored at each site and provided to the imaging review vendor designated by the sponsor as electronic data after masking personal information of the subject.

Refer to the procedure manual (defined separately) for the provision of data.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Plasma trough concentrations of tazemetostat will be measured to evaluate pharmacokinetics in all of registered subjects.

Detailed blood sampling schedule for PK assessment is shown in Table 3. Procedures for collection, handling, and shipping for PK samples will be provided in a separate manual.

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

Actual time and date of PK blood samplings will be recorded in the CRF.

Table 3 Blood Sampling Schedule for Pharmacokinetic Assessment

Tazemetostat

Day	Sampling Time	Allowance (as a Target)
C1D15	Predose of first administration	Within 60 minutes before dosing
C2D1	Predose of first administration	Within 120 minutes before dosing

C#D# = Cycle # Day #.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

For subjects who provided informed consent for tumor EZH2 gene mutation test, archival formalin fixed paraffin embedded (FFPE) tumor samples will be submitted to the central laboratory to determine an EZH2 gene mutation (codons* Y646, A682, and A692) at Screening 1. Fresh biopsy of tumor is not available as the sample at Screening 1. Sampling date of tissues will be noted on the CRF.

* Y646F, Y646N, Y646S, Y646H, Y646C, A682G, A692V; results for codons Y646S, Y646H, and Y646C are not reported individually (grouped as Y646X).

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.

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.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, the sponsor will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as the results of the research project.

Subject Privacy and Disclosure of Data

Samples will be single coded (Subject ID number). No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample.

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible.

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

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

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

9.5.1.5 Safety Assessments

Safety assessments are shown in Table 5 (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, electrocardiograms (ECGs), ECOG-PS, and physical examinations.

9.5.1.5.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient. 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 protocol-required and 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, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the final observation visit. When subject needs to receive other anti-tumor therapy within 30 days after the final study drug administration, final observation must be conducted before initiation of other anti-tumor therapy. SAEs will be collected until the final observation visit.

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 (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator 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. When subject needs to receive other anti-tumor therapy within 30 days after the

final study drug administration considering the deterioration of subject's physical condition, final observation must be conducted before initiation of other anti-tumor therapy. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. For subjects who withdraw from the study and continuously use commercial tazemetostat, all AEs will be followed until discontinuation visit.

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 v4.03. 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

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

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. If subject experiences T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia, enrollment of subject should be discontinued.

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 Sections 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" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed 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 4. The Schedule of Procedures/Assessments (Table 5) 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 4 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, LDH, creatine phosphokinase, amylase, uric acid, glucose, triglycerides, cholesterol, sodium, chloride, potassium, calcium, phosphorus, INR[b]
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, RBC = red blood cell, WBC = white blood cell.

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).

b: Screening 2 only.

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/HEIGHT 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 5) 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 5). Documentation of the physical examination will be included in the source documentation at the site. Only changes from Screening 2 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 5) at each site. 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 ECOG PS

An ECOG performance status should be done at each visit as designated in the Schedule of Procedures/Assessments (Table 5).

9.5.1.5.7.2 Pregnancy Test

An hCG or β-hCG test will be performed for women of childbearing potential at each site. A serum or urine sample will be taken at visits as designated in the Schedule of Procedures/Assessments (Table 5).

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).

9.5.1.6.7.3 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 2.

When subjects have HBs antibody or HBc antibody positive results, HBV-DNA tests will be performed. When subjects have HCV antibody positive results, HCV-RNA tests will be performed. Viral tests will be performed at each site.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 5 presents the schedule of procedures/assessments for the study.

Table 5 Schedule of Procedures/Assessments in Study E7438-J081-206 (EZH-206)

Phase	Pre-treatment			Treatment				Follow-up	
Period	**Screening 1**	**Screening 2[a]**	**Baseline**	**Cycle 1**		**Cycle 2 and later**		**Discontinuation**	**Final observation**
Day		Within 28 days before admin	Within 3 days before admin	1	15 (±3)	1 (±3)	15[k] (±3)	(+7)	30 days after last dosing (+7)[b, l]
IC for EZH2 gene mutation test	X								
Archival tumor sample submission	X								
IC for study treatment[c]		X							
Demographic data	[X][d]	X							
Inclusion/exclusion Criteria		X	X						
Enrollment		X							
Medical history/Current medical condition		X							
Previous therapy		X							
Height		X							
Body weight		X	X		X	X	X	X	X
Physical examination		X	X		X	X	X	X	X
Vital signs		X	X		X	X	X	X	X
ECOG performance status		X	X			X		X	
12-lead ECGs		X	X		X	X	X	X	
Pregnancy test (if applicable)		X						X	
Virus test		X							
Hematology[j]		X	X		X	X	X	X	X
Blood chemistry		X	X		X	X	X	X	X
Urinalysis		X	X		X	X	X	X	X
PK blood sampling[e]					X	[X]			
Tumor assessments (CT/endoscopy)[f]		X				[X]		X	
Tumor assessments (PET)[g]		X				[X]			
Bone marrow examination (bone marrow aspiration or biopsy)[h]		X				[X]			
Tazemetostat administration[i]				Continuous 28-day cycle of twice daily (BID)					
Adverse events		From informed consent for study treatment to final observation							
Concomitant drug/therapies		From informed consent for study treatment to final observation							

