Report on the Deliberation Results

June 1, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Tazverik Tablets 200 mg
Non-proprietary Name	Tazemetostat Hydrobromide (JAN*)
Applicant	Eisai Co., Ltd.
Date of Application	June 30, 2020

Results of Deliberation

In its meeting held on May 28, 2021, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of extremely limited data from Japanese clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product in the post-marketing setting until data are available from a certain number of patients, to understand the characteristics of patients using the product and to collect safety and efficacy data promptly so that necessary measures are taken to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

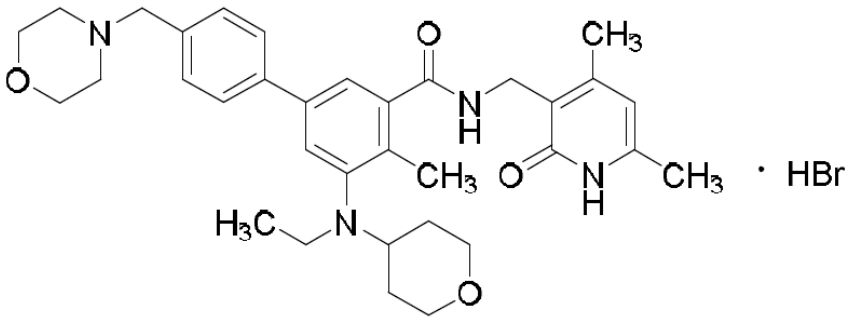
Review Report

April 28, 2021
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Tazverik Tablets 200 mg
Non-proprietary Name	Tazemetostat Hydrobromide
Applicant	Eisai Co., Ltd.
Date of Application	June 30, 2020
Dosage Form/Strength	Tablets, each containing 228.3 mg of Tazemetostat Hydrobromide (200 mg of Tazemetostat)
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{34}H_{44}N_4O_4$•HBr

Molecular weight: 653.65

Chemical name: *N*-[(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-5-[ethyl(oxan-4-yl)amino]-4-methyl-4'-[(morpholin-4-yl)methyl]biphenyl-3-carboxamide monohydrobromide

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with relapsed or refractory *EZH2* gene mutation-positive follicular lymphoma (limited to those refractory to standard treatments), and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Infection, bone marrow depression, secondary malignant tumor, and photosensitivity should be further evaluated in the post-marketing investigations.

Indication

Relapsed or refractory *EZH2* gene mutation-positive follicular lymphoma (limited to those refractory to standard treatments)

Dosage and Administration

The usual adult dosage is 800 mg of Tazemetostat administered orally twice daily. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of extremely limited data from Japanese clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product in the post-marketing setting until data are available from a certain number of patients, to understand the characteristics of patients using the product and to collect safety and efficacy data promptly so that necessary measures are taken to ensure the proper use of the product.

Attachment

Review Report (1)

March 15, 2021

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Tazverik Tablets 200 mg
Non-proprietary Name	Tazemetostat Hydrobromide
Applicant	Eisai Co., Ltd.
Date of Application	June 30, 2020
Dosage Form/Strength	Tablets, each containing 228.3 mg of Tazemetostat Hydrobromide (200 mg of Tazemetostat)
Proposed Indication	Relapsed or refractory *EZH2* gene mutation-positive follicular lymphoma (excluding treatment-naïve patients)
Proposed Dosage and Administration	The usual adult dosage is 800 mg of Tazemetostat administered orally twice daily. The dose may be reduced according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Enhancer of zeste homolog 2 (EZH2) is one of the components that constitute a polycomb repressive complex that regulates gene expression through histone modification. EZH2 catalyzes the reaction (methylation), in which methyl residues are added to lysine residues in proteins such as histone, leading to the aggregation of chromatin structure, thereby suppressing gene transcription. This action mechanism is involved in differentiation, growth, etc. of germinal center cells (*Proc Natl Acad Sci USA*. 2015;112:E1116-25, etc.).

Tazemetostat Hydrobromide (hereinafter referred to as tazemetostat) is a low molecular weight compound that inhibits EZH2, discovered by Epizyme, Inc (US). Tazemetostat is thought to inhibit EZH2 methylation thereby inducing cell cycle arrest and apoptosis, consequently suppressing tumor growth.

1.2 Development history, etc.

Overseas, a phase I/II study (Study E7438-G000-101 [Study 101]) began in patients with relapsed or refractory B cell lymphoma, etc. in June 2013 by Epizyme, Inc. (US).

In the US, an application for tazemetostat was submitted in December 2019 with data from Study 101, a pivotal study, and tazemetostat was granted an accelerated approval with the following indication: "TAZVERIK is indicated for the treatment of: adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options. These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)."

As of February 2021, tazemetostat has been approved in the US only for the indication of relapsed or refractory follicular lymphoma (FL).

In Japan, the applicant began a phase I study (Study E7438-J081-106 [Study 106]) in patients with relapsed or refractory FL or diffuse large B-cell lymphoma (DLBCL) in January 2017 and a phase II study (Study E7438-J081-206 [Study 206]) in patients with relapsed or refractory *EZH2* gene mutation-positive FL or DLBCL in April 2018.

Recently, the approval application for tazemetostat was submitted with the pivotal data from Studies 101 and 206.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder. Its general properties, including description, solubility, dissociation constant, partition coefficient, thermal analysis, and hygroscopicity were determined. The drug substance occurs in 3 different crystalline forms (Crystalline Forms A, B, and C) as [redacted], but only Crystalline Form A has been confirmed to be produced in the commercial-scale production and shown not to convert into other forms in a stability study.

The chemical structure of the drug substance was elucidated by elemental analysis, ultraviolet spectrophotometry, infrared absorption spectrum (IR), mass spectrometry, nuclear magnetic resonance spectrum (NMR) (^{1}H-NMR and ^{13}C-NMR), and single crystal X-ray diffractometry.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted], [redacted], [redacted], [redacted], and [redacted] as the starting materials.

The quality control strategy was developed through the following investigations, etc. using a quality-by-design (QbD) approach (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) and the investigation of acceptable range of manufacturing process parameters based on the quality risk assessment and on the experimental design method

Table 1. Outline of the quality control strategy for the drug substance

CQA	Controlling method
Identification	Specifications
Content	Specifications
Related substances	Manufacturing process and specifications
Content of hydrobromic acid	Manufacturing process and specifications
Residual solvents	Manufacturing process and specifications
Elemental impurities	Specifications
Crystalline form	Manufacturing process and specifications
Particle size distribution	Manufacturing process and specifications

Synthesis of [redacted],[1)] [redacted],[2)] [redacted], and [redacted], and [redacted] are identified as the critical steps, and in-process control parameters and the action limits are defined in all synthesis steps. [redacted],[3)] [redacted], [redacted],[4)] [redacted],[5)] [redacted], [redacted], and [redacted] are controlled as critical intermediates.

1) [redacted]
2) [redacted]
3) [redacted]
4) [redacted]
5) [redacted]

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR and liquid chromatography [LC]), crystalline form (X-ray powder diffractometry), purity (related substances [LC], residual solvents [gas chromatography (GC)], elemental impurities [inductively coupled plasma mass spectrometry]), water content, residue on ignition, particle size, microbial limit, and assay (drug substance [LC] and hydrobromic acid [potentiometric titration]).

2.1.4 Stability of drug substance

Table 2 shows main stability studies for the drug substance. Results demonstrated the stability of the drug substance. The photostability testing showed that the drug substance was photo-unstable.

Table 2. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 pilot-scale batches	25°C	60% RH	[redacted] polyethylene bag (double-layered) + [redacted] drum	24 months
Testing under intermediate conditions	3 pilot-scale batches	30°C	75% RH		24 months
Accelerated testing	3 pilot-scale batches	40°C	75% RH		6 months

Based on the above, a retest period of [redacted] months was proposed for the drug substance when stored at room temperature protected from light in a double-layered [redacted] polyethylene bag, which is placed in [redacted] drum, according to "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Q1E Guideline). A long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release film-coated tablets, each containing 228.3 mg of the drug substance (200 mg of tazemetostat). The drug product contains, as excipients, lactose hydrate, low substituted hydroxypropylcellulose, hydroxypropylcellulose, sodium starch glycolate, magnesium stearate, and Opadry Red [redacted].

2.2.2 Manufacturing process

Two manufacturing processes (batch method and continuous production method) were proposed in the present application. In both methods, the process is comprised of the following steps: mixing 1, granulation, drying, particle size refining, mixing 2, tableting, coating, and filling/packaging/labeling. The continuous production method employs wet granulation technique, in which the steps from [redacted] to [redacted] are integrated in one system, and the [redacted], [redacted], and [redacted] steps are performed continuously by [redacted].

The strategy for quality control was developed by the following investigations, etc. using a QbD approach (Table 3):

- Identification of CQAs

- Investigation of the acceptable range of manufacturing process parameters based on the quality risk assessment and on the experimental design method

Table 3. Outline of the control strategy for drug product

CQA	Controlling method
Appearance (description)	Manufacturing process and specifications
Identification	Specifications
Content	Manufacturing process and specifications
Related substances	Specifications
Uniformity of dosage units	Manufacturing process and specifications
Dissolution	Manufacturing process and specifications
Crystalline form	-
Water content	Manufacturing process
Microbiological characteristics	Manufacturing process and specifications

-, Not applicable

The critical steps include [redacted],[6] [redacted],[6] [redacted], [redacted],[6] and [redacted] steps, and in-process control parameters and action limits are specified in [redacted], [redacted], [redacted], [redacted], [redacted], [redacted],[7] and [redacted] steps.

2.2.3 Control of drug product

The proposed specifications for the drug product include content, description, identification (ultraviolet spectrophotometry and LC), purity (related substances [LC]), uniformity of dosage units (content uniformity [ultraviolet and visible spectrophotometry]), dissolution (ultraviolet and visible spectrophotometry), microbial limit, and assay (LC).

2.2.4 Stability of drug product

Table 4 shows the main stability studies conducted on the drug product. Results demonstrated the stability of the drug product. The photostability testing showed that the drug product was photo-stable.

Table 4. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term testing	Pilot scale: 3 batches each of (a) [redacted] and (b) [redacted]	25°C	60% RH	Blister pack (polyvinyl chloride and aluminum)	(a) 18 months (b) [redacted] months
Accelerated testing		40°C	75% RH		6 months

Based on the above results and on the investigation described in Section "2.R.3 Shelf-life of drug product," a shelf-life of 30 months was proposed for the drug product when stored at room temperature in blister pack (polyvinyl chloride and aluminum), according to ICH Q1E Guideline. A long-term storage testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data and on the results of the following reviews, PMDA concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

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6) Defined as a critical step only in the continuous production method.
7) Specified only in the batch production method.

2.R.1 Definition of batch in the continuous production method

The applicant's explanation about (a) the definition of batch and (b) the sampling method in release testing in the continuous production method:

(a) One batch is defined by [redacted] and based on the load of [redacted] in the [redacted] step.

(b) In the release testing of the drug product manufactured by the continuous production method, the sampling method was the same as that in [redacted], because the comparability of the quality of [redacted] is adequately guaranteed by the process control based on the following:

- In the steps from [redacted] to [redacted] in the continuous production method, process control is designed to verify the comparability of the quality of [redacted] and to detect quality variations owing to [redacted].
- The process control in the [redacted] step is designed to verify over-time quality.

PMDA accepted the applicant's explanation.

2.R.2 Granulation in continuous production method

The applicant's explanation:

Granulation starts after the mixed powder is produced in the mixing 1 step and is [redacted] in a loss in weight feeder (LIW feeder) [redacted]. A fixed amount of mixed power is supplied from the LIW feeder and mixed with [redacted] added from a [redacted], and poured into the granulator. The [redacted] is granulated continuously with [redacted] and [redacted], and discharged from the granulator. [redacted] of the granules produced are measured by [redacted] before being poured into a [redacted]. If [redacted] of the granules deviates from the acceptance range ([redacted]), the [redacted] located between the [redacted] and the [redacted] is switched over to sequester granules of acceptable [redacted], during which [redacted] and [redacted] continue operating. In addition to the acceptance range of [redacted], an action limit ([redacted]) is determined. When [redacted] alerts the deviation of granule [redacted] from the action limit, the operator changes [redacted] or [redacted] according to the product master formula.

PMDA asked the applicant to explain the reason for controlling [redacted] at [redacted] in the granulation step.

The applicant's explanation:

Because the [redacted] of granules may affect the quality attributes of the product such as [redacted], the [redacted] of granules was defined as a material attribute for the [redacted] of the drug product. The [redacted] of the drug product has been confirmed to meet the specification if the [redacted] of granules is within the acceptable range ([redacted]).

Regarding the change in [redacted] and [redacted] of granules when [redacted] or [redacted], both of which are CPPs of the granulation step, is changed, the correlation coefficient (R) to [redacted] and [redacted] was [redacted] and [redacted] (a) if [redacted] was changed and [redacted] and [redacted] (b) if [redacted] was changed. R of [redacted] and [redacted] in (a) and (b) is [redacted] and showed a sufficient correlation to change in the CPP. However, since [redacted] showed a higher correlation, it was decided to control [redacted] of granules in the granulation step by [redacted].

PMDA accepted the applicant's explanation.

2.R.3 Shelf-life of drug product

The applicant's explanation about the shelf-life of the drug product:

The following points indicate no clear difference in the quality and stability between products manufactured by the batch method and those manufactured by the continuous production method. Therefore, the shelf-life of the drug product can be determined based on long-term testing using the drug product manufactured by the [redacted] method.

- The batch method and the continuous production method share the same manufacturing theory (tablet production by wet granulation), and also the [redacted] of both drug products are the same.
- Batch analyses of both drug products gave identical results.
- A dissolution test conducted based on "Guidelines for bioequivalence studies for different strength of oral solid dosage forms (PMSB/ELD Notification No. 64, dated February 14, 2000) demonstrated identical dissolution behavior of both drug products.
- Comparative studies on both drug products identified no clear difference.

PMDA's view:

Based on the applicant's explanation above and in light of the following points, it is considered acceptable to determine the shelf-life of the drug product according to the results of the long-term testing using the drug product manufactured by the [redacted] method.

- The following controls on the drug product manufactured by the [redacted] method will ensure the comparability of quality with the drug product manufactured by the [redacted] method.
  - It is ensured that the quality is controlled [redacted] in the mixing 1, mixing 2, and drying steps.
  - It is ensured that [redacted] of the granules measured by [redacted] is controlled in the granulation step that uses [redacted].
  - It is ensured that [redacted] is measured and controlled in the tableting step.

- The results of long-term testing up to [redacted] months and the accelerated testing up to 6 months did not detect any difference in the stability between the 2 drug products.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The dosage amount and concentration of tazemetostat are expressed in terms of hydrobromide unless specified otherwise.

3.1 Primary pharmacodynamics

3.1.1 Inhibition effect against histone methylation

3.1.1.1 *In vitro* (CTD 4.2.1.1.1, 4.2.1.1.3, 4.2.1.1.7, and 4.2.1.1.9)

The inhibitory effect of tazemetostat against histone methylation by 19 types of human histone methyltransferases (HMTs) (recombinant protein) including EZH2 mutants was investigated by determining the amount of radiolabeled methyl group transferred by the enzymatic reaction. Table 5 shows IC_{50} of tazemetostat against each HMT.

Table 5. Inhibitory effect of tazemetostat against histone methylation by each HMT

HMT	n	IC_{50} (nmol/L)	HMT	n	IC_{50} (nmol/L)
CARM1	2	>50,000, >50,000	$EZH2^{Y646H*5}$	1	6
DOT1L	1	>50,000	$EZH2^{Y646N*6}$	2	9.4, 66.4
EHMT1	1	>50,000	$EZH2^{Y646S*7}$	1	6
EHMT2	1	>50,000	PRMT1	1	>50,000
EZH1	4	392 ± 72	PRMT5/MEP50	1	>50,000
EZH2	4	11 ± 5	PRMT8	1	>50,000
$EZH2^{A682G*1}$	2	1.3, 2.2	SMYD2	1	>50,000
$EZH2^{A692V*2}$	2	1.5, 1.9	WHSC1	1	>100,000
$EZH2^{Y646C*3}$	1	16	WHSC1L1	1	>100,000
$EZH2^{Y646F*4}$	3	14 ± 5			

Mean ± standard deviation (SD), Individual values for n = 1 or 2
*1, Alanine at position 682 is replaced by glycine. *2, Alanine at position 692 is replaced by valine. *3, Tyrosine at position 646 is replaced by cysteine. *4, Tyrosine at position 646 is replaced by phenylalanine. *5, Tyrosine at position 646 is replaced by histidine. *6, Tyrosine at position 646 is replaced by asparagine. *7, Tyrosine at position 646 is replaced by serine.

Using human DLBCL-derived OCI-Ly19 cell line expressing wild-type EZH2, the inhibitory effects of tazemetostat against methylation of lysine residues in histone H3 (histone H3 lysine 4 [H3K4], histone H3 lysine 9 [H3K9], histone H3 lysine 27 [H3K27], histone H3 lysine 36 [H3K36], and histone H3 lysine 79 [H3K79]) were investigated by Western blotting. Results showed the inhibitory effect of tazemetostat against methylation of H3K27.

Using human DLBCL-derived cell lines expressing 6 types of wild-type and mutant EZH2, the inhibitory effect of tazemetostat against histone H3 lysine 27 trimethylation (H3K27me3) was investigated by Western blotting. Table 6 shows IC_{50} of tazemetostat.

Table 6. Inhibitory effect of tazemetostat against H3K27me3 in DLBCL-derived cell lines

Cell line	EZH2	IC_{50} (nmol/L)
OCI-Ly19	Wild type	8
Pfeiffer	A682G	2
WSU-DLCL2	Y646F	9
SU-DHL-6	Y646N	20
KARPAS-422	Y646N	90
RL	Y646N	22

n = 1

Using 10 types of cell lines derived from human malignant tumors, the inhibitory effect of tazemetostat against H3K27me3 was investigated by Western blotting. Table 7 shows IC_{50} of tazemetostat.