Note, [X]: In case to perform.
admin = administration, BID = twice daily, C#D# = Cycle # Day #, CR = complete response, CT = computed tomography, ECG = electrocardiogram, ECOG-PS = Eastern Cooperative Oncology Group-Performance Status, IC = informed consent, PET = positron emission tomography, PK = pharmacokinetics.

a: Screening 2 assessments may be used as baseline assessments if performed within 3 days of the first administration of study drug.

b: When subject needs to receive other anti-tumor therapy 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.

c: Obtain from the patients who has confirmed tumor EZH2 gene mutation in central laboratory.

d: Collect demography information described in Section 9.5.1.1.

e: Blood samples for PK analyses of tazemetostat will be collected in C1D15 and C2D1 predose of first administration.

f: The data of CT scan/endoscopy before informed consent within 28 days from study drug administration can be used as Screening 2 data if it meets the requirement of the protocol. Perform tumor assessment at Screening 2, every 8 weeks from first study drug administration for first 32 weeks (±1 week, eg, C2D21 to C3D7, C4D21 to C5D7…C8D21 to C9D7), then every 12 weeks (±1 week, eg, C11D21 to C12D7, C14D21 to C15D7…) and discontinuation. The data within 28 days can be used as discontinuation data. If gastrointestinal disease were suspected, endoscopic examination will be performed at Screening 2. If exists, perform when it is required to confirm CR as soon as possible or when clinically indicated.

g: The data of PET scan before informed consent within 28 days from study drug administration can be used as Screening 2 data if it meets the requirement of the protocol. If positive, perform when it is required to confirm CR as soon as possible or when clinically indicated.

h: The data of bone marrow examination before informed consent within 42 days from study drug administration can be used as Screening 2 data if it meets the requirement of the protocol. If positive or indeterminate, perform when it is required to confirm CR as soon as possible or when clinically indicated.

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

j: 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.

k: 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.

l: Final observation is unnecessary for subjects who meet approved indication and receive commercial tazemetostat.

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, 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

All SAEs, regardless of their relationship to study treatment, 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 event. Completed 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 treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion. For subjects who withdraw from the study and continuously take commercial tazemetostat, all SAEs will be followed until discontinuation visit.

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's assessment of causality.

Any follow-up information received on SAEs should be forwarded 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. However, any pregnancy in which the estimated conception is after using commercial tazemetostat is not required to report, as these events are separately collected as spontaneous report.

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 to the sponsor 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 directly 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.

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 sites provide complete SAE information in the manner described above.

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 5).

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.

For subjects who discontinue the study early, 1 primary reason for discontinuation and study disposition information will be collected on the CRF.

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 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 1) after data cut-off for primary analysis or 2) after the study is completed and the database is locked and released. Data cut-off will be performed at Week 56 (after more than 12 months from the start of treatment to all subjects), or after the discontinuation of treatment before 12 months. 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 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

- ORR of BOR

9.7.1.1.2 SECONDARY ENDPOINTS

- PFS
- DOR
- TTR
- Safety assessments (AEs, clinical laboratory tests, vital signs, body weight, 12-lead ECGs, ECOG-PS, and physical examinations)

9.7.1.1.3 EXPLORATORY ENDPOINTS

- Concentration of tazemetostat
- Frequency of EZH2 gene mutation

9.7.1.2 Definitions of Analysis Sets

Efficacy Analysis Set will include efficacy evaluable subjects who received at least 1 administration of the study drug and who has at least 1 appropriate tumor assessment data of Screening 2 and post-baseline.

Pharmacokinetic Analysis Set will include subjects who received at least 1 administration of the study drug and had at least 1 concentration data of tazemetostat.

Biomarker Analysis Set will include subjects who have conducted EZH2 gene mutation assessment at Screening.

Safety Analysis Set will include subjects who received at least 1 administration of the study drug.

9.7.1.3 Subject Disposition

Subjects who signed informed consent (for tumor EZH2 gene mutation test and study treatment), were registered in the study, and failed screening (Screening 1 and Screening 2) 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 (cohort). Continuous demographic and baseline variables include age, height, and body weight; categorical variables include sex, age group, race, ethnics, ECOG-PS, diagnosis (including COO, as needed), clinical staging, B symptoms, and prior therapies for primary disease (chemotherapy, radiotherapy, and autologous stem cell transplantation, etc.).