Table 7. Inhibitory effect of tazemetostat against H3K27me3 in cell lines derived from malignant tumors

Cell line	Origin	EZH2	IC_{50} (nmol/L)
RD	Rhabdomyosarcoma	Wild type	5.6
SJCRH30			4.9
G401	Malignant rhabdoid tumor	Active form[8)]	2.7
A204			1.4
G402			1.7
KYM-1			4.3
Bin-67	Small cell ovarian carcinoma of the hypercalcemic type		8
COV434			8
TOV112D			10
OVK18			32

n = 1

3.1.1.2 *In vivo* (CTD 4.2.1.1.10 and 4.2.1.1.13)

Using (a) severe combined immunodeficient (SCID) mice subcutaneously transplanted with WSU-DLCL2 cell line expressing mutant EZH2 (Y646F) and (b) nude mice subcutaneously transplanted with KARPAS-422 cell line expressing mutant EZH2 (Y646N) (n = 6/group), the inhibitory effect of tazemetostat against H3K27me3 was investigated by enzyme-linked immunosorbent assay (ELISA). The following results were obtained:

(a) Starting from the day when the tumor volume reached 117 to 119 mm^3 (Day 1), tazemetostat was administered orally TID for 7 days at a dose of 160 mg/kg[9)] or for 28 days at a dose of 40, 80, or 160 mg/kg,[9)] and the expression level of H3K27me3 protein in the tumor tissue was measured at 3 hours after the last dose. The results showed the inhibitory effect of tazemetostat against H3K27me3 in all tazemetostat groups.

(b) Starting from the day when the tumor volume reached 250 mm^3 (Day 1), tazemetostat was administered orally for 7 days QD at a dose of 150, 301, 602, or 1,203 mg/kg or BID at a dose of 75, 150, 301, or 602 mg/kg, and the expression level of H3K27me3 protein in the tumor tissue was measured at 3 hours after the last dose. The results showed a statistically significant inhibitory effect against H3K27me3 in all tazemetostat groups compared with the control group[10)] ($P < 0.05$, Dunnett test).

3.1.2 Cell cycle-arresting effect (CTD 4.2.1.1.3 and 4.2.1.1.7)

Using RD cell line expressing wild-type EZH2, G401 cell line expressing active[8)] EZH2, and WSU-DLCL2 cell line expressing mutant EZH2 (Y646F), the cell cycle-arresting effect of tazemetostat[9)] was investigated using flow cytometry with propidium iodide (PI) staining as the index. The results showed tazemetostat-induced cell cycle arrest at stage G1 in G401 and WSU-DLCL2 cell lines.

3.1.3 Apoptosis induction (CTD 4.2.1.1.3 and 4.2.1.1.7)

Using RD cell line expressing wild-type EZH2, G401 cell line expressing active[8)] EZH2, and WSU-DLCL2 cell line expressing mutant EZH2 (Y646F), the apoptosis induction of tazemetostat was investigated with terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL)

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8) Despite no mutation in *EZH2* gene, (a) G401, A204, G402, KYM-1, Fuji, and HS-SY-II cell lines and (b) Bin-67, COV434, TOV112D, and OVK18 cell lines have a deletion, etc. of (a) SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member1 (*SMARCB1*) gene and (b) SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member2 (*SMARCA2)* gene, and SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member4 (*SMARCA4*) gene, which suppressively regulate the methylating activity of EZH2 (*Cancer Cell*. 2010;18:316-28, *Biochemistry.* 2016;55:1600-14, etc.).

9) The amount as tazemetostat hydrochloride

10) 0.5% Carboxymethylcellulose sodium and 0.1% polysorbate 80

staining as the index. Results showed the apoptosis induction of tazemetostat in G401 and WSU-DLCL2 cell lines.

3.1.4 Growth-inhibitory effect against malignant tumor-derived cell lines

3.1.4.1 *In vitro* (CTD 4.2.1.1.3, 4.2.1.1.6, 4.2.1.1.7, 4.2.1.1.8, and 4.2.1.1.9)

The growth-inhibitory effect of tazemetostat[11)] against human DLBCL-derived cell lines expressing 10 types of wild-type and mutant EZH2 was investigated by flow cytometry. Table 8 shows IC_{50} of tazemetostat.

Table 8. Growth-inhibitory effect of tazemetostat against human DLBCL-derived cell lines

Cell line	EZH2	n	IC_{50} (nmol/L)
OCI-Ly19	Wild type	5	5,700 ± 4,900
DOHH-2		1	1,700
Farage		1	99
Toledo		1	7,600
Pfeiffer	A682G	1	0.83
WSU-DLCL2	Y646F	8	12 ± 2.3
SU-DHL-10		1	5.8
SU-DHL-6	Y646N	1	4.7
KARPAS-422		1	1.8
RL		1	5,800

Mean ± standard error (SE), Individual value for n = 1

The growth-inhibitory effect of tazemetostat against human malignant tumor-derived cell lines expressing 12 types of wild-type and mutant EZH2 was investigated using the amount of viable cell-derived adenosine triphosphate (ATP) as the index. Table 9 shows IC_{50} of tazemetostat.

Table 9. Growth-inhibitory effect of tazemetostat against human malignant tumor-derived cell lines

Cell line	Origin	EZH2	n	IC_{50} (μmol/L)
RD	Rhabdomyosarcoma	Wild type	2	6.1, >10
SJCRH30			2	5.1, >10
SW982	Synovial sarcoma		3	>10
Fuji		Active form[8)]	3	0.15 ± 0.029
HS-SY-II			3	0.52 ± 0.042
G401	Malignant rhabdoid tumor		2	0.141, 0.129
A204			3	1.11 ± 0.262
G402			2	0.170, 0.119
KYM-1*			3	0.032 ± 0.007
Bin-67	Small cell ovarian carcinoma of the hypercalcemic type		1	0.29
COV434			1	0.073
TOV112D			1	0.34
OVK18			1	0.86

Mean ± SE; Individual values for n = 1 or 2

* The growth inhibitory effect of tazemetostat against strain KYM-1 was investigated by flow cytometry.

3.1.4.2 *In vivo* (CTD 4.2.1.1.10, 4.2.1.1.11, 4.2.1.1.12, 4.2.1.1.14, 4.2.1.1.15, 4.2.1.1.16, 4.2.1.1.17, and 4.2.1.1.18)

Using SCID mice subcutaneously transplanted with WSU-DLCL2 cell line expressing mutant EZH2 (Y646F) (n = 6 or 12/group), the growth-inhibitory effect of tazemetostat was investigated. Starting from the day when the tumor volume reached 117 to 119 mm^3 (Day 1), tazemetostat 40, 80, or

11) Hydrochloride was used. Types of the salt used with OCI-Ly19, Pfeiffer, and WSU-DLCL2 cell lines are unknown. With SU-DHL-10, DOHH-2, Farage, and Toledo cell lines, multiple types of salts were used while the table provides only the results of cell lines investigated using hydrochloride.

160 mg/kg[9] was administered orally TID for 28 days, or cyclophosphamide hydrate (cyclophosphamide) 100 mg/kg was administered intraperitoneally QD for 5 days, and tumor volume was calculated. On Day 29, a statistically significant tumor growth-inhibitory effect was observed in the cyclophosphamide group and in the tazemetostat 160 mg/kg group as compared with the control[10] group (Figure 1).

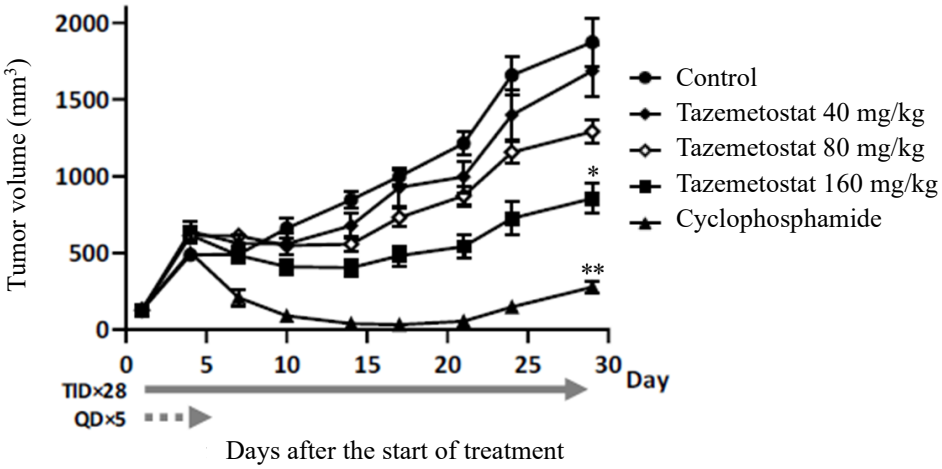

Figure 1. Tumor growth-inhibitory effect against SCID mice subcutaneously transplanted with WSU-DLCL2 cell line

N = 6 or 12; Mean ± SE; * $P < 0.01$ against the control group (Dunnett test); ** $P < 0.001$ against the control group (Dunnett test)

Using nude mice subcutaneously transplanted with KARPAS-422 cell line expressing mutant EZH2 (Y646N) (n = 9/group), the tumor growth-inhibitory effect of tazemetostat was investigated. The dosing method is as follows: (a) Starting from the time point when tumor volume reached 150 mm^3 (Day 1), tazemetostat 80.5, 161, 322, or 644 mg/kg[9] was administered orally BID for 28 days, or starting from the time point when tumor volume reached 203 to 209 mm^3 (Day 1), (b) tazemetostat 90 or 361 mg/kg was administered orally BID for 28 days, (c) in a 14-day treatment cycle, tazemetostat 90 or 361 mg/kg was administered orally BID for 7 days, followed by a 7-day withdrawal period, and the treatment cycle was repeated again (intermittent administration), or (d) tazemetostat 90 or 361 mg/kg was administered orally BID for 21 days, followed by a 7-day withdrawal period. On Day 29, a statistically significant tumor growth-inhibitory effect was observed in all tazemetostat groups compared with the control[10] group ($P < 0.05$, Dunnett test).

Using NSG mice[12] subcutaneously transplanted with Pfeiffer cell line expressing mutant EZH2 (Y682G) (n = 9/group), the tumor growth-inhibitory effect of tazemetostat was investigated. Starting from the time point when tumor volume reached 323 mm^3 (Day 1), tazemetostat was administered orally QD at a dose of 34.2, 114, or 342 mg/kg for 28 days or at a dose of 1,140 mg/kg for 12 days. On Day 29, a statistically significant tumor growth-inhibitory effect was observed in all tazemetostat groups compared with the control[10] group ($P < 0.05$, Dunnett test).

Using SCID mice subcutaneously transplanted with (a) OCI-Ly19, (b) Toledo, or (c) human B-cell lymphoma-derived MC116 cell line, each expressing wild-type EZH2, (n = 8/group), the tumor growth-

[12] A mouse strain without IL-2 receptor γ chain, originated from non-obese diabetic/severe combined immunodeficient (NOD/SCID) mice

inhibitory effect of tazemetostat was investigated. Starting from the time point when tumor volume reached 120 to 140 mm^3 (Day 1), tazemetostat 143 or 571 mg/kg was administered orally BID for (a) 20 days, (b) 28 days, or (c) 17 days. The following results were obtained:

(a) On Day 21, a statistically significant tumor growth-inhibitory effect was observed in all tazemetostat groups as compared with the control[10] group ($P < 0.05$ in the tazemetostat 143 mg group, $P < 0.001$ in the tazemetostat 571 mg group; Games-Howell test).
(b) On Day 29, a statistically significant tumor growth-inhibitory effect was observed in the tazemetostat 571 mg/kg group as compared with the control[10] group ($P < 0.01$, Games-Howell test).
(c) On Day 17, a statistically significant tumor growth-inhibitory effect was observed in the tazemetostat 571 mg/kg group as compared with the control[10] group ($P < 0.01$, Games-Howell test).

Using SCID mice subcutaneously transplanted with (a) WSU-DLCL2 cell line or (b) SU-DHL-10 cell line, both of which express mutant EZH2 (Y646F), the tumor growth-inhibitory effect of tazemetostat was investigated (n = 12/group in [a], n = 16/group in [b]). The following results were obtained:

(a) A statistically significant tumor growth-inhibitory effect was observed in the group receiving the combination of tazemetostat[9] and cyclophosphamide, doxorubicin, vincristine, prednisolone/prednisone/methylprednisolone (CHOP) as compared with the control[10] group ($P < 0.0001$, Bonferroni test).
(b) A statistically significant tumor growth-inhibitory effect was observed in the group receiving the combination of tazemetostat and cyclophosphamide, vincristine, prednisolone/prednisone/methylprednisolone (CVP) as compared with the control[10] group ($P < 0.001$, Dunnett test).

3.2 Secondary pharmacology

3.2.1 Effect on receptors, ion channels, and transporters (CTD 4.2.1.2.1)

The inhibitory effect of tazemetostat against 80 types of receptors, ion channels, and transporters was investigated. Tazemetostat[9] 10 μmol/L inhibited muscarine M4 receptor by ≥50%, with IC_{50} of 4.6 μmol/L.

The applicant's explanation:

Tazemetostat in clinical use is unlikely to cause safety problems due to the inhibitory effect against this receptor because C_{max} of unbound tazemetostat in plasma at the recommended clinical dose (800 mg BID) was 0.261 μmol/L.[13]

3.2.2 Inhibitory effect against H3K27me3 in normal tissues (CTD 4.2.1.2.3, 4.2.1.2.4, and 4.2.1.2.5)

The inhibitory effect of tazemetostat against H3K27me3 in normal tissues of rats (n = 4/group in [a] or n = 8/group in [b]) was investigated by ELISA. The following results were obtained:

(a) Tazemetostat 106 or 319 mg/kg[9] was administered orally QD for 7 days, and the expression level of H3K27me3 protein in peripheral blood mononuclear cells (PBMC), bone marrow, spleen, and skin

[13] Calculated from C_{max} of tazemetostat (1,290 ng/mL) on Day 15 following oral doses of tazemetostat 800 mg BID in Study 106 in patients with relapsed or refractory FL and patients with DLBCL [see Section 6.2.1.1] and from the plasma protein-unbound rate (0.116) at tazemetostat 1 μmol/mL [see Section 4.2.2].

at 3 hours after the final dose was measured. The inhibitory effect of tazemetostat against H3K27me3 of PBMC, bone marrow, and spleen was observed in all tazemetostat groups.

(b) Tazemetostat 100, 300, or 1,000 mg/kg was administered orally QD for 22 or 28 days, and the expression level of H3K27me3 protein in PBMC, bone marrow, spleen, and skin at 29 hours after the final dose was measured. The inhibitory effect of tazemetostat against H3K27me3 was observed in all tissues tested in all tazemetostat groups.

Using cynomolgus monkeys (n = 8/group), the inhibitory effect of tazemetostat against H3K27me3 in normal tissues was investigated by ELISA. Tazemetostat 50, 150, or 500[14)] mg/kg was administered orally BID for 28 days, and the expression level of H3K27me3 in PBMC, bone marrow, spleen, and skin was measured at 14 to 17 hours after the final dose. A statistically significant inhibitory effect of tazemetostat against H3K27me3 compared with the control[10)] group was observed in tazemetostat 150 mg/kg group in PBMC, tazemetostat 50 and 150 mg/kg groups in the bone marrow, tazemetostat 150 and 500 mg/kg groups in the spleen, and all tazemetostat groups in the skin ($P < 0.05$ for PBMC; $P < 0.01$ for the spleen; $P < 0.0001$ for the bone marrow and skin; Bonferroni test).

3.3 Safety pharmacology

3.3.1 Effect on the central nervous system

Tazemetostat 100, 300, or 1,000 mg/kg was administered orally for 4 weeks to cynomolgus monkeys (n = 8/group), and the effect of tazemetostat on the central nervous system was investigated [see Section 5.2]. Decreased muscle tone in the hind legs was observed in the tazemetostat 1,000 mg/kg group.

3.3.2 Effect on cardiovascular system

3.3.2.1 Effect on hERG potassium current (CTD 4.2.1.3.1 [non-GLP])

Using human embryonic kidney-derived HEK 293 cell line transduced with human *ether-a-go-go*-related gene (hERG), the effect of tazemetostat 10 μmol/L on hERG potassium current was investigated. The inhibition rate of tazemetostat 10 μmol/L against hERG potassium current was 15.1% ± 1.4% (mean ± standard error, n = 4).

3.3.2.2 Effect on heart rate, blood pressure, and electrocardiogram (CTD 4.2.1.3.3)

Tazemetostat 0, 100, 300, and 1,000 mg/kg was administered orally sequentially to cynomolgus monkeys (n = 4), and the effect of tazemetostat on heart rate, blood pressure, and electrocardiogram (PR, QT, QTc, and QRS intervals) was investigated. Results showed that tazemetostat had no effect.

3.3.3 Effect on respiratory system

Tazemetostat 100, 300, or 1,000 mg/kg was administered orally for 4 weeks to cynomolgus monkeys (n = 8/group), and the effect of tazemetostat on respiratory rate, tidal volume, minute volume of ventilation, etc. was investigated [see Section 5.2]. Results showed that tazemetostat had no effect.

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14) After oral doses of tazemetostat 500 mg/kg for 8 to 9 days, all animals presented with a poor clinical condition. In 4 animals spared from euthanasia, tazemetostat administration was suspended for 2 days and was thereafter resumed at a reduced dose of 300 mg/kg.

3.R Outline of the review conducted by PMDA

As a result of the review of the submitted data, PMDA concluded that the applicant's explanations about the nonclinical pharmacology of tazemetostat is acceptable, except those discussed in the following section.

3.R.1 Mechanism of action and efficacy of tazemetostat:

The applicant's explanation about the action mechanism of tazemetostat and its efficacy against *EZH2* gene mutation-positive FL:

EZH2 is one of the factors that constitute polycomb repressive complex which regulates gene expression through histone modification. EZH2 catalyzes the reaction (methylation) that adds methyl residue to lysine residues in proteins such as histone, thereby leading to the aggregation of chromatin structure, resulting in the suppression of gene transcription. EZH2 is thus involved in differentiation, growth, etc. of germinal center cells (*Proc Natl Acad Sci USA*. 2015;112:E1116-25, etc.).

EZH2 gene mutation is observed in malignant lymphoma such as FL and DLBCL. In FL, the mutation of EZH2 Y646 and other *EZH2* genes are identified in 7% to 27% of patients (*Proc Natl Acad Sci USA*. 2010;107:20980-5, etc.). *EZH2* gene mutation is considered to be involved in the proliferation of FL through abnormal accumulation of trimethylated H3K27 (*Nat Genet*. 2010;42:181-5, etc.).

Tazemetostat is a low molecular weight compound with EZH2-inhibiting activity. Tazemetostat inhibits the methylating activity of EZH2 [see Section 3.1.1], thereby inducing cell cycle arrest and apoptosis through the regulation of the expression of PR domain zinc finger protein 1 (*PRDM1)* and tumor protein p53 inducible nuclear protein1 *(TP53INP1)* genes involved in cell cycle regulation and in apoptosis regulation (*Cancer Cell.* 2013;23:677-92, etc.), resulting in tumor growth inhibition.

Although nonclinical data have not been available on the growth-inhibitory effect of tazemetostat against human FL-derived cell lines, tazemetostat may possibly show efficacy against *EZH2* gene mutation-positive FL, given the observation that tazemetostat inhibited the growth of multiple cell lines derived from *EZH2* gene mutation-positive human malignant lymphoma (human DLBCL-derived cell lines) [see Section 3.1.4].

PMDA's view:

The applicant's explanation is generally acceptable. However, many factors affected by the inhibitory effect of tazemetostat against methylation in *EZH2* gene mutation-positive FL remain unelucidated, and the direct association between the methylation-inhibiting activity of tazemetostat and tumor growth suppression is unclear. Factors influential to the efficacy of tazemetostat against *EZH2* gene mutation-positive FL may be important for the projection of the efficacy of tazemetostat in clinical use and the selection of appropriate patients. Data collection should be continued and new findings should be communicated to healthcare professionals appropriately as soon as available.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

In this section, the dose and concentration of tazemetostat are expressed in terms of free base, unless specified otherwise.

The pharmacokinetics (PK) of tazemetostat was investigated in rats, monkeys, and other animals. Investigations on the binding of tazemetostat to plasma proteins, drug-metabolizing enzymes, transporters, etc. were conducted using human- or animal-derived biomaterials.

4.1 Absorption

4.1.1 Single-dose administration

A single dose of tazemetostat was administered to male rats intravenously at 5 or 10 mg/kg[15)] or orally at 5, 30, or 100 mg/kg,[15)] and plasma tazemetostat concentration was measured (Table 10). C_{max} and AUC_{inf} of tazemetostat increased more than dose proportionally within the dose range tested. The applicant explained that the result was due to the saturation of the metabolism of tazemetostat in the liver with the increase in dose. Bioavailability (BA)[16)] following the oral dose of tazemetostat 5 mg/kg was 3.2%.

Table 10. PK parameters of tazemetostat (male rats, a single intravenous or oral administration)

Dose (route of administration)	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{inf} (ng•h/mL)	$t_{1/2}$ (h)	CL (L/h/kg)	V_{ss} (L/kg)
5 mg/kg (i.v.)	-	-	1,263 ± 111	0.4 ± 0.1	3.49 ± 0.30	1.80 ± 0.12
10 mg/kg (i.v.)*2	-	-	2,792 ± 1,061	0.7 ± 0.2	3.53 ± 1.40	2.56 ± 0.59
5 mg/kg (p.o.)	41.9 ± 21.0	0.5 (0.5, 0.5)	-	0.8	-	-
30 mg/kg (p.o.)	836 ± 544	0.5 (0.5, 0.5)	1,624 ± 924	0.9 ± 0.2	-	-
100 mg/kg (p.o.)	4,965 ± 2,406	4.0 (4.0, 4.0)	21,653 ± 12,463	1.1 ± 0.3	-	-

Mean ± SD (individual value for n = 1); n = 4; -, Not calculated
*1 Median (range); *2 Bile duct-cannulated rats

4.1.2 Repeated-dose administration

Tazemetostat 50, 150, or 300 mg/kg[15)] was administered orally BID for 13 weeks to male and female monkeys, and plasma concentrations of tazemetostat and EPZ-6930 (*N*-deethylated form) were measured (Table 11). C_{max} and AUC_{12h} of tazemetostat and EPZ-6930 on Day 91 were generally lower than those on Day 1. No clear sex difference was observed in the PK parameters of tazemetostat.

15) The amount of tazemetostat hydrobromide
16) Calculated based on AUC_{2h}.

Table 11. PK parameters of tazemetostat and EPZ-6930 (male and female monkeys, 13-week repeated oral administration)

Analyte	Day of measurement	Dose (mg/kg)	C_{max} (ng/mL)		t_{max}* (h)		AUC_{12h} (ng•h/mL)	
			Male	Female	Male	Female	Male	Female
Tazemetostat	1	50	483 ± 429	501 ± 182	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1,560 ± 1,278	1378 ± 361
		150	2,481 ± 1,688	1,998 ± 1,333	3.0 (2.0, 4.0)	2.0 (2.0, 8.0)	9,707 ± 4,496	7118 ± 4686
		300	4,651 ± 2,692	1,612 ± 1,714	4.0 (2.0, 4.0)	2.0 (1.0, 2.0)	23,875 ± 15,825	8071 ± 9322
	43	50	139 ± 86	142 ± 52	2.0 (1.0, 2.0)	0.5 (0.5, 2.0)	537 ± 259	454 ± 181
		150	462 ±174	934 ± 723	3.0 (2.0, 4.0)	2.0 (1.0, 2.0)	2,487 ± 990	3062 ± 2225
		300	1,312 ± 782	863 ± 762	4.0 (2.0, 4.0)	2.0 (1.0, 4.0)	8,048 ± 5,517	4292 ± 3070
	91	50	148 ± 111	166 ± 32	1.5 (0.5, 4.0)	1.5 (0.5, 2.0)	641 ± 427	599 ± 68
		150	597 ± 301	725 ± 654	3.0 (2.0, 4.0)	2.0 (2.0, 2.0)	3,137 ± 1,331	3575 ± 3328
		300	1,298 ± 879	1,241 ± 1,008	4.0 (4.0, 4.0)	4.0 (2.0, 4.0)	8,117 ± 4,921	6215 ± 4583
EPZ-6930	1	50	1,620 ± 1,200	1,988 ± 433	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)	4,815 ± 3,380	4,593 ± 1,822
		150	5,836 ± 3,185	4,839 ± 2,503	3.0 (2.0, 4.0)	2.0 (2.0, 8.0)	25,037 ± 8,313	1,8033 ± 1,1221
		300	7,398 ± 2,097	3,768 ± 2,868	3.0 (2.0, 4.0)	2.0 (1.0, 2.0)	47,767 ± 17,687	18,890 ± 19,323
	43	50	1,025 ± 739	673 ± 201	2.0 (1.0, 2.0)	1.5 (1.0, 2.0)	3,093 ± 1,799	1,697 ± 837
		150	2,979 ± 1,267	4,835 ± 2,442	3.0 (2.0, 4.0)	2.0 (1.0, 2.0)	15,554 ± 9,042	1,5422 ± 8,561
		300	5,473 ± 3,203	3,434 ± 1,798	4.0 (2.0, 4.0)	3.0 (2.0, 4.0)	40,680 ± 31,970	17,842 ± 9,685
	91	50	860 ± 617	1,126 ± 773	2.0 (2.0, 2.0)	2.0 (1.0, 2.0)	3,154 ± 2,143	2,878 ± 1,660
		150	3,427 ± 1,573	3,669 ± 1,693	4.0 (2.0, 4.0)	3.0 (2.0, 4.0)	20,238 ± 9,915	18,073 ± 11,202
		300	4,084 ± 1,747	4,507 ± 2,752	4.0 (4.0, 4.0)	4.0 (2.0, 4.0)	31,036 ± 15,844	26,806 ± 18,848

Mean ± SD; n = 4; * Median (range)

4.1.3 *In vitro* membrane permeability

The membrane permeability of tazemetostat was investigated using Caco-2 cell line derived from human colorectal cancer. Apparent permeability in apical to basolateral direction ($P_{appA \rightarrow B}$) of tazemetostat 152 µmol/L was 13.3 × 10^{-6} cm/second. The applicant explained that the result was suggestive of a high membrane permeability of tazemetostat, which is also supported by $P_{appA \rightarrow B}$ of 0.201 × 10^{-6} cm/second for atenolol (10 µmol/L), an intermediary-permeability compound, and 18.4 × 10^{-6} cm/second for propranolol, a high-permeability compound.

4.2 Distribution

4.2.1 Tissue distribution

A single dose of ^{14}C-labeled tazemetostat (^{14}C-tazemetostat) 50 mg/kg was administered orally to male pigmented rats and male albino rats, and tissue distribution of radioactivity was investigated by quantitative whole-body autoradiography. In albino rats, radioactivity was distributed over a wide range of tissues, reaching a maximum level within 1 hour after administration in most of tissues including blood. In albino rats, the maximum level of radioactivity in the liver, renal medulla, small intestine, Harderian gland, renal cortex, and thyroid (193.170, 29.099, 24.288, 20.599, 20.580, and 20.021 µg Eq./g, respectively) was particularly higher than the maximum level in blood (7.549 µg Eq./g). The tissue radioactivity concentration at 168 hours post-dose was below the lower limit of quantitation (0.237 µg Eq./g) in most of the tissues. The tissue distribution of radioactivity in pigmented rats was similar to that observed in albino rats, except in the uvea and pigmented skin. The maximum level of radioactivity in the uvea was higher in pigmented rats (19.096 µg Eq./g) than in albino rats (2.919 µg Eq./g), and the applicant explained that this suggests the binding of tazemetostat or its metabolites to melanin.

4.2.2 Plasma protein binding

Plasma samples of mice, rats, rabbits, monkeys, and humans were incubated with tazemetostat (1-30 μmol/L) at 37°C for 6 hours, and binding of tazemetostat to plasma protein was investigated by equilibrium dialysis. The plasma protein binding of tazemetostat was 91.8% to 98.1% in mice, 88.8% to 94.7% in rats, 91.1% to 91.9% in rabbits, 83.3% to 84.7% in monkeys, and 87.7% to 91.1% in humans.

Human serum albumin (40 mg/mL), human α1-acid glycoprotein (1 mg/mL), and human γ-globulin (12 mg/mL) were incubated with tazemetostat (1-10 μmol/L) at 37°C for 20 hours, and binding of tazemetostat to human serum albumin, human α1-acid glycoprotein, and human γ-globulin was investigated by equilibrium dialysis. The binding of tazemetostat was 63.7% to 64.2% for human serum albumin, 10.7% to 15.1% for human α1-acid glycoprotein, and 10.6% to 15.6% for human γ-globulin. The applicant explained that the results suggest that tazemetostat binds mainly to albumin in human plasma.

4.2.3 Distribution in blood cells

Blood samples of mice, rats, monkeys, and humans were incubated with tazemetostat (50-50,000 ng/mL) at 37°C for 30 minutes, and the distribution of tazemetostat in blood cells was investigated. The blood/plasma ratio of tazemetostat concentration was generally constant regardless of concentration level, being 0.53 to 0.87 in mice, 0.61 to 0.78 in rats, 0.76 to 1.06 in monkeys, and 0.71 to 0.96 in humans. The applicant explained that the results demonstrated that tazemetostat is distributed mainly in plasma.

4.2.4 Placental and fetal transfer

Placental and fetal transfer of tazemetostat was not investigated. The applicant explained that tazemetostat may possibly cross the placenta and be distributed in fetuses, judging from the teratogenicity in fetuses observed in embryo-fetal development studies in rats and rabbits [see Section 5.5].

4.3 Metabolism

4.3.1 *In vitro*

Hepatocytes of mice, rats, dogs, monkeys, and humans were incubated with tazemetostat (20 μmol/L) at 37°C for 4 hours, and metabolites of tazemetostat were investigated. In all animal species and humans, mainly M11 (oxidated and dehydrated form) and M13 (*N*-dealkylated pyridone form) were detected. In addition, mainly EPZ-6930 was detected in monkeys and humans.

Liver microsomes of mice, rats, dogs, monkeys, and humans were incubated with tazemetostat (20 μmol/L) at 37°C for 30 minutes,[17)] and metabolites of tazemetostat were investigated. In all animal species and humans, mainly M7 (oxidized pyridone form) and M12 (double oxide form) were detected. In addition, mainly EPZ-6930 was detected in mice, rats, monkeys, and humans.

The following investigations were conducted on cytochrome P450 (CYP) isoforms involved in the metabolism of tazemetostat and EPZ-6930 in humans. Based on the results, the applicant explained that

[17)] Hepatocytes of monkeys and humans were incubated for 5 and 20 minutes, respectively.

mainly CYP3A4 contributes to the metabolism of tazemetostat and EPZ-6930. The pharmacokinetic interaction of tazemetostat with a CYP3A inhibitor is described in Section "6.2.3.1 Drug interaction with fluconazole."

- Human liver microsomes and tazemetostat (1 μmol/L) were incubated at 37°C for 30 minutes in the presence of an inhibitor[18)] of CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH). Tazemetostat metabolism was inhibited by 35.3%, 20.3%, and 94.8%, respectively, in the presence of the inhibitor of CYP2C8, CYP2D6, and CYP3A, and by ≤8.2% in the presence of the inhibitors of other CYP isoforms tested.
- Recombinant human CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) and tazemetostat (0.1 μmol/L) were incubated at 37°C for 30 minutes in the presence of NADPH. The residual rate of tazemetostat was 44.2% in the presence of CYP3A4 and ≥91.0% in the presence of other CYP isoforms tested.
- Human liver microsomes and recombinant human CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, and CYP3A5) were incubated with tazemetostat (0.2 or 2 μmol/L) or with EPZ-6930 (0.2 or 2 μmol/L) at 37°C for 120 minutes in the presence of NADPH. The contribution rate of CYP3A4, CYP3A5, and CYP2J2 to tazemetostat metabolism in human liver microsomes was 99%, <1%, and <1%, respectively, while tazemetostat was not metabolized by other CYP isoforms tested. The contribution rate of CYP3A4 and CYP2J2 to EPZ-6930 metabolism in human liver microsomes was 89% to 92% and 8% to 11%, respectively, while EPZ-6930 was not metabolized by other CYP isoforms tested.

4.3.2 *In vivo*

A single dose of ^{14}C-tazemetostat (50 mg/kg) was administered orally to non-cannulated, bile duct-cannulated, or carotid artery-cannulated male rats, and metabolites in plasma, urine, feces, and bile were investigated. The following results were obtained:

- Mainly unchanged tazemetostat and EPZ-6930 were detected in plasma collected up to 8 hours post-dose from carotid artery-cannulated male rats, accounting for 11.56% and 62.86%, respectively, of the total radioactivity in plasma.
- Mainly EPZ-6930 was detected in urine collected up to 168 hours post-dose from non-cannulated male rats (5.35% of the administered radioactivity). Mainly M576_2 (oxidated form of EPZ-6930), EPZ-6930, and M560_3 (oxidated form of EPZ-6930) were detected in feces collected up to 168 hours post-dose (11.55%, 11.13%, and 9.13%, respectively).
- Mainly M720 (glucuronate of EPZ-6930), M576_2, and M764_3 (oxidized and glucuronide form, respectively) were detected in bile collected up to 96 hours post-dose from bile duct-cannulated male rats (4.98%, 4.07%, and 3.53%, respectively).

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

A single dose of ^{14}C-tazemetostat (50 mg/kg) was administered orally to bile duct non-cannulated male rats, and the excretion rate of radioactivity in urine and feces (percentage of the administered

[18)] Inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, 2C19, CYP2D6, and CYP3A used were furafylline, 2-phenyl-2-(1-piperidinyl) propane, montelukast, sulfaphenazole, *S*-benzylnirvanol, quinidine, and ketoconazole, respectively.

radioactivity) was investigated. The excretion rate of radioactivity in urine and feces up to 168 hours post-dose was 8.0% and 86.1%, respectively.

A single dose of ^{14}C-tazemetostat (50 mg/kg) was administered orally to bile duct-cannulated male rats, and the excretion rate of radioactivity in urine, feces, and bile (percentage of the administered radioactivity) was investigated. The excretion rate of radioactivity in urine, feces, and bile up to 96 hours post-dose was 17.9%, 24.0%, and 53.5%, respectively.

Based on the above results, the applicant explained that tazemetostat and its metabolites are excreted mainly in feces via bile.

4.4.2 Excretion in milk

The excretion of tazemetostat in milk was not investigated. However, the applicant explained that tazemetostat may possibly be excreted in milk, given the physicochemical properties of tazemetostat (acid dissociation constant [pKa] 5.26 or 6.88; logP 4.14; and binding to human plasma protein [see Section 4.2.2]).

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation:

In clinical use, tazemetostat may possibly cause pharmacokinetic interactions mediated by CYP2C8, CYP2C19, and CYP3A inhibition, in view of (a) the following study results, (b) C_{max} (0.261[13)] and 3.58 μmol/L,[19)] respectively) of unbound tazemetostat and EPZ-6930 at steady state post-dose of tazemetostat according to the proposed dosage regimen, and (c) the estimated tazemetostat concentration (5,587 μmol/L) in the digestive tract post-dose of tazemetostat according to the proposed dosage regimen. These pharmacokinetic interactions are described in Sections "6.2.3.2 Drug interaction with repaglinide or omeprazole" and "6.2.3.3 Drug interaction with midazolam."