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

This analysis will be performed on the Efficacy Analysis Set. All summary of efficacy will be conducted for each disease (cohort).

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

BOR will be summarized. The rate of subjects whose BOR is CR or PR is calculated as ORR, and its corresponding 2-sided exact 90% confidence intervals (CIs) using the method of Clopper–Pearson will also be calculated. 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.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

- Analysis of PFS
  PFS will be summarized by Kaplan-Meier method using median with 95%CI.
- Analysis of DOR
  DOR will be summarized by Kaplan-Meier method in responders.
- Analysis of TTR
  TTR will be summarized by descriptive statistics in responders.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

This analysis will be performed on the Pharmacokinetic Analysis Set. The plasma concentrations of tazemetostat will be summarized by timepoint.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

This analysis will be performed on the Biomarker Analysis Set. The rate of the tumor EZH2 gene mutation will be calculated in each disease.

9.7.1.8 Safety Analyses

This analysis will be performed on the Safety Analysis Set in whole or each disease (cohort).

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 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 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 by the investigator 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.

9.7.1.8.3 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 to 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.

9.7.1.8.4 VITAL SIGNS

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

9.7.1.8.5 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 msec
- QTcF interval >480 msec
- QTcF interval >500 msec

Change from baseline in QTcF interval:

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

9.7.1.8.6 OTHER SAFETY ANALYSES

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

9.7.2 Determination of Sample Size

In cohort 1, 8 efficacy evaluable FL patients with EZH2 mutation are required to detect lower limit of the 90% CI that exceed the 10% threshold in ORR, which is the primary endpoint of the study, with the expected ORR of 50% with power of approximately 80%.

In cohort 2, 13 efficacy evaluable DLBCL patients with EZH2 mutation are required to detect lower limit of the 90% CI that exceed the 10% threshold in ORR, which is the primary endpoint of the study, with the expected ORR of 40% with power of approximately 80%.

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 SAP 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.

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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 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 will conduct the study in strict accordance with the protocol.

11.3 Monitoring Procedures

The CRA will maintain contact with the investigator 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 IxRS, x-rays, and other imaging reports regardless of how these images are stored, including microfiche and photographic negatives
- 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
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs

11.4 Recording of Data

A CRF is required and must be completed for each subject who signed informed consent with regard to tumor EZH2 gene mutation test 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 correct 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 that are not documented in the medical records, including medical chart and worksheets, 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
- 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, assessment date, 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 until the approval of a marketing application, until at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product as directed by the sponsor, or until at least 3 years have elapsed since the discontinuation or completion of this clinical study, whichever comes later.

It is requested that at the completion of the required retention period the medical institution discuss with the sponsor if the relevant documents should be retained or not, as it may be necessary to retain the study records further period.

Note: The site should plan to retain all study documents of post-marketing study until the day of completion of the reexamination of Tazemetostat (the day of notification of the reexamination results).

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 drugs 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 investigators/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/the head of the medical 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 head of medical institution where applicable, and the investigator/the head of medical institution should promptly inform the sponsor and the IRB and provide the sponsor and the IRB with 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 2 Study of Tazemetostat in Relapsed or Refractory B-cell Non-Hodgkin's Lymphoma with EZH2 Gene Mutation

Study Protocol Number: E7438-J081-206 (EZH-206)

Protocol Pages	Before revision (Protocol V 3.0), 15 Nov 2019	After revision (Protocol V 4.0), 29 Jan 2021	Rationale
1	**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.	**GCP Statement:** This study is to be performed in full compliance with all applicable local Good Clinical Practice (GCP) and regulations (Good Post-marketing Study Practice [GPSP] in case of post-marketing study). All required study documentation will be archived as required by regulatory authorities.	Addition of the description for transition to a post-marketing study
2	Phase of development: Phase 2	Phase of development: Phase 2 (Note: subjects who meet approved indication of E7438 in Japan will continue this study as a post-marketing study.)	The same as above
7	**Duration of Treatment** Treatment will continue until disease progression (site evaluation), development of unacceptable toxicity, subject's requests to discontinue, withdrawal of consent, or study termination by the sponsor.	**Duration of Treatment** Treatment will continue until disease progression (site evaluation), development of unacceptable toxicity, subject's requests to discontinue, withdrawal of consent, or study termination by the sponsor. [Subjects who meet approved indication of tazemetostat in Japan] As per regulatory requirements in Japan, from the time tazemetostat is approved by the regulatory authority, these subjects will continue this study as a post-marketing study. Treatment will continue until tazemetostat is commercially	The same as above