- Human liver microsomes were incubated with tazemetostat (0.027-20 μmol/L) in the presence of a substrate[20)] of CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A) and NADPH, and the inhibitory effect of tazemetostat against each CYP isoform was investigated. Tazemetostat inhibited the metabolism of the substrates of CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A with IC_{50} of 6.3, 9.0, 3.8, 15.5, and 5.9[21)] μmol /L, respectively, whereas tazemetostat did not show any clear inhibitory effect against the metabolism of the substrates of other CYP isoforms tested.
- Human liver microsomes and tazemetostat (0.195-100 μmol/L) were incubated in the presence of NADPH, followed by incubation with substrates[22)] of CYP isoforms (CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A), and the time-dependent inhibitory effect of tazemetostat against each CYP

19) Calculated based on C_{max} of EPZ-6930 (1,950 ng/mL) on Day 15 following the multiple oral administration of tazemetostat 800 mg BID in Study 106 in patients with relapsed or refractory FL or DLBCL [see Section 6.2.1.1], and on the estimated plasma protein-unbound rate of EPZ-6930 (1.00).

20) Phenacetin, bupropion, amodiaquine, tolbutamide, *S*-mephenytoin, bufuralol, and chlorzoxazone were used as substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1, respectively. Midazolam, nifedipine, and testosterone were used as substrates of CYP3A.

21) IC_{50} obtained with testosterone as the substrate. IC_{50} obtained with midazolam and nifedipine as the substrates was 12.7 and 19.4 μmol/L, respectively.

22) Amodiaquine, tolbutamide, *S*-mephenytoin, bufuralol, and testosterone were used as substrates of CYP2C8, CYP2C9, CYP2C19 CYP2D6, and CYP3A, respectively.

isoform was investigated. Tazemetostat inhibited the metabolism of the substrate of CYP3A in a time-dependent manner with K_i and K_{inact} of 6.4 μmol/L and 0.077 min^{-1}, respectively, while not showing any clear time-dependent inhibitory effect against the metabolism of the substrates of other CYP isoforms tested.

- Human liver microsomes and EPZ-6930 (0.146-200 μmol/L) were incubated in the presence of a substrate[23)] of CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) and NADPH, and the inhibitory effect of EPZ-6930 against CYP isoforms was investigated. EPZ-6930 did not show any clear inhibitory effect against the metabolism of the substrates of CYP isoforms tested.

4.5.2 Enzyme induction

The applicant's explanation:

Tazemetostat may cause pharmacokinetic interactions mediated by the induction of CYP2C8, CYP2C9, and CYP3A4 in clinical use, in view of (a) the following study results and (b) C_{max} (0.261 μmol/L[13)]) of unbound tazemetostat at steady state post-dose of tazemetostat according to the proposed dosage regimen. The pharmacokinetic interactions mediated by CYP2C8 and CYP3A4 are described in Sections "6.2.3.2 Drug interaction with repaglinide or omeprazole" and "6.2.3.3 Drug interaction with midazolam."

- Human hepatocytes were treated with tazemetostat (0.03-30 μmol/L) for 2 days, and messenger ribonucleic acid (mRNA) expression level and enzyme activity of CYP1A2, CYP2B6, CYP2C9, and CYP3A4 were investigated. Tazemetostat induced the expression of mRNA of CYP3A4 with the maximum of 93.8% induction relative to the positive control rifampicin (10 μmol/L), with EC_{50} and E_{max} of 2.18 to 2.96 μmol/L and 15.6- to 103.5-fold induction, respectively. In contrast, tazemetostat did not clearly induced the mRNA of CYP1A2, CYP2B6, or CYP2C9. Also, tazemetostat did not clearly induce the enzyme activity of any CYP isoforms tested.
- Human hepatocytes were treated with tazemetostat (0.2-50 μmol/L[24)]) for 3 days, and mRNA expression level of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 and enzyme activity of CYP1A2, CYP2B6, and CYP3A4 were investigated. Tazemetostat induced the expression of the mRNA of CYP2C8, CYP2C9, and CYP3A4, which maximum levels were 68.4%, 69.1%, and 85.2%, respectively, relative to the induction by the positive control rifampicin (50 μmol/L). In contrast, tazemetostat showed neither clear induction of the expression of mRNA of CYP1A2, CYP2B6, or CYP2C19, nor the enzyme activity of any CYP isoforms tested.

4.5.3 Transporters

The applicant's explanation;

The following study results demonstrated that tazemetostat is a substrate of P-glycoprotein (P-gp).

- Using porcine kidney-derived LLC-PK1 cell line expressing human P-gp, P-gp-mediated transport of tazemetostat (approximately 6-80 μmol/L) was investigated. The ratio of the efflux ratio (the ratio of permeability coefficient in the secretary direction to that in the absorptive direction) of

23) Phenacetin, efavirenz, amodiaquine, diclofenac, *S*-mephenytoin, and bufuralol were used as substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, respectively. Midazolam and testosterone were used as substrates of CYP3A.

24) Tazemetostat (50 μmol/L) was used in the study of enzyme activity.

tazemetostat in P-gp-expressing cell line to that in P-gp-non-expressing cell line was 2.4 to 3.5 in the presence of a P-gp inhibitor (elacridar, 5 μmol/L) and 5.1 to 133.6 in the absence of P-gp inhibitor.

- Using canine kidney-derived MDCKII cell line expressing human breast cancer resistance protein (BCRP), BCRP-mediated transport of tazemetostat (approximately 5-50 μmol/L) was investigated. The ratio of the efflux ratio of tazemetostat in BCRP-expressing cell line to that in BCRP-non-expressing cell line was 0.9 to 1.4 in the presence of a BCRP inhibitor (Ko143, 10 μmol/L) and 0.7 to 1.5 in the absence of BCRP inhibitor.
- Using Chinese hamster ovary-derived CHO cell line expressing human organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)2, or organic anion transporter (OAT)1, transport of tazemetostat (1-10 μmol/L) medicated by OATP1B1, OATP1B3, OCT2, or OAT1 was investigated. The ratio of the uptake velocity of tazemetostat in OATP1B1-, OATP1B3-, OCT2-, or OAT1-expressing cell line to that in the non-expressing cell line showed no clear difference in the presence or absence of the inhibitor[25)] of each transporter.
- Using HEK293 cell line expressing human OAT3, OAT3-mediated transport of tazemetostat (1-10 μmol/L) was investigated. The ratio of the uptake velocity of tazemetostat in OAT3-expressing cell line to that in the non-expressing cell line was <1 within the tazemetostat concentration range tested.
- Using MDCKII cell line expressing human OATP1B1, OATP1B3, or multidrug and toxin extrusion (MATE)1, the transport of tazemetostat (1-10 μmol/L) mediated by OATP1B1, OATP1B3, or MATE1 was investigated. The ratio of the uptake of tazemetostat by OATP1B1-, OATP1B3-, or MATE1- expressing cell line to that by non-expressing cell lines was <2 in all transporters within the concentration range of tazemetostat tested.

In clinical use, tazemetostat may cause a pharmacokinetic interaction mediated by (i) inhibition of P-gp, BCRP, OATP1B1, OATP1B3, MATE1, or MATE2-K by tazemetostat or (ii) inhibition of MATE1 or MATE2-K by EPZ-6930, in view of (a) the following study results, (b) C_{max} (0.261[13)] and 3.58 μmol/L,[19)] respectively) of unbound tazemetostat and EPZ-6930 at steady state post-dose of tazemetostat according to the proposed dosage regimen, and (c) the estimated concentration of tazemetostat (5,587 μmol/L) in the gastrointestinal tract post-dose of tazemetostat according to the proposed dosage regimen.

- Using LLC-PK1 cell line expressing human P-gp, the inhibitory effect of tazemetostat (1-200 μmol/L) against the transport of ^{3}H-labeled digoxin (10 nmol/L) was investigated. Tazemetostat inhibited the transport of the substrate of P-gp with IC_{50} of 5.9 μmol/L.
- Using MDCKII cell line expressing human BCRP, the inhibitory effect of tazemetostat (1-200 μmol/L) against the transport of ^{3}H-labeled prazosin (7 nmol/L) was investigated. Tazemetostat inhibited the transport of the substrate of BCRP with IC_{50} of 34.1 μmol/L.
- Using CHO cell line expressing human OATP1B1, OATP1B3, OCT2, or OAT1, the inhibitory effect of tazemetostat (0.1-300 μmol/L[26)]) against the transport of the substrate[27)] of each transporter was investigated. Tazemetostat inhibited the transport of the substrates of OATP1B1, OATP1B3, and

25) The used inhibitors were rifampicin (100 μmol/L) against OATP1B1 and OATP1B3, quinidine (100 μmol/L) against OCT2, and probenecid (100 μmol/L) against OAT1.
26) Tazemetostat (0.03-100 μmol/L) was used in the study on OCT2 and OAT1.
27) The used substrates were ^{3}H-labeled estrone-3-sulfate (0.1 μmol/L) for OATP1B1, ^{3}H-labeled estradiol-17β-glucuronide (0.1 μmol/L) for OATP1B3, ^{14}C-labeled metformin (8 μmol/L) for OCT2, and ^{3}H-labeled *p*-aminohippuric acid (0.5 μmol/L) for OAT1.

OCT2 with IC_{50} of 19.7, 14.4, and 14.7 μmol/L, respectively, but showed no clear inhibitory effect against the transport of the substrate of OAT1.

- Using HEK293 cell line expressing human OAT3, the inhibitory effect of tazemetostat (0.03-300 μmol/L) against the transport of the substrate of OAT3 (^{3}H-labeled estrone-3-sulfae, 0.1 μmol/L) was investigated. Tazemetostat inhibited the transport of the substrate of OAT3 with IC_{50} of 10.0 μmol/L.
- Using MDCKII cell line expressing human MATE1, MATE2-K, OCT1, or OCT2, the inhibitory effect of tazemetostat (20 μmol/L) against the transport of the substrate[28)] of each transporter was investigated. Tazemetostat inhibited the transport of the substrates of MATE1 and MATE2-K by 87.7% and 84.6%, respectively, but did not clearly inhibit the transport of the substrates of OCT1 and OCT2.
- Using membrane vesicles expressing human bile salt export pump (BSEP), the inhibitory effect of tazemetostat (0.3-100 μmol/L) against the transport of the substrate of BSEP (^{3}H-labeled taurocholic acid, 2 μmol/L) was investigated. Tazemetostat inhibited the transport of the substrate of BSEP with IC_{50} of 20.0 μmol/L.
- Using MDCKII cell line expressing human P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K, the inhibitory effect of EPZ-6930 (25 μmol/L) against the transport of the substrate[29)] of each transporter was investigated. EPZ-6930 inhibited the transport of the substrates of P-gp, OCT2, MATE1, and MATE2-K by 54.6%, 25.7%, 79.9%, and 64.4%, respectively, but showed no clear inhibitory effect against the transport of the substrates of BCRP, OAT1, OAT3, OCT1, OATP1B1, and OATP1B3.

4.R Outline of the review conducted by PMDA

Based on the data submitted and on the results of the reviews in the following sections, PMDA concluded that the applicant's explanation about the nonclinical pharmacokinetics of tazemetostat is acceptable.

4.R.1 Tissue distribution

PMDA asked the applicant to explain the safety of tazemetostat in melanin-containing tissues, taking account of the results of studies suggesting the binding of tazemetostat or its metabolites to melanin [see Section 4.2.1].

The applicant's response:

The distribution of tazemetostat or its metabolites in melanin-containing tissues is unlikely to cause any safety problem in clinical use, given the following observations:

- The repeated oral dose toxicity study in monkeys revealed no toxicity finding in the skin or eye that are composed of melanin-containing tissues [see Section 5.2].
- In the pooled analysis of patients with FL enrolled in the Japanese phase I study (Study 106), the Japanese phase II study (Study 206), and phase II part of the foreign phase I/II study (Study 101),

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28) The used substrates were ^{14}C-labeled metformin (10 μmol/L) for MATE1, MATE2-K, and OCT2, and ^{3}H-labeled 1-methyl-4-phenylpyridinium (2 μmol/L) for OCT1.

29) The used substrates were ^{3}H-labeled quinidine (100 nmol/L) for P-gp, ^{3}H-labeled prazosin (2 μmol/L) for BCRP, ^{3}H-labeled *p*-aminohippuric acid (2 μmol/L) for OAT1, ^{3}H-labeled *p*-aminohippuric acid (10 μmol/L) for OAT3, ^{3}H-labeled 1-methyl-4-phenylpyridinium (2 μmol/L) for OCT1, ^{14}C-labeled metformin (10 μmol/L) for OCT2, ^{3}H-labeled estradiol-17β-glucuronide (2 μmol/L) for OATP1B1, ^{3}H-labeled cholecystokinin octapeptide (2 μmol/L) for OATP1B3, and ^{14}C-labeled metformin (10 μmol/L) for MATE1 and MATE2-K.

the incidence of adverse events classified as skin or subcutaneous tissue disorders and as eye disorders was 42.5% (51 of 120 patients) and 7.5% (9 of 120 patients), respectively (Japanese patients, 52.4% [11 of 21 patients] and 19.0% [4 of 21 patients]; non-Japanese patients, 40.4% [40 of 99 patients] and 5.1% [5 of 99 patients]), but all observed events were Grade ≤2, indicating no clinically significant problems.

PMDA accepted the applicant's explanation.

4.R.2 Pharmacokinetic interactions

The applicant's explanation about the pharmacokinetic interactions of tazemetostat:
Tazemetostat may possibly show pharmacokinetic interactions mediated by CYP3A [see Sections 4.5.1 and 4.5.2]. Therefore, the applicant plans to conduct a clinical study to investigate the pharmacokinetic interactions of tazemetostat with a potent CYP3A inducer (rifampicin) and a potent CYP3A inhibitor (itraconazole).

In vitro studies suggested that tazemetostat shows pharmacokinetic interactions mediated by CYP2C9, P-gp, BCRP, OATP1B1, OATP1B3, MATE1, and MATE2-K [see Section 4.5.2 and 4.5.3]. However, in view of the following observations, tazemetostat is unlikely to raise clinical concerns, although the small number of patients receiving a substrate or inhibitor of these metabolic enzymes or transporters in combination allowed for limited evaluation.

- No particular safety problems were observed in patients who received tazemetostat in combination with a substrate of CYP2C9, P-gp, BCRP, OATP1B1, OATP1B3, MATE1, or MATE2-K or an inhibitor of P-gp in the Japanese phase I study (Study 106), Japanese phase II study (Study 206), and phase II part of foreign phase I/II study (Study 101).

PMDA's view:
The applicant's explanation is generally acceptable. Information about the pharmacokinetic interactions of tazemetostat mediated by CYP2C9, P-gp, BCRP, OATP1B1, OATP1B3, MATE1, and MATE2-K is essential for the proper use of tazemetostat, and relevant information, including data from clinical studies on the pharmacokinetic interactions of tazemetostat with potent CYP3A inducers and inhibitors, should be further collected, and any useful information should be provided appropriately to healthcare professionals.

5. Toxicity and Outline of the Review Conducted by PMDA

Tazemetostat hydrobromide was used unless specified otherwise. Also, the dose of tazemetostat is expressed in terms of hydrobromide, and the concentration is expressed in terms of free base, unless specified otherwise.

The vehicle used was 0.5% methylcellulose 400 solution or 0.5% methylcellulose 400 solution containing 0.1% polysorbate 80 in *in vivo* studies, and dimethyl sulfoxide (DMSO) in *in vitro* studies.

5.1 Single-dose toxicity

A single oral dose toxicity study in rats and a dose-escalation study in cynomolgus monkeys were conducted. Acute toxicity of tazemetostat was evaluated based on the results of these studies (Table 12).

Table 12. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg/day)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female rats (Sprague Dawley)	p.o.	100, 300, 1,000[a)]	1,000: Transient inanimation, transient decreases in body weight and food consumption	>1,000	Reference 4.2.3.1.1
Male and female cynomolgus monkeys	p.o.	100, 300, 1,000	1,000: Vomiting	>1,000	Reference 4.2.3.2.4

a) Expressed in the amount of tazemetostat hydrobromide.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in rats (4 and 13 weeks) and in cynomolgus monkeys (4 and 13 weeks) (Table 13). Tazemetostat-associated findings included gastrointestinal toxicity and reduced lymphocyte count in lymphatic tissues in rats and cynomolgus monkeys; T cell lymphoblastic lymphoma (T-LBL) [see Section 5.R.1], effects on bones and teeth, and ulcer of skin/subcutaneous loci in rats; and enlarged hepatocytes and Kupffer cells, pigmentation, bile duct hyperplasia, glomerular lesion, etc. in cynomolgus monkeys. Sex difference was observed in the tazemetostat level in blood (higher in female than in male) in rats, while no clear sex difference was observed in the onset of toxicity.

At the no observed adverse effect level (NOAEL) in the 13-week repeated-dose toxicity studies in rats and cynomolgus monkeys (<100 mg/kg/day in male rats, 100 mg/kg/day in female rats, 100 mg/kg/day in male and female cynomolgus monkeys), C_{max} and AUC_{24h} of tazemetostat were (a) <4,311 ng/mL and <18,033 ng•h/mL, respectively, in male rats, (b) 13,488 ng/mL and 55,037 ng•h/mL, respectively, in female rats, and (c) 157 ng/mL and 1,240 ng•h/mL, respectively, in male and female cynomolgus monkeys, which were (a) <3.3 times and <2.0 times, respectively, (b) 10 and 6.1 times, respectively, and (c) 0.12 and 0.14 times, respectively, the clinical exposure.[30)] At the T-LBL-inducing dose in the 13-week repeated-dose toxicity study in rats (300 mg/kg in both male and female rats), C_{max} and AUC_{24h} of tazemetostat were 10,018 ng/mL and 99,546 ng•h/mL, respectively, in male rats, and 20,720 ng/mL and 166,305 ng•h/mL, respectively, in female rats, which were 7.8 and 11 times, respectively, (males) and 16 and 18 times, respectively, (females) the clinical exposure.[30)]

[30)] C_{max} (1,290 ng/mL) and AUC_{12h} (4,500 ng•h/mL) of tazemetostat on Day 15 observed in oral doses of tazemetostat 800 mg multiple BID in Study 106 in patients with relapsed or refractory FL or DLBCL [see Section 6.2.1.1]. AUC was calculated using twice the observed value (9,000 ng•h/mL) to adjust to the daily exposure.

Table 13. Repeated-dose toxicity studies

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague-Dawley)	p.o.	4 weeks (QD)	0, 100, 300, 1,000[a)]	Death/moribund euthanasia: 1,000 (2 of 10 males, 5 of 10 females), inanimation, soiled fur, decreased feces, chromaturia (bright yellow), decreased food consumption, hematological changes suggesting hemoconcentration, increased neutrophil count, decreased lymphocyte count/reticulocyte count, prolonged prothrombin time/APTT, increased blood AST/total bilirubin/BUN/creatinine/total cholesterol, decreased total protein/glucose, erosion/ulcer of anterior/glandular stomach mucosa, degeneration/necrosis of glandular stomach mucosa/intestinal epithelium, decreased cell count in various lymphatic tissues/bone marrow, eosinophilic droplets/denaturation/necrosis of epithelial cells of renal tubules, etc. ≥100[b)]: Small granular substances (urinary sediment) ≥300[b)]: Increased liver weight, decreased hemoglobin, decreased total blood protein 1000: Abdominal distension, increased reticulocyte count/neutrophil count, increased total blood bilirubin/total cholesterol, decreased red blood cell count/lymphocyte count, decreased blood albumin/globulin/glucose, gastric distension, erosion/ulcer of anterior stomach/glandular stomach mucosa, degeneration/necrosis of glandular stomach mucosa/duodenal epithelium/jejunal epithelium/ileal epithelium, trabecular formation in bone marrow, decrease/necrosis of lymphocytes in thymus/spleen/submandibular lymph nodes, infiltration of inflammatory cells around pulmonary bronchus, hypertrophy of adrenal cortex, atrophy of seminal gland/ coagulating gland	300	4.2.3.2.2
Male and female rats (Sprague-Dawley)	p.o.	13 weeks (QD) + 4-week withdrawal	0, 100, 300, 600	Death/moribund euthanasia: 300 (1 of 16 males, 4 of 16 females), decreased food consumption, decreased feces, inanimation, decreased respiration, decreased body temperature, increased white blood cell count, decreased red blood cell count/hemoglobin/hematocrit/platelet count/reticulocyte count, thymic T-LBL and related changes (thymic mass, enlarged spleen/lymph nodes), metastasis to various organs/tissues (peri-thymic adipose tissue, heart, spleen, lymph nodes, bone marrow, bones, liver, gastrointestinal tract, ovary, and eye), etc. ≥100: Labial nodes (male),[c) d)] microgranular substances (urinary sediment)[b)] ≥300: Reduced body weight gain, thymic T-LBL and related changes (see changes observed in dead/moribund euthanized animals), atrophy of thymus/spleen/submandibular lymph nodes, trabecular formation in femur/sternum, erosion/ulcer/regenerative changes of gastric mucosa, hyperplasia of duodenal crypt 600: Inanimation, labial nodes (female),[b)] swollen limb[c)] induration[c)]/mass[c)] of tail, decreased respiration, decreased feces, increased eosinophil count/neutrophil count/monocyte count/reticulocyte count/platelet count/total blood bilirubin, decreased hemoglobin/MCV/MCH, gastric distension, shortened lower incisor accompanied by gingival swelling, enhanced osteogenesis in alveolar bone, gingival dysplasia,	Male: <100 Female: 100	4.2.3.2.3

				inflammation/abscess in skin/subcutaneous sites accompanied by bacterial flora, granular substances in renal pelvis Reversibility: Reversible except decreased splenic lymphocyte count and changes in bone/incisors		
Male and female cynomolgus monkeys	p.o.	4 weeks (BID)	0, 100, 300, 1,000/600[e)]	Death/moribund euthanasia: 1,000/600 (2 of 4 males, 1 of 4 females), inanimation, lethargy, hunchback position, impaired motor coordination, anemia, increased blood ALT/triglycerides/bilirubin, decreased blood albumin/total protein/cholesterol, flatulence of stomach/colon, discoloration of liver, duodenal erosion/ulcer, hypertrophy of centrilobular hepatocytes/Kupffer cells, decreased lymphocyte count in thymus/spleen/submandibular lymph nodes/mesenteric lymph nodes, pigmentation of renal tubules, etc. ≥300: Decreased lymphocyte count in thymus/spleen 1,000/600: Decreased muscle tone in hind legs, transient heart rate increase, increased blood ALT/triglycerides/total bilirubin, weight increase in liver/kidney, discoloration of liver, hypertrophy of centrilobular hepatocytes/Kupffer cells, decreased lymphocyte count in submandibular lymph nodes/mesenteric lymph nodes, pigmentation of renal tubules	100	4.2.3.2.5
Male and female cynomolgus monkeys	p.o.	13 weeks (BID) + 4-week withdrawal	0, 100, 300, 600	Moribund euthanasia: 600 (1 of 6 females), inanimation, feeling cold, hunchback position, shivering/tremor, increased blood ALT/AST/ALP, hypertrophy/pigmentation of Kupffer cells, centrilobular hypertrophy of hepatocytes, bile duct hyperplasia, decreased lymphocyte count in thymus, decrease in germinal center of spleen/submandibular lymph nodes/mesenteric lymph nodes, pigmentation of epithelial cells of renal tubules, localized infiltration of inflammatory cells in lung, atrophy of bone-marrow fat cells, regenerative hyperplasia of glandular stomach mucosa, etc. ≥100: Vomiting,[f)] abnormal feces (soft feces, mucous stools, colored feces),[f)] blood AST,[b)] increased liver weight[b)] ≥300: PR interval decreased,[g)] increased blood ALT, hypertrophy/pigmentation of Kupffer cells, centrilobular hypertrophy of hepatocytes, bile duct hyperplasia, decreased lymphocyte count in thymus, decrease in germinal center of spleen/submandibular lymph nodes/mesenteric lymph nodes, hypertrophy of adrenal cortex 600: Increased blood ALP, increased kidney weight, pigmentation of renal tubules, localized infiltration of inflammatory cells in lung Reversibility: Reversible except mild increase in blood ALT/AST/ALP and hypertrophy/pigmentation of Kupffer cells at ≥300 mg/kg/day, and increased liver weight and hyperplasia of bile duct at 600 mg/kg/day	100	4.2.3.2.6

a) In the 1,000 mg/kg/day group, death or moribund animals were observed from Days 7 to 21. In females of this group, the administration was discontinued from Day 21 and reversibility was evaluated after a 2-week withdrawal. b) Because of the extent of the change and the lack of related histopathological changes, it was not considered as toxicity. c) These findings were subjected to an observation as inflammation or abscess related changes in skin/subcutaneous sites accompanied by bacterial flora. These were considered secondary changes to some effect on the lymphatic system. d) Although affecting only 1 male animal, it was an obvious change and thus considered a toxicity. e) In the 1,000 mg/kg/day group, moribund animals were observed from Days 8 to 9. In this group, the dose was reduced to 600 mg/kg/day from Day 11 in males and from Day 12 in females. f) These changes were observed sporadically in all treatment groups including the control group. The incidence of vomiting was higher in the 600 mg/kg/day group. g) The change was considered unrelated to tazemetostat administration because (1) it was not dependent on tazemetostat concentration in blood, and (2) in the safety pharmacology study [see Section 3.3.2.2], decrease in PR interval was not observed up to 1,000 mg/kg/day.

5.3 Genotoxicity

In vitro genotoxicity studies consisted of a bacterial reverse mutation assay and a micronucleus assay in cultured mammalian cells; and an *in vivo* micronucleus assay was conducted in rodents (Table 14). All assays were negative, based on which the applicant explained that tazemetostat is unlikely to induce genotoxicity.

Table 14. Genotoxicity studies

Study type		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Results	Attached document CTD
In vitro	Bacterial reverse mutation test	*Salmonella typhimurium*: TA100, TA1535, TA98, TA1537 *Escherichia coli:* WP2*uvrA*	S9-	0, 20.6,[a] 61.7, 185, 556,[b] 1,667,[b] 5,000[b] [c]	Negative	4.2.3.3.1.2
			S9+	0, 20.6,[d] 61.7, 185, 556, 1,667, 5,000[b] [c]		
	Micronucleus test in cultured mammalian cells	Human peripheral lymphocytes	S9- (4 hours)	0, 32, 64, 128	Negative	4.2.3.3.1.3
			S9+ (4 hours)	0, 64, 128, 256[e]		
			S9+ (4 hours)	0, 125, 145, 165		
			S9- (24 hours)	0, 32, 64, 128[e]		
			S9- (24 hours)	0, 50, 60, 70, 80		
In vivo	Micronucleus test in rodents	Male and female rats (Sprague-Dawley)		0, 500, 1,000, 2,000 (p.o. 2 days)	Negative	4.2.3.3.2.1

a) For TA1537 only; b) Precipitates were observed at the end of treatment with tazemetostat.; c) Growth inhibition was observed in some bacterial strains; d) For TA1535 and TA1537 only; e) Growth inhibition was observed.

5.4 Carcinogenicity

Because tazemetostat is an antineoplastic agent intended for the treatment of advanced cancer, no carcinogenicity study was conducted. However, the applicant explained that tazemetostat is carcinogenic in light of T-LBL observed in the 13-week repeated-dose toxicity study in rats. Carcinogenicity-related risk of tazemetostat is described in Section "5.R.1 T-LBL observed in repeated administration."

5.5 Reproductive toxicity

Because tazemetostat is an antineoplastic agent intended for the treatment of advanced cancer, no studies were conducted on the fertility and early embryonic development to implantation, or on the effects on pre- and postnatal development, including maternal function.

The applicant's explanation:

Tazemetostat did not affect the reproductive organs of male and females in the repeated-dose toxicity studies in rats and cynomolgus monkeys [see Section 5.2]. However, EZH2 has been reported to be involved in the development and function of germ cells and reproductive organs, based on the following results. Tazemetostat may thus affect fertility and early embryonic development to implantation in both males and females.

- An association of EZH2 with male reproductive organs and/or fertility in male mice is suggested by (a) EZH2 expressing in spermatogonia, spermatocytes, and round spermatids in mature male mice, and the involvement of EZH2 in the differentiation of male germ cells, and (b) reduced sperm count in EZH2-deficient male mice, and a decreased fetal number when EZH2-deficient male mice and wild-type female mice are mated (*Reproduction*. 2017;154:615-25).

- An association of EZH2 with female reproductive organs and/or fertility in female mice is suggested by the following findings:
  - EZH2 is expressed at a particularly high level in the uterine epithelium of neonatal female mice. Although the expression level decreases with age, it is still expressed in the uterine luminal epithelia, glandular epithelia, and stroma of matured female mice. In EZH2-deficient female mice, increased weight and size of the uterus are observed and, after 5 months of age, fertility decreases resulting in infertility. Offspring, if any, is small in size and survives for only a short period (*Biol Reprod*. 2019;101:306-17).
  - An association between EZH2 and the decidualization of the human uterine epithelium was suggested (*Mol Endocrinol.* 2011;25:1892-903).
- In germ cells under development and in mature oocytes, EZH2-mediated H3K27me3 formation was observed (*Epigenetics Chromatin.* 2017;10:1-20, *Proc Natl Acad Sci USA*. 2013;110:16061-6, etc.).

Studies on embryo-fetal development were conducted in rats and rabbits (Table 15). In both rats and rabbits, skeletal variations were observed at and above the lowest dose (50 and 100 mg/kg/day, respectively), and teratogenicity was observed at and above the intermediate dose (100 and 200 mg/kg/day, respectively). These findings will be provided in the package insert, etc., and physicians will be advised to avoid using tazemetostat to pregnant women or women who may possibly be pregnant.

C_{max} and AUC_{24h} of tazemetostat at the NOAEL for embryo-fetal development in rats and rabbits ([a] <50 mg/kg/day in rats, [b] <100 mg/kg/day in rabbits) and at the non-teratogenic dose ([c], 50 mg/kg/day in rats, [d] 100 mg/kg/day in rabbits) were (a) <2,190 ng/mL and <14,300 ng•h/mL, respectively, (b) <4,390 ng/mL and <10,100 ng•h/mL, respectively, (c) 2,190 ng/mL and 14,300 ng•h/mL, respectively, and (d) 4,390 ng/mL and 10,100 ng•h/mL, respectively, which were (a) <1.7 times and <1.6 times, respectively, (b) <3.4 times and <1.1 times, respectively (c) 1.7 times and 1.6 times, respectively, and (d) 3.4 times and 1.1 times, respectively, the clinical exposure.[30)]

Table 15. Reproductive and developmental toxicity studies

Study type	Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Study of fertility and embryo-fetal development	Female rats (Sprague Dawley)	p.o.	Gestation Day 7-17 (QD)	0, 50, 100, 200	Maternal animals 200: Reduced body weight gain Embryos/fetuses: ≥50: Skeletal variation (short ribs, deformation of cervical spinal arch) ≥100: Skeletal anomaly (missing ribs/cervical spines), skeletal variation (deformation of exoccipital bone, cranial suture), delayed ossification of thoracic vertebra 200: Increase in post-implantation loss of embryos, decrease in the number of live fetuses, low fetal weight, external anomalies (domed head, brachyury, generalised edema, small/missing palm), skeletal anomaly (fused cervical spinal arch, missing supraoccipital bone/phalanges), skeletal variation (imperfect formation of supraoccipital bone, deformed sternum), imperfect ossification (cervical spinal arch/supraoccipital bone/ischial bone)	Maternal animals: 100 Embryos/fetuses: <50	4.2.3.5.2.2
	Female rabbits (NZW)	p.o.	Gestation Day 7-19 (QD)	0, 100, 200, 400	Maternal animals[a)]: 400[b)]: Reduced body weight gain Embryos/fetuses ≥100: Skeletal variation (fusion/separation/deformation of sternebrae, perfect cervical rib, short cervical rib) ≥200: Skeletal anomaly (missing interparietal bone, fused ribs), skeletal variation (small interparietal bone, imperfect ossification of sternebrae, imperfect ossification of cervical spinal arch) 400: Increased early/late resorption, increased post-implantation loss, decreased number of live fetuses, external anomalies (small auricles, open eyelid, limb hyperextension/missing fingers, short tail, systemic edema), abnormalities of visceral organs (dilatation of aortic arch, diaphragmatic hernia, microphthalmia, persistent truncus arteriosus, ventricular septal defect, pulmonary stenosis, kidney malposition/defect), skeletal anomaly (missing digital phalanges, fused caudal vertebrae, fused cervical spinal arch, missing cervical spine), skeletal variation (sutural bones)	Maternal animals: 400 Embryos/fetuses: <100	4.2.3.5.2.5

a) Death or moribund euthanasia was observed in 3 of 20 animals (including 1 animal with abortion) in the control group, 1 of 20 animals in the 100 mg/kg group, and 1 of 20 animals (with abortion) in the 400 mg/kg group, but was considered unrelated to tazemetostat because the events were unrelated to dosage amounts and observed in the control group as well, and the events in some animals were caused by errors in tazemetostat administration. b) At this dose, reduced body weight gain was observed but the body weight per se was not affected.

5.6 Other toxicity studies

5.6.1 Studies in juvenile animals

Four and 13-week repeated-dose toxicity studies were conducted in 7-day-old rats (Table 16). The exposure level in blood (higher in female than in male) tended to be higher toxicity in females. However, no significant qualitative difference was observed in toxicity between males and females. Tazemetostat had no effect on the postnatal development and differentiation or on the central nervous system. In the 13-week repeated-dose toxicity study, T-LBL was observed in juvenile rats as in mature rats [see Section 5.2] at a lower dose and exposure level in blood than in mature rats. At the NOAEL (<50 mg/kg/day in

both males and females) in the 13-week repeated-dose toxicity study in juvenile rats, (a) C_{max} and (b) AUC_{24h} of tazemetostat were (a) <1,410 ng/mL and (b) <6,340 ng•h/mL in males and (a) <3,900 ng/mL and (b) <18,500 ng•h/mL in females, which were (a) <1.1 and (b) <0.70 times (males) and (a) <3.0 and (b) <2.1 times (females) the clinical exposure.[30)] At the T-LBL-inducing dose (100 mg/kg/day in males, 50 mg/kg/day in females), (a) C_{max} and AUC_{24h} of tazemetostat were (a) 3,800 ng/mL and (b) 19,200 ng•h/mL, respectively, in males and (a) 3,900 ng/mL and (b) 18,500 ng•h/mL, respectively, in females, which were (a) 2.9 and (b) 2.1 times (males) and (a) 3.0 and (b) 2.1 times (females) the clinical exposure.[30)]

Table 16. Studies in juvenile animals

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague-Dawley)	p.o.	4 weeks (QD, Day 7-34 after birth)	0, 50, 150, 500,[a)] 1,000[b)]	Moribund euthanasia: 500 (3 of 5 males, 3 of 5 females), 1,000 (3 of 5 males, 3 of 5 females), inanimation, feeling cold, pale body surface, erosion of glandular stomach, decrease/necrosis of lymphocytes in thymus/lymph nodes, single cell necrosis of hematopoietic cells in bone marrow/spleen/liver, renal papillary calcinosis, vacuolization of tubular epithelium 50, 150: No changes with toxicological significance	Not evaluated	Reference 4.2.3.5.4.1
Male and female rats (Sprague-Dawley)	p.o.	13 weeks (QD, Day 7-98 after birth)	0, 50,[c)] 100,[c)] 150/300,[b) c)] 150/600[b) c)]	Death/moribund euthanasia: 50 (1 of 20 males, 1 of 20 females), 100 (2 of 21 males), 150/600 (3 of 20 males, 1 of 20 females), dyspnoea, rale, labored breathing, red substance around eye/nose/oral cavity, crust formation, swollen fore limbs, swollen testis, mass in fore limbs/ventral trunk, thymic T-LBL, pyelonephritis, thymic lymphocyte hyperplasia, inflammatory granulomatous mass, etc. in cheek ≥50: Increased blood glucose,[d)] thymic T-LBL,[e)] increased cell density in splenic white pulp. ≥100: Increased body weight/food consumption, increased white blood cell count, decreased red blood cell count/hemoglobin, increased blood chloride/calcium[d)]/magnesium[d)] decreased blood albumin/total protein, thymic lymphocyte hyperplasia, increased femoral trabeculae, increased monocyte count in splenic red pulp/decreased lymphocyte count in splenic marginal zone, increased splenic white blood cell count (CD8-positive T cells in particular), increased thymic white blood cell count (CD8-positive T cells in particular)[f)] ≥150/300: Increased white blood cell count/lymphocyte count/neutrophil count/monocyte count, prolongation of prothrombin time, decreased hematocrit[d)]/hemoglobin[d)]/MCV, decreased blood globulin, suppurative granulomatous inflammation of subcutaneous tissue 150/600: Increased eosinophil count/mean platelet volume[d)]/reticulocyte count, decreased red blood cell count[d)]/MCH,[d)] increased blood ALP[d)]/total bilirubin/phospholipids,[d)] decreased blood potassium	Male: 50 Female: <50	4.2.3.5.4.2

a) Males and females in 500 and 1,000 mg/kg/day groups showed aggravation in clinical signs on Days 1 to 2. All animals in these dose groups were moribund euthanized. b) In 150/300 and 150/600 mg/kg/day groups, the study drug was administered at 150 mg/kg/day from Days 7 to 21 after birth, and at 300 or 600 mg/kg/day from Day 22 after birth. c) The dose of tazemetostat is expressed in terms of free base. d) Females only; e) Observed in males of ≥100 mg/kg/day groups and in females of ≥50 mg/kg/day groups. f) Increased thymic white blood cell (CD8-positive T cells, etc.) count was observed in animals in ≥100 mg/kg/day groups showing hyperplasia of thymic lymphocytes and in those in ≥150/300 mg/kg/day groups showing T-LBL.

5.6.2 Photosafety

The applicant's explanation:

A preliminary evaluation of phototoxicity (evaluation of absorption of ultraviolet [UV]-visual spectrum) showed an absorption maximum from 290 nm and tazemetostat was distributed in the skin and eyes after administration [see Section 4.2.1]. Therefore, an *in vitro* phototoxicity study was conducted using a mouse fibroblast cell line. Tazemetostat was shown to be phototoxic (Table 17).

Based on the above findings and taking account of photosensitivity observed in 1 subject in a clinical study [see 7.R.3.5], caution will be given against the risk of tazemetostat-induced phototoxicity via the package insert, etc.

Table 17. Photosafety study

Study type	Test system	Testing method	Main findings	Attached document
In vitro	Mouse fibroblast strain Balb/c 3T3	1.78-100 μg/mL (with UV irradiation[a)]) 1.78-100 μg/mL (without UV irradiation)	Phototoxic (PIF: >4.176 and >5.310, MPE: 0.270 and 0.347)	4.2.3.7.7.1

a) Irradiated with ultraviolet A [UVA] (5 J/cm^2) and ultraviolet B [UVB] (21 mJ/cm^2) for 30 minutes.

5.6.3 Studies on T-LBL observed in rats

5.6.3.1 Study in rats receiving tazemetostat

T-LBL was detected in the 13-week repeated-dose toxicity study of tazemetostat in rats [see Section 5.2]. In response, the following studies were conducted using samples obtained from rats receiving tazemetostat (Table 18). An immunophenotyping analysis using lymphatic tissues (thymus, spleen, bone marrow, and lymph nodes), rat leukemia virus reactivation study, *Notch* gene expression analysis, etc. were conducted but failed to identify the onset mechanism of T-LBL.

Table 18. Studies on samples obtained from rats treated with tazemetostat

Study	Test system	Testing method	Main findings	Attached document CTD
Analysis of cell lineage in samples of thymus, bone marrow, and spleen	*Ex vivo*	Lymphocytes and hematopoietic cells were isolated from lymphatic tissues (thymus, spleen, bone marrow, and lymph nodes) of animals with or without thymic T-LBL in the 13-week repeated-dose toxicity study in rats (CTD 4.2.3.2.3), and subjected to immunophenotyping by flow cytometry.	In the thymus, bone marrow, and spleen of animals with T-LBL, the percentage of CD8-positive T cells and αβ T cells increased and the percentage of CD4-positive T cells and γδ T cells decreased as compared with the levels in the control group. In the thymus, bone marrow, and spleen of animals without T-LBL, the percentage of αβ T cells decreased and the percentage of γδ T cells increased in a dose-dependent manner as compared with the levels in the control group.	4.2.3.7.3.1 Reference
Study on reactivation of rat leukemia virus	*Ex vivo*	DNA was isolated from the thymus of rats treated with tazemetostat in the 13-week repeated-dose toxicity study (CTD 4.2.3.2.3), and subjected to detection for the reactivation of RaLV, an endogenous retrovirus.	Regardless of T-LBL, no data suggestive of RaLV reactivation were obtained.	4.2.3.7.3.2 Reference
Analysis of Notch target gene expression	*Ex vivo*	mRNA was extracted from the thymus of rats treated with tazemetostat in the 13-week repeated-dose toxicity study (CTD 4.2.3.2.3), and subjected to quantitative analysis of expression of mRNA of Notch target genes (*Dtx1, Hes1*, and *Hey1*)	Increase in *Dtx1, Hes1*, or *Hey1* expression was not observed regardless of T-LBL. *Dtx1* and *Hes1* expression levels were lower in the thymus of rats with T-LBL than in the thymus of rats without T-LBL.	4.2.3.7.3.3 Reference

5.6.3.2 Studies using EZH2-inhibitory compounds with structure unrelated to tazemetostat

Thirteen (13)-week repeated-dose toxicity studies in rats were conducted using 2 types of EZH2-inhibitory compounds (EPZ-10961 and EPZ011989) with structure unrelated to tazemetostat (Table 19). Both EPZ-10961 and EPZ011989 caused T-LBL in the thymus as is the case with tazemetostat, albeit through unknown mechanism.

Table 19. Studies with EPZ-10961 and EPZ011989

Study	Test system	Testing method	Main findings	Attached document CTD
Evaluation of general toxicity of EPZ-10961	Male and female rats (Sprague-Dawley)	EPZ-10961 was administered orally at 0, 50, 100, and 300 mg/kg/day for 13 weeks, followed by an 8-week recovery period, and general toxicity was evaluated.	Thymic T-LBL was detected in the EPZ-10961 50 and 100 mg/kg/day groups, but not in the 300 mg/kg/day group.[a)]	4.2.3.7.3.4
Cell lineage analysis using thymus samples isolated from rats treated with EPZ-10961	*Ex vivo*	Lymphocytes were isolated from animals with or without T-LBL in 13-week repeated-dose toxicity study (CTD 4.2.3.7.3.4), and subjected to immunophenotyping by flow cytometry.	In the thymus of animals with T-LBL, the percentage of CD8-positive T cells and αβ T cells increased while the percentage of CD4-positive T cells and γδ T cells decreased, compared with the levels in the control group. In the thymus of animals without T-LBL, the percentage of αβ T cells decreased while the percentage of γδ T cells increased in a dose-dependent manner, compared with the levels in the control group.	4.2.3.7.3.5 4.2.3.7.3.6 4.2.3.7.3.7 Reference
Evaluation of general toxicity of EPZ011989	Male and female rats (Sprague-Dawley)	EPZ011989 was administered orally at 0, 100, 300, and 600 mg/kg/day for 13 weeks, and general toxicity was evaluated. Lymphocytes were isolated from animals with or without T-LBL in the thymus, and subjected to immunophenotyping by flow cytometry.	• In the EPZ011989 100 and 300 mg/kg/day groups, T-LBL was observed in the thymus and lymphoma cells (metastatic) were detected in the spleen, lymph nodes, bone marrow, etc. • In the thymus of animals with T-LBL, the percentage of CD8-positive T cells and CD4-positive/CD8-positive T cells increased, and the percentage of CD4-positive T cells decreased. • As for peripheral lymphocytes, the proportion of B cells decreased in males of the ≥100 mg/kg/day group, the absolute B cell count decreased in males of the 600 mg/kg/day group, the absolute B cell count tended to decrease in females of the ≥100 mg/kg/day group, and the proportion of B cells decreased while the proportion of T cells (including CD4-positive, CD8-positive, and αβ T cells) increased in females of the 600 mg/kg/day group. In females of the 100 mg/kg/day group, the ratio of CD4-positive/CD8-positive cells increased.	4.2.3.7.3.8 Reference
Gene expression analysis in thymus of rats treated with EPZ011989	*Ex vivo*	mRNA was extracted from the thymus of rats in the 13-week repeated-dose toxicity study on EPZ011989, (CTD 4.2.3.7.3.8), and subjected to quantitative analysis of expression of mRNA of Notch target genes (*Dtx1, Hes1*) and *Myc* gene.	• In the thymus of rats with T-LBL, the expression level of *Dtx1* and *Hes1* mRNA was lower than in the thymus of rats without T-LBL • In the thymus of rats with T-LBL, the expression level of *Myc* mRNA was higher than in the thymus of rats without T-LBL	4.2.3.7.3.9 4.2.3.7.3.10 Reference
Analysis of RNA sequence in T-LBL of rats treated with EPZ011989	*Ex vivo*	The gene expression pattern was investigated in T-LBL of rats treated with EPZ011989 in the 13-week repeated-dose toxicity study (CTD 4.2.3.7.3.8), with the focus on the (a) known transcription characteristics in human T-ALL and (b) homology to the known gene expression pattern in the mouse model of T-ALL.	The gene expression pattern in the thymus of rats with T-LBL was not identical with the gene expression pattern common to human T-ALL, nor with the pattern in human T-ALL with missing PRC2 or in the mouse model.	4.2.3.7.3.11 Reference

a) A marked decrease in thymic lymphocyte count was observed at this dose, which may have been the cause of no T-LBL observed.

5.6.3.3 Study on age-related thymic involution in rats

Age-related thymic involution in normal rats was investigated to search for factors other than tazemetostat that had caused T-LBL in rats (Table 20). Results showed pathological changes suggesting age-related weight decrease and involution in the thymus.

Table 20. Study on age-related thymic involution in rats

Test system	Study method	Main findings	Attached document CTD
Ex vivo	Thymic cells and peripheral blood were isolated from 6-, 8-, 10-, and 12-month-old normal untreated rats and subjected to immunophenotyping. The thymus was measured for weight and subjected to histopathological examination.	Immunophenotyping of blood: • Decrease in T cell count and in the proportion of CD8-positive T cells (12-month-old males), decrease in total lymphocyte count, T cell count, and CD4-positive T cell count (8- and 12-month-old females), and decrease in CD4-positive/CD8-positive T cell count (8-, 10-, and 12-month-old females) were observed. Immunophenotyping of thymus • Decrease in CD4-positive/CD8-positive T cell count and increase in CD4-negative/CD8-negative T cell count (8-month-old males and 10- and 12-month-old males and females) and increase in T cell count, CD4-positive T cell count, and CD8-positive T cell count (8-, 10-, and 12-month-old males and females) were observed. Thymic weight and histopathology: • Age-related change in thymic weight was not observed in males, whereas in females, thymic weight tended to decrease with age, showing a significant decrease in 12-month-old females. • Histopathological examination showed thymic involution in males and females of all groups (6 to 12 months of age). Mild involution was observed in all 6-month-old females, and the extent and frequency of involution tended to increase with age	4.2.3.7.7.2 Reference

5.6.4 Toxicity study of impurities

The safety of impurities (Impurity A, Impurity B, and Impurity C) which are present in excess of the qualification threshold was evaluated in accordance with "Revision of the Guideline on Impurities in New Drug Substances" (ICH Q3A Guideline) and "Revision of the Guideline on Impurities in New Drug Products" (Q3B Guidelines).

The applicant's explanation:

General toxicity was evaluated based on the results of the 13-week repeated-dose toxicity study in rats which was conducted using the drug substance[31)] containing the above impurities [see Section 5.2], and there are no safety problems with the drug substance and the drug product at the upper limit of acceptance criteria. Although no genotoxicity study was conducted on these impurities because tazemetostat was considered carcinogenic [see Section 5.R.1], (a) the impurities were non-genotoxic in an *in silico* analysis and (b) the result of the genotoxicity study using the drug substance[31)] containing the impurities was negative [see Section 5.3].

5.R Outline of the review conducted by PMDA

Based on the data submitted and on the results of the reviews in the following sections, PMDA concluded that the applicant's explanation about the toxicity of tazemetostat is acceptable.

5.R.1 T-LBL observed in repeated administration

The applicant's explanation about T-LBL observed during repeated administration of tazemetostat:

In the 13-week repeated-dose toxicity study in mature rats, T-LBL was observed in the thymus in the ≥300 mg/kg/day groups after ≥10 weeks of treatment [see Section 5.2]. Tazemetostat has been shown to be non-genotoxic [see Section 5.5], and its non-genotoxic mechanism is considered to be associated

[31)] Contains Impurity A ([redacted]%), Impurity B ([redacted]%), and Impurity C ([redacted]%).

with the onset of T-LBL. Although the mechanism of tazemetostat-induced T-LBL is currently unclear [see Section 5.6.3.1], the following findings indicate that the EZH2-inhibitory effect of tazemetostat may possibly be involved in the onset of T-LBL:

- EZH2 inactivation induces acute lymphoblastic leukemia (T-ALL), a malignant tumor of T cells, in mice (*Genes Dev.* 2012;26:651-6, *Blood*. 2015;126:1172-83).
- EPZ-10961 and EPZ011989, compounds that have EZH2-inhibitory activity with structures unrelated to tazemetostat, caused T-LBL in the thymus of rats [see Section 5.6.3.2].

In the repeated-dose toxicity study in mature and juvenile rats, the comparison of the dose causing T-LBL and thymic lymphocyte hyperplasia with its exposure level in blood (Table 21) suggested that juvenile rats are more susceptible than mature rats to tazemetostat-induced T-LBL. Possible reasons for these results are that (a) malignant tumors of T cells such as T-LBL are derived from immature thymic precursor cells (*Cancer J.* 2012;18:432-8, *Leukemia*. 2014;28:349-61, etc.), (b) thymic involution occurs with aging in rats [see Section 5.6.3.3], and (c) immature thymic precursor cells grow actively in juvenile rats.

Table 21. Occurrences of T-LBL and thymic lymphocyte hyperplasia in 13-week repeated-dose toxicity study in rats

Age at the start of treatment	Dose (mg/kg/day)	Incidence of T-LBL[a)]	Incidence of thymic lymphocyte hyperplasia[a)]	AUC_{24h} (ng•h/mL) (safety margin of clinical exposure[30)])	
				Male	Female
8 weeks	100	0/28	Not observed	18,033 (×2.0)	55,037 (×6.1)
	300	11/40	Not observed	99,546 (×11)	166,305 (×18)
	600	1/40	Not observed	285,998 (×32)	286,031 (×32)
7 days	50	1/40	Not observed	6,340 (×0.7)	18,500 (×2.1)
	100	1/41	6/41	19,200 (×2.1)	67,200 (×7.5)
	150/300	11/40	3/40	125,000 (×14)	229,000 (×25)
	150/300	12/40	11/40	290,000 (×32)	425,000 (×47)

a) Number of animals including those in the main study groups and in the recovery group (sum of males and females)

Thus, although tazemetostat is a carcinogenic compound, risk of T-LBL is considered low in patients treated with tazemetostat, for the following reasons: (a) In the 13-week repeated-dose toxicity study in mature rats, the blood exposure to tazemetostat (AUC_{24h}, 18,033 ng•h/mL in males; 55,037 ng•h/mL in females) at the dose without T-LBL (100 mg/kg/day) was approximately 2 to 6 times the clinical exposure, (b) the risk of T-LBL may possibly decrease with the decrease in immature thymic precursor cells accompanying thymic involution, and (c) age-associated thymic involution occurs in adult patients, the intended population tazemetostat treatment. However, one case of myelodysplastic syndrome (MDS) for which a causal relationship to tazemetostat could not be ruled out was reported in patients with FL in the phase II part of Study 101 [see Section 7.R.3.4]. The package insert will give caution against tazemetostat-induced secondary malignant tumor, and further information will be collected in the post-marketing setting.

PMDA's view:

In the 13-week repeated-dose toxicity study in mature rats, the safety margin between the highest dose without T-LBL and the clinical dose was only 2- to 6-fold. In this study, T-LBL was observed within a short time after the start of treatment with tazemetostat, and the effect of long-term repeated administration is unknown. These observations preclude a definite conclusion about a risk of

tazemetostat-induced T-LBL in clinical settings at present. The package insert should inform of T-LBL identified in the toxicity study of tazemetostat and the clinical study in children, and further information should be collected in the post-marketing settings.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

In this section, the dose and concentration of tazemetostat are expressed in terms of free base.

6.1 Summary of biopharmaceutic studies and associated analytical methods

The oral formulations of tazemetostat are available in liquid, suspension, and tablets. The PK, etc. of tazemetostat were investigated using these formulations and injection (Table 22). The proposed commercial formulation is 200-mg tablets which are manufactured by 2 different manufacturing methods (batch method and continuous production method). The bioequivalence of these formulations has been confirmed by the dissolution test conducted according to the "Guidelines for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 67 dated February 14, 2000)."

Table 22. Formulations used in clinical studies

Formulation	Study
Injection containing ^{14}C-tazemetostat	Foreign phase I study (Study 103)
Oral solution containing ^{14}C-tazemetostat	Foreign phase I study (Study 103)
Suspension	Foreign phase I/II study (phase I part of Study 101)
Tablets (100, 200,[*1] and 400 mg)	Japanese phase I study (Study 106[*2]), foreign phase I study (Studies 103[*3] and 105[*3]), foreign phase I/II study (phase I[*4] and II[*2] parts of Study 101, Japanese phase II study (Study 206[*2])

*1, Manufactured by batch method. *2, 200 mg tablets were used. *3, 300 and 400 mg tablets were used. *4, 100 and 200 mg tablets were used.

6.1.1 Assay

Tazemetostat and EPZ-6930 (*N*-deethylated form) in human plasma was determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation was 1.00 ng/mL for both compounds.

6.1.2 Foreign clinical studies

6.1.2.1 Foreign phase I/II study (CTD 5.3.5.2.1, 5.3.5.2.2, and 5.3.5.2.2-2; Study 101, phase I part; meal effect cohort [June 2013 to September 2016])

A 2-treatment, 2-period cross-over study in patients with relapsed or refractory B cell lymphoma and patients with advanced solid tumor (13 patients, 12 included in the PK analysis) was conducted to investigate meal effect on the PK of tazemetostat. A single oral dose of tazemetostat 200 mg was administered QD under fasting conditions[32)] or within 30 minutes after a high-fat meal (lipid accounting for 53.8 g of total calorie [841 kcal]) with a 7-day washout between treatment periods.

The geometric mean ratio [90% confidence interval (CI)] of C_{max} and AUC_t of tazemetostat taken after a high-fat meal to that under fasting condition was 0.62 [0.41, 0.93] and 0.69 [0.44, 1.08], respectively.

32) Tazemetostat was administered after 8 hour-fasting, The fasting continued until immediately after the administration.

The applicant's explanation about meal effect on the PK of tazemetostat, based on the above results: (1) Food intake caused a slowdown in gastric emptying, leading to delayed t_{max} and decreased C_{max}. (2) The decreased tazemetostat concentration and prolonged retention of the content in the digestive tract increased susceptibility to the first-pass effect. These changes may have caused a decrease in AUC_t. However, the interquartile ranges of C_{max} and AUC_t following the fasting dose (114 to 680 ng/mL and 315 to 2,680 ng•h/mL, respectively) and following the dose after a high-fat meal (78.5-506 ng/mL and 372-1,930 ng•h/mL, respectively) overlapped each other, suggesting that the variations in C_{max} and AUC_t are unlikely to pose any clinical problem. The efficacy and safety of tazemetostat were demonstrated in the phase II part of Study 101 and Study 206 (the population with unrestricted meal timing in the dosage regimen for tazemetostat). Based on these results, tazemetostat may be administered regardless of food intake status.

6.1.2.2 Foreign phase I study (CTD 5.3.3.4.1, 5.3.3.4.2, and 5.3.3.4.2-2; Study EZH-105 [Study 105], Part B [ongoing since March 2017 (data cut-off, May 24, 2019)])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory B cell lymphoma and patients with advanced solid tumor (16 patients, 12 included in the PK analysis) to investigate the effect of omeprazole (proton pump inhibitor) on the PK of tazemetostat and the effect of tazemetostat on the PK of repaglinide and omeprazole. Repaglinide 0.25 mg was administered orally QD on Days 1 and 16, omeprazole 20 mg was administered orally QD on Day 1 and on Days 16 through 19, and tazemetostat 800 mg was administered orally BID from Days 2 through 28. Based on the results on Days 16[33)] and 19, the effect of omeprazole on the PK of tazemetostat was investigated. The effect of tazemetostat on the PK of repaglinide and omeprazole is summarized in Section "6.2.3.2 Drug interaction with repaglinide or omeprazole."

The geometric mean of ratio [90% CI] of C_{max} and AUC_t of tazemetostat in combination with omeprazole to that in the administration tazemetostat alone was 1.06 [0.70, 1.58] and 1.17 [0.80, 1.69], respectively.

Based on the above, the applicant explained that the combination of tazemetostat with a drug affecting intragastric pH (such as proton pump inhibitor) is unlikely to cause a pharmacokinetic interaction.

6.1.2.3 Foreign phase I study (CTD 5.3.1.1.1 and 5.3.1.1.2; Study EZH-103 [Study 103], Part A [ongoing since June 2018 (data cut-off, May 7, 2019)])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory B cell lymphoma and patients with advanced solid tumor (3 patients, all included in the PK analysis) to investigate absolute BA (part A, Days 1 through 15), mass balance (part B, Day 16), etc. Tazemetostat 800 mg was administered orally BID from Days 1 through 14, tazemetostat 800 mg was administered orally QD as a single dose on Day 15, followed by a single intravenous QD administration of ^{14}C-tazemetostat (approximately 12 μg) after 60 minutes, and a single dose of ^{14}C-tazemetostat 800 mg was administered orally QD on Day 16. Results in part B are summarized in Section 6.2.2.2.

33) On Day 16, omeprazole and repaglinide were administered approximately 1 hour after the first dose of tazemetostat.

The mean absolute BA[34] (range) calculated from AUC of tazemetostat on Day 15 was 33.9% (20.2%-49.8%).

6.2 Clinical pharmacology

The PK of tazemetostat in patients with cancer was investigated after the administration of tazemetostat alone and after the co-administration of tazemetostat and fluconazole. Also, the effect of tazemetostat on the PK of repaglinide, omeprazole, and midazolam was investigated.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.5.2.4 and 5.3.5.2.5; Study 106 [ongoing since January 2017 (data cut-off, December 2, 2019)])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory FL or DLBCL (7 patients, all included in the PK analysis) to investigate the PK, etc. of tazemetostat. Tazemetostat 800 mg was administered orally QD as a single dose and, after 4 to 9 days, tazemetostat 800 mg was administered orally BID. Plasma concentrations of tazemetostat and EPZ-6930 were measured.

Table 23 shows the PK parameter values of tazemetostat and EPZ-6930. The AUC ratio of EPZ-6930 to tazemetostat after a single dose and Day-15 multiple doses was 1.41 and 2.56, respectively. The accumulation ratio[35] of tazemetostat and EPZ-6930 was 1.09 and 2.58, respectively.

Table 23. PK parameters of tazemetostat and EPZ-6930

Day of measurement	Analyte	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{12h} (ng•h/mL)	AUC_t (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_Z/F (L)
After a single dose	Tazemetostat	7	1,150 ± 787	1.97 (0.95, 4.08)	4,700 ± 2,810	5,990 ± 3,460	7.59 ± 1.24	175 ± 90.4	1,910 ± 1,050
	EPZ-6930	7	948 ± 556	1.97 (1.12, 4.08)	5,280 ± 2,890	7,700 ± 4,090	8.83 ± 1.43	-	-
Day-15 multiple doses	Tazemetostat	7	1,290 ± 582	1.05 (0.88, 2.03)	4,500 ± 1,570	4,490 ± 1,560	4.59 ± 1.93	205 ± 98.6	1,580 ± 1,540
	EPZ-6930	7	1,950 ± 773	1.07 (0.88, 2.03)	10,800 ± 3,600	10,800 ± 3,560	4.91 ± 2.32	-	-

Mean ± SD; * Median (range); -, Not calculated.

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I/II study (CTD 5.3.5.2.1, 5.3.5.2.2, and 5.3.5.2.2-2; Study 101, phase I part, dose escalation and dose expansion cohorts [June 2013 to September 2016])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory B cell lymphoma and patients with advanced solid tumor (38 patients, all included in the PK analysis) to investigate the PK, etc. of tazemetostat. Tazemetostat 100 to 1,600 mg was administered orally BID, and plasma concentrations of tazemetostat and EPZ-6930 were investigated.

Tables 24 and 25 show the PK parameter values of tazemetostat and EPZ-6930. C_{max} and AUC_{12h} of tazemetostat increased more than dose-proportionally within the dose range studied. The applicant explained that the results were attributable to metabolism saturation in the liver with dose increase.

[34] Calculated based on AUC_{12h} after a single oral QD administration of tazemetostat 800 mg and on AUC_{inf} after a single intravenous QD administration of ^{14}C-tazemetostat (approximately 12 µg).
[35] Ratio of AUC_{12h} on Day 15 following multiple administration to that after a single administration

Table 24. PK parameters of tazemetostat

Dose (mg)	Day of measurement	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{12h} (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
100	1	3	102 ± 80	1.08 (1, 2)	326 ± 251	2.46, 2.79	155, 559	550, 2,250
	15	3	62.2 ± 60.8	2 (0.95, 2)	252 ± 184	2.96	217	928
200	1	3	363 ± 155	1 (0.5, 1)	1,260 ± 634	-	-	-
	15	3	355 ± 130	1 (0.5, 2.08)	974 ± 421	-	-	-
400	1	3	476 ± 258	2 (2, 4)	1,730 ± 561	2.64	303	1,150
	15	3	416 ± 99.9	1.08 (1, 2)	1,480 ± 798	3.02	362	1,570
800	1	14	1,540 ± 499	2 (0.5, 4)	6,320 ± 2,840	3.06 ± 0.31*2	130 ± 33*2	567 ± 119*2
	15	13	933 ± 440	1.1 (1, 4)	3,670 ± 1,620	3.12 ± 0.41*3	293 ± 115*3	1,310 ± 536*3
1,600	1	12	3,650 ± 1,870	2 (1, 2.08)	16,300 ± 7,710	3.53 ± 0.40*4	172 ± 226*4	821 ± 958*4
	15	12	1,980 ± 813	2 (1, 4)	8,190 ± 3,090	3.43 ± 0.62*5	241 ± 97.9*5	1,240 ± 624*5

Mean ± SD (individual values for n = 1 or 2); *1 Median (range); *2 n = 5; *3 n = 3; *4 n = 8; *5 n = 6; -, Not calculated

Table 25. PK parameters of EPZ-6930

Dose (mg)	Day of measurement	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{12h} (ng•h/mL)	$t_{1/2}$ (h)
100	1	3	102 ± 37.5	2 (1, 2)	436 ± 189	2.53, 3.4
	15	3	81.4 ± 38.1	2 (0.95, 2)	445 ± 163	2.33
200	1	3	267 ± 47.8	1 (1, 1.25)	1,080 ± 226	3.21
	15	3	358 ± 69.8	2 (1, 2.08)	1,230 ± 225	-
400	1	3	384 ± 80.9	2 (2, 4)	2,030 ± 637	-
	15	3	574 ± 211	2 (1.08, 4)	2,730 ± 632	-
800	1	14	837 ± 207	2 (0.5, 6)	4,710 ± 1,210	3.65 ± 0.36*2
	15	13	1,270 ± 358	2 (1, 4.05)	7,080 ± 1,940	-
1,600	1	12	1,320 ± 597	2 (1, 8)	9,320 ± 3,920	3.21
	15	12	2,670 ± 278	2 (1, 8.12)	16,900 ± 3,160	2.77, 3.51

Mean ± SD (individual values for n = 1 or 2); *1 Median (range); *2 n = 4; -, Not calculated

6.2.2.2 Foreign phase I study (CTD 5.3.1.1.1 and 5.3.2.2.13; Study 103, part B [ongoing since June 2018 (data cut-off, May 7, 2019)])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory B cell lymphoma and patients with advanced solid tumor (3 patients, all included in the PK analysis) to investigate the absolute BA (part A, Day 1 through 15), mass balance (part B, Day 16), etc. Tazemetostat 800 mg was administered orally BID from Days 1 through 14, a single dose of tazemetostat 800 mg was administered orally QD on Day 15 and, after 60 minutes, a single dose of ^{14}C-tazemetostat (approximately 12 μg) was administered intravenously QD, and a single dose of ^{14}C-tazemetostat 800 mg was administered orally QD on Day 16. After the administration on Day 16, radioactivity concentration in plasma, urine, and feces was measured.

Mainly unchanged tazemetostat, EPZ-6930, and EPZ006931 (*N*-detetrahydropyranylated form) were detected in plasma up to 12 hours post-dose (the proportion relative to AUC_{12h} of total plasma radioactivity was 22.4%, 31.8%, and 11.0%, respectively).

The urinary and fecal excretion rate of radioactivity (proportion to the administered radioactivity) up to 192 hours post-dose was 15.36% and 78.85%, respectively. Mainly unchanged tazemetostat and EPZ-6930 were detected in urine up to 48 hours post-dose (1.4% and 6.7%, respectively). Mainly, M518_1

(double *N*-deethylated form), M604_5 (double oxidized form), and EPZ-6930 were detected in feces pooled up to 96 hours[36] post-dose (8.75%[37] and 10.9%,[38] respectively).

6.2.3 Drug-drug interactions

6.2.3.1 Drag interaction with fluconazole (CTD 5.3.3.4.1, 5.3.3.4.2, and 5.3.3.4.2-2; Study 105, part A [ongoing since March 2017 (data cut-off, May 24, 2019)])

An open-label, uncontrolled study was conducted in 16 patients with relapsed or refractory B cell lymphoma and patients with advanced solid tumor (14 patients included in the PK analysis) to investigate the effect of fluconazole (moderate inhibitor of CYP3A) on the PK of tazemetostat and EPZ-6930. Tazemetostat 400 mg was administered orally BID from Days 1 through 24, and fluconazole 400 mg was administered orally QD from Days 16 through 19.

The geometric mean ratio [90% CI] of C_{max} and AUC_t of tazemetostat and EPZ-6930 in combination with fluconazole to that of tazemetostat alone was 2.27 [1.75, 2.95] and 3.07 [2.57, 3.66], respectively, for tazemetostat and 0.87 [0.74, 1.02] and 1.10 [0.97, 1.26], respectively, for EPZ-6930.

The applicant explained that the results indicated increased exposure to tazemetostat in its combination use with a moderate CYP3A inhibitor, warranting caution against the co-administration of tazemetostat with a CYP3A inhibitor, and that such advice would be given.

6.2.3.2 Drag interaction with repaglinide or omeprazole (CTD 5.3.3.4.1, 5.3.3.4.2, and 5.3.3.4.2-2; Study 105, part B [ongoing since March 2017 (data cut-off, May 24, 2019)])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory B cell lymphoma and patients with advanced solid tumor (16 patients, 12 included in the PK analysis) to investigate the effect of tazemetostat on the PK of repaglinide (substrate of CYP2C8) and omeprazole (substrate of CYP2C19) and the effect of omeprazole on the PK of tazemetostat. Repaglinide 0.25 mg was administered orally QD on Days 1 and 16, omeprazole 20 mg was administered orally QD on Days 1 and on Days 16 through 19, and tazemetostat 800 mg was administered orally BID from Days 2 through 28. The effect of tazemetostat on the PK of repaglinide and omeprazole was investigated based on the data on Days 1 and 16.

The geometric mean ratio [90% CI] of C_{max} and AUC_t of repaglinide and omeprazole in combination with tazemetostat to that of repaglinide or omeprazole alone was 1.93 [1.22, 3.07] and 2.17 [1.51, 3.11], respectively, for repaglinide and 0.84 [0.49, 1.44] and 0.80 [0.51, 1.27], respectively, for omeprazole.

The applicant's explanation about co-administration with substrates of CYP2C8 and CYP2C19, based on the above results:
Exposure to repaglinide was increased by co-administered tazemetostat, warranting caution against the co-administration of tazemetostat with a drug that is a substrate of CYP2C8, and thus such caution will

[36] Up to 144 hours post-dose in 1 of 3 patients.
[37] The sum of the proportion of M518_1 and M604_5 relative to the radioactivity administered because both metabolites were co-eluted.
[38] The peaks of EPZ-6930, EPZ006633 (*N*-de-ethylated form), and EPZ006931 overlapped. The data were handled as a reference value.

be given. In contrast, a clear increase in exposure to omeprazole was not observed by its co-administration with tazemetostat, thus cautionary advice on the co-administration of tazemetostat with a substrate of CYP2C19 is unnecessary.

6.2.3.3 Drug interaction with midazolam (CTD 5.3.5.2.1, 5.3.5.2.2, and 5.3.5.2.2-2; Study 101, part I, drug interaction cohort [June 2013 to September 2016])

An open-label, uncontrolled study was conducted in 13 patients with relapsed or refractory B cell lymphoma and patients with advanced solid tumor (all patients included in the PK analysis) to investigate the effect of tazemetostat on the PK of midazolam (substrate of CYP3A). Midazolam 2 mg was administered orally QD on Days −1 and 15, and tazemetostat 800 mg was administered orally BID from Days 1 through 15.

The geometric mean ratio [90% CI] of C_{max} and AUC_t of midazolam co-administered with tazemetostat to that of midazolam alone was 0.80 [0.57, 1.11] and 0.62 [0.48, 0.81], respectively.

The study results showed that exposure to midazolam was decreased by co-administered tazemetostat. The applicant explained that the co-administration of tazemetostat with a drug that is a substrate for CYP3A warrants caution and such advice will be given.

6.2.4 Tazemetostat administration in patients with renal impairment

No clinical study was conducted to investigate the effect of renal impairment on the PK of tazemetostat in patients with renal impairment.

The applicant's explanation:
The dose adjustment of tazemetostat is not necessary for patients with renal impairment, given the following study results:

- The results of the foreign phase I study (Study 103) suggested that renal excretion minimally contributes to the clearance of tazemetostat [see Section 6.2.2.2].
- According to the results of the pooled analysis of patients with FL enrolled in the Japanese phase I study (Study 106), the Japanese phase II study (Study 206), and the foreign phase I/II study (Study 101), the incidence of serious adverse events in patients with normal renal function[39] (53 patients), mild renal impairment (43 patients), and moderate renal impairment (23 patients), was 28.3%, 32.6%, and 21.7%, respectively, that of Grade ≥3 adverse events 41.5%, 39.5%, and 47.8%, respectively, that of adverse events leading to discontinuation of tazemetostat 9.4%, 11.6%, and 4.3%, respectively, and that of adverse events leading to dose reduction of tazemetostat 9.4%, 7.0%, and 21.7%, respectively, showing no clear difference in the incidences of these adverse events among patients with normal renal function, patients with mild renal impairment, and those with moderate renal impairment.

[39] Renal impairment was classified according to the following CrCL (mL/min) level: normal, ≥90; mild impairment, ≥60 and <90; moderate impairment, ≥30 and <60; and severe impairment, ≥15 and <30. CrCL <15 was classified as terminal-stage renal impairment regardless of the need of dialysis.

6.2.5 Relationship between exposure and change in QT/QTc intervals

In the phase I part of the foreign phase I/II study (Study 101), the relationship between plasma tazemetostat and EPZ-6930 concentrations and individual-corrected QT interval (ΔQTcI) was investigated in 36 subjects whose plasma concentration measurements were available at the time of electrocardiography, using linear and non-linear mixed effect models with the drug effect, non-drug effect, and residual. The estimated upper limit of 90% CI of ΔQTcI was 6.47 milliseconds at the mean C_{max} (geometric mean, 2,979 ng/mL) following a single oral administration of tazemetostat 1,600 mg, and 1.72 milliseconds at the mean C_{max} (geometric mean, 794 ng/mL) at steady state in BID administration of tazemetostat 800 mg. No clear relationship was observed between plasma EPZ-6930 concentration and ΔQTcI.

Based on the above, the applicant explained that the prolongation of QT/QTc interval is unlikely to occur in the clinical use of tazemetostat.

6.2.6 PPK analysis

A population pharmacokinetic (PPK) analysis was performed using the nonlinear mixed effect model (software used, NONMEM Version 7.3), based on the PK data (5,769 measuring time points in 681 subjects) of tazemetostat obtained from foreign clinical studies (Studies 101, 105, EZH-202 [Study 202],[40)] and EZH-203 [Study 203][41)]). The PK of tazemetostat was described by a 2-compartment model with first-order absorption process with lag time and a linear elimination process.

The investigated possible covariates of (a) CL/F, (b) Vc/F, and (c) absorption rate constant (k_a) were (a) body surface area, body weight, BMI, age, sex, smoking history, carcinoma, race, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, albumin, CrCL, eGFR, hepatic impairment, renal impairment, CYP3A inhibitors, CYP3A inducers, CYP2D6 inhibitors, CYP2D6 inducers, and gastric pH-elevating drugs and dose, (b) body surface area, body weight, BMI, age, sex, and albumin, and (c) age and gastric pH-elevating drugs, respectively. As a result of assessment, the identified covariates were body surface area, AST, bilirubin, albumin, CrCL, and dose for CL/F, body surface area for Vc/F, and gastric pH-elevating drugs for k_a.

The applicant explained that all of the above covariates other than albumin only minimally affected the PK parameters of tazemetostat and they are unlikely to have a clinically significant effect on the PK of tazemetostat.

6.2.7 Relationship between exposure and efficacy or safety

6.2.7.1 Relationship between exposure and efficacy

A relationship between the exposure[42)] to tazemetostat (AUC[43)]) and its efficacy was investigated based on the results of the foreign clinical study (Study 101, phase II part). No clear relationship was observed between them.

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40) Foreign phase II study in patients with epithelioid sarcoma, etc.
41) Foreign phase II study in patients with malignant mesothelioma
42) Estimated by the PPK analysis [see Section 6.2.6].
43) The mean AUC per day obtained by dividing AUC from the start of administration until the efficacy evaluation (patients with response) or AUC throughout the treatment period (patients without response) by the number of days of tazemetostat administration.

6.2.7.2 Relationship between exposure and safety

A relationship between the exposure[42)] to tazemetostat (AUC[44)]) and the incidence of Grade ≥3 adverse events was investigated based on the results of the foreign clinical studies (Studies 101, 105, and 202[40)]). The results suggested that the incidence of Grade ≥3 adverse events increased with increasing exposure to tazemetostat.

6.2.8 Difference in PK of tazemetostat between Japanese and non-Japanese patients

In the Japanese phase I study (Study 106) and in the phase I part of the foreign phase I/II study (Study 101), no clear difference was observed in C_{max} or AUC_{12h} of tazemetostat on Day 15 in multiple BID oral administration of tazemetostat 800 mg [see Sections 6.2.1.1 and 6.2.2.1]. Based on these results, etc., the applicant explained that no clear difference was observed in the PK of tazemetostat between Japanese and non-Japanese patients.

6.R Outline of the review conducted by PMDA

Based on the data submitted and on the results of the reviews in the following section, PMDA concluded that the applicant's explanation about the clinical pharmacology, etc. of tazemetostat is acceptable.

6.R.1 Administration of tazemetostat in patients with hepatic impairment

No clinical study was conducted in patients with hepatic impairment to investigate the effect of hepatic impairment on the PK of tazemetostat.

The applicant's explanation about the administration of tazemetostat in patients with hepatic impairment:

Tazemetostat is eliminated mainly by metabolism in the liver [see Section 6.2.2.2], and therefore hepatic impairment may possibly affect the PK of tazemetostat. However, the following results indicate that the dose adjustment of tazemetostat is not necessary for patients with mild hepatic impairment:

- A pooled analysis of data in the population of patients with FL enrolled in the Japanese phase I study (Study 106), the Japanese phase II study (Study 206), and the phase II part of the foreign phase I/II study (Study 101) showed that in patients with normal hepatic function[45)] (98 patients) and patients with mild hepatic impairment (15 patients), the incidence of serious adverse events was 26.5% and 40.0%, respectively, Grade ≥3 adverse events 36.7% and 66.7%, respectively, adverse events leading to discontinuation of tazemetostat 8.2% and 6.7%, respectively, and adverse events leading to dose reduction of tazemetostat 11.2% and 6.7%, respectively. These results showed no clear difference between patients with normal hepatic function and patients with mild hepatic impairment.
- Of 681 patients subjected to the PPK analysis, 166 patients had mild hepatic impairment. AST and bilirubin were found to be significant covariates of CL/F of tazemetostat. However, these covariates had only a minimal effect on the PK parameters of tazemetostat, suggesting that they are unlikely to have a clinically significant effect on the PK of tazemetostat [see Section 6.2.6].

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44) The mean AUC per day obtained by AUC from the start of administration until the occurrence of Grade ≥3 adverse events (patients with Grade ≥3 adverse events) or AUC throughout the treatment period (patients without Grade ≥3 adverse events) by the number of days of tazemetostat administration.

45) Classified according to National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria.

At the same time, tazemetostat should be used with caution in patients with moderate or severe hepatic impairment for the following reasons: (a) There is no experience of treatment with tazemetostat in patients with moderate or severe hepatic impairment, and (b) in the PPK analysis, albumin was found to be a significant covariate for CL/F of tazemetostat, and exposure to tazemetostat tended to increase in patients with a decreased albumin level.[46)] This information will be provided in the package insert to raise caution.

The applicant plans to conduct a clinical study to investigate the PK of tazemetostat in patients with moderate or severe hepatic impairment.

PMDA's view:
PMDA accepted the applicant's explanation. The results of the above clinical study investigating the PK of tazemetostat in patients with moderate or severe hepatic impairment should be provided appropriately to healthcare professionals as soon as available.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data in the form of results from a total of 3 clinical studies, i.e., 1 Japanese phase I study, 1 Japanese phase II study, and 1 foreign phase I/II study as shown in Table 26. The applicant also submitted the results of 2 foreign phase I studies as reference data as shown in Table 26. In this section, the dose of tazemetostat is expressed in terms of free base.

[46)] Patients with albumin level of <2.8 g/L, who are considered to have moderate or severe hepatic impairment according to Child-Pugh classification

Table 26. Clinical studies on efficacy and safety

Data category	Region	Study ID	Phase	Patient population	Number of enrollments	Dosage regimen	Main endpoint
Evaluation	Japan	106	I	Patients with relapsed or refractory FL or DLBCL	7 (FL 4, DLBCL 3)	A single dose of tazemetostat 800 mg QD was administered orally and, after a 4- to 9-day withdrawal period, tazemetostat 800 mg BID was administered orally daily.	Safety PK
		206	II	Patients with relapsed or refractory *EZH2* gene mutation-positive FL or DLBCL	20 (FL 17, DLBCL 3)	Tazemetostat 800 mg BID was administered orally daily.	Efficacy Safety PK
	Foreign	101	I/II	Phase I part: Patients with relapsed or refractory B cell lymphoma or advanced solid tumor Phase II part: Patients with relapsed or refractory FL or DLBCL	(a) 24 (b) 14 (c) 13 (d) 13 (e) 262[*1] (f) 71	Phase I part: (a) Dose escalation cohort: Tazemetostat 100-1,600 mg BID was administered orally daily. (b) Dose expansion cohort: Tazemetostat 800 or 1,600 mg BID was administered orally daily. (c) Meal effect cohort: A single dose of tazemetostat 200 mg QD was administered orally under fasting conditions or after a meal, followed by oral tazemetostat 400 mg BID daily. (d) Drug interaction cohort: Tazemetostat 800 mg BID was administered orally in combination with midazolam daily. Phase II part (e) Cohorts 1-5: Tazemetostat 800 mg BID was administered orally daily. (f) Cohort 6: Tazemetostat 800 mg BID was administered orally in combination with prednisolone[*2] daily.	Efficacy Safety PK
Reference	Foreign	103	I	Patients with relapsed or refractory B cell lymphoma or advanced solid tumor	3	Tazemetostat 800 mg BID was administered orally daily, followed by a single intravenous dose of a minute amount of ^{14}C-tazemetostat and, on Day 16, by a single oral dose of ^{14}C-tazemetostat 800 mg.	Safety PK
		105	I	Patients with relapsed or refractory B cell lymphoma or advanced solid tumor	32	Part A: Tazemetostat 400 mg BID was administered orally in combination with fluconazole from Days 1 through 24, followed by oral tazemetostat 800 mg BID from Days 25 through 28. Part B: Tazemetostat 800 mg BID was administered orally in combination with repaglinide and omeprazole daily.	Safety PK

*1, 99 patients with FL (45 patients with *EZH2* gene mutation, 54 patients without *EZH2* gene mutation), 163 patients with DLBCL
*2, In a 28-day treatment cycle, prednisolone 40 mg/m^2 was administered orally QD on Days 1 through 5 and on Day 15s through 19 in Cycles 1 to 4.

The clinical studies are summarized below. Major adverse events other than death observed in each clinical study are described in Section "7.3 Adverse events, etc. observed in clinical studies," and clinical studies on PK in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical studies

7.1.1.1 Japanese phase I study (CTD 5.3.5.2.4 and 5.3.5.2.5; Study 106 [ongoing since January 2017 (data cut-off, December 2, 2019)])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory FL or DLBCL (target sample size, 6 patients) to investigate the safety and the PK of tazemetostat at 2 study sites in Japan.

A single dose of tazemetostat 800 mg was administered orally QD and, after a 4-9-day withdrawal period, tazemetostat 800 mg was administered orally BID daily until disease progression or until any criterion for treatment discontinuation was met.

A total of 7 patients enrolled in the study, all of whom received tazemetostat and were included in the safety analysis population. Of these, (6 patients except for 1[47]) were included in the analysis for dose limiting toxicity (DLT).

No DLT was observed during the DLT evaluation period of 32 to 37 days after the start of treatment.

No death occurred during the treatment with tazemetostat or within 30 days after the end of treatment.

7.1.1.2 Japanese phase II study (CTD 5.3.5.2.6, Study 206 [ongoing since April 2018 (data cut-off, December 2, 2019)])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory *EZH2* gene mutation-positive[48] FL or DLBCL[49] (target sample size, 8 patients in Cohort 1 [patients with FL], 13 patients in Cohort 2 [patients with DLBCL]) to investigate the efficacy, safety, and PK of tazemetostat at 28 study sites in Japan.

Tazemetostat 800 mg was administered orally BID daily until disease progression or any discontinuation criterion was met.

All 20 patients enrolled in the study (17 in Cohort 1, 3 in Cohort 2[50]) received tazemetostat and were included in the efficacy and safety analysis population.

Table 27 shows the results of the response rate[51] by central assessment based on Revised Response Criteria for Malignant Lymphoma (Revised RC) (*J Clin Oncol.* 2007;25:579-86)," the primary efficacy endpoint.

Table 27. Best overall response and response rate (central assessment, data cut-off December 2, 2019)

Best overall response	Number of patients	
	Cohort 1 (patients with FL) n = 17	Cohort 2 (patients with DLBCL) n = 3
CR	6 (35.3)	0
PR	7 (41.2)	3 (100)
SD	3 (17.6)	0
PD	1 (5.9)	0
Response (CR+PR)	13	3
Response rate [90% CI]* (%)	76.5 [53.9, 91.5]	100 [36.8, 100]

* Clopper-Pearson method

47) The patient with a compliance rate of ≤75% during the DLT evaluation period for reason other than toxicity
48) Patients who were found to have mutation Y646F, Y646N, Y646S, Y646H, Y646C, A682G, or A692V in *EZH2* gene by cobas EZH2 Mutation Test of Roche Molecular Systems, Inc., conducted by the central laboratory using tumor tissue samples
49) Patients who had a history of ≥1 prior chemotherapies and had no option of a standard treatment
50) When Study 206 was ongoing, the results of the interim analysis of Study 101 failed to demonstrate the efficacy of tazemetostat in patients with DLBCL. Accordingly, patient enrollment in Cohort 2 in Study 206 was discontinued.
51) Since patients in Study 206 had no standard treatment option, the threshold response rate was 10% as a clinically significant rate.

The response rate [90% CI] in patients with relapsed[52] FL by central assessment was 91.7% [66.1%, 99.6%] (11 of 12 patients) and the response rate [90% CI] in patients with refractory[53] FL[54] by central assessment was 66.7% [13.5%, 98.3%] (2 of 3patients).

No death occurred during the treatment with tazemetostat or within 30 days after the end of treatment.

7.1.2 Foreign clinical study

7.1.2.1 Foreign phase I/II study (CTD 5.3.5.2.1, 5.3.5.2.2, and 5.3.5.2.3; Study 101 [ongoing since June 2013 (data cut-off, August 9, 2019)])

An open-label, uncontrolled study was conducted to investigate the efficacy, safety, and PK of tazemetostat at 38 study sites in foreign countries. The study participants included[55] patients with relapsed or refractory B cell lymphoma or those with advanced solid tumor (target sample size in phase I part, 64 patients [38 in dose escalation and dose expansion cohort, 13 each in meal effect cohort and drug interaction cohort]) and patients with relapsed or refractory FL or DLBCL (target sample size in phase II part, 340 patients [60 each in Cohorts 1, 2, and 3; 45 each in Cohorts 4 and 5; and 70 in Cohort 6]).[56]

The dosage regimens in Phase I part were: (a) in the dose escalation cohort, oral tazemetostat 100, 200, 400, 800, or 1,600 mg was administered BID daily; (b) in the dose expansion cohort, oral tazemetostat 800 or 1,600 mg BID daily; (c) in the meal effect cohort, a single dose of oral tazemetostat 200 mg fasted or fed, followed by multiple oral tazemetostat 400 mg BID; and (d) in the drug interaction cohort, oral tazemetostat 800 mg BID daily in combination with midazolam. The dosage regimens in Phase II part were: (e) Cohorts 1 to 5, oral tazemetostat 800 mg BID daily; and (f) Cohort 6: oral tazemetostat 800 mg BID daily in combination with prednisolone.[57]

Patients in the dose escalation, meal effect, and drug interaction cohorts continued with the treatment for 28 days, and those in the dose expansion cohort, Cohorts 1 to 5 and 6 until disease progression or until any discontinuation criterion was met.

Of 397 patients enrolled in the study, 396 patients received tazemetostat and were included in the efficacy and safety analysis population. A total of 24 patients enrolled in the dose escalation cohort of the phase I part were subjected to DLT evaluation.

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52) The best overall response in the prior treatment was complete response (CR) or partial response (PR).
53) The best overall response in the prior treatment was stable disease (SD) or progressive disease (PD).
54) Two patients without data on best overall response in the prior treatment were excluded from the analysis.
55) Patients with ≥2 prior treatments were enrolled.
56) Cohort 1, patients with relapsed or refractory *EZH2* gene mutation-positive germinal-center B-cell-like (GCB)-type DLBCL; Cohort 2, patients with relapsed or refractory *EZH2* gene mutation-negative GCB-type DLBCL; Cohort 3, patients with relapsed or refractory non-GCB-type DLBCL; Cohort 4, patients with relapsed or refractory *EZH2* gene mutation-positive FL; Cohort 5, patients with relapsed or refractory *EZH2* gene mutation-negative FL; Cohort 6, patients with relapsed or refractory *EZH2* gene mutation-negative DLBCL. The central laboratory conducted the cobas EZH2 Mutation Test (Roche Molecular Systems, Inc) with tumor tissue samples. Patients with mutation Y646F, Y646N, Y646S, Y646H, Y646C, A682G, or A692V in *EZH2* gene were regarded as *EZH2* gene mutation-positive, and those without these mutations were regarded as *EZH2* gene mutation-negative.
57) In the 28-day treatment cycle, prednisolone 40 mg/m^2 was administered orally QD on Days 1 through 5 and on Days 15 through 19 in the Cycles 1 to 4.

During the DLT evaluation period of 28 days after the start of the treatment in the dose escalation cohort of the phase I part, DLT (Grade 4 thrombocytopenia) was observed in 1 of 6 patients receiving 1,600 mg