Protocol Pages	Before revision (Protocol V 3.0), 15 Nov 2019	After revision (Protocol V 4.0), 29 Jan 2021	Rationale
		available for individual subjects at each study site, at which time the subjects will be switched to commercial tazemetostat.	
7	**Assessments** **Efficacy Assessments** Efficacy assessment will be performed by investigator or subinvestigator based on "Revised response criteria for malignant lymphoma (IWG-2007)" (Cheson, et al., 2007). Overall response and best overall response (BOR) (best response recorded at the designated visits during the study) will be assessed. …. Also, central review will be conducted by the Imaging Review Committee for CT and PET assessment.	**Assessments** **Efficacy Assessments** Efficacy assessment will be performed by investigator or subinvestigator based on "Revised response criteria for malignant lymphoma (IWG-2007)" (Cheson, et al., 2007). Overall response and best overall response (BOR) (best response recorded at the designated visits during the study) will be assessed. …. Also, central review will be conducted by the Imaging Review Committee for CT and PET assessment which is obtained within 24 months after the last subject's enrollment (cut-off date: 02 Dec 2020).	To clarify the rules about central review

Protocol Pages	Before revision (Protocol V 3.0), 15 Nov 2019	After revision (Protocol V 4.0), 29 Jan 2021	Rationale
16	**4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS** No corresponding description	**4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS** Added: GPSP Good Post-marketing Study Practice	Addition of the description for transition to a post-marketing study
18	**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	**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 In addition, after tazemetostat is approved by the Japanese regulatory authority, the study will be conducted as a post-marketing study as per regulatory requirements of GPSP.	The same as above
31	**9.1 Overall Study Design and Plan** The study will assess efficacy and safety of tazemetostat in FL patients with EZH2 gene mutation in cohort 1, and DLBCL (including primary mediastinal B-cell lymphoma and transformed FL) patients with EZH2 gene mutation in cohort 2.	**9.1 Overall Study Design and Plan** The study will assess efficacy and safety of tazemetostat in FL patients with EZH2 gene mutation in cohort 1, and DLBCL (including primary mediastinal B-cell lymphoma and transformed FL) patients with EZH2 gene mutation in cohort 2. Note: As per regulatory requirements in Japan, from the time tazemetostat is approved by the regulatory authority,	The same as above

Protocol Pages	Before revision (Protocol V 3.0), 15 Nov 2019	After revision (Protocol V 4.0), 29 Jan 2021	Rationale
		subjects who meet approved indication of tazemetostat will continue this study as a post-marketing study (clinical study shall be deemed to post-marketing study in this protocol) until tazemetostat is commercially available for individual subjects at each study site. For these subjects, the end of the study will be the date of the last study treatment or evaluation at discontinuation, whichever comes later.	
32	9.1.1.3 Follow-up Phase 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.	9.1.1.3 Follow-up Phase 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. Final observation is unnecessary for subjects who withdraw from the study and continuously take commercial tazemetostat.	The same as above
47	9.5.1.5.1 Adverse Events All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.	9.5.1.5.1 Adverse Events All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. For subjects who withdraw from the study and continuously use commercial tazemetostat, all AEs will be followed until discontinuation visit.	The same as above

Protocol Pages	Before revision (Protocol V 3.0), 15 Nov 2019	After revision (Protocol V 4.0), 29 Jan 2021	Rationale
48	9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations ● Requires inpatient hospitalization or prolongation of existing hospitalization for the purpose of therapy	9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations ● Requires inpatient hospitalization or prolongation of existing hospitalization	For the updated protocol template
53	9.5.2.1 Schedule of Procedures/Assessments No corresponding description	9.5.2.1 Schedule of Procedures/Assessments Addition of the footnote l	Additional description for transition to a post-marketing study
54	9.5.4.1 Reporting of Serious Adverse Events Any SAE judged by the investigator or subinvestigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.	9.5.4.1 Reporting of Serious Adverse Events Any SAE judged by the investigator or subinvestigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion. For subjects who withdraw from the study and continuously take commercial tazemetostat, all SAEs will be followed until discontinuation visit.	The same as above

Protocol Pages	Before revision (Protocol V 3.0), 15 Nov 2019	After revision (Protocol V 4.0), 29 Jan 2021	Rationale
54-55	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.	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. However, any pregnancy in which the estimated conception is after using commercial tazemetostat is not required to report, as these events are separately collected as spontaneous report.	The same as above
69	**11.6 Retention of Records** It is requested that at the completion of the required retention period the medical institution discuss with the sponsor if the relevant documents should be retained or not, as it may be necessary to retain the study records further period.	**11.6 Retention of Records** It is requested that at the completion of the required retention period the medical institution discuss with the sponsor if the relevant documents should be retained or not, as it may be necessary to retain the study records further period. Note: The site should plan to retain all study documents of post-marketing study until the day of completion of the reexamination of Tazemetostat (the day of notification of the reexamination results).	The same as above

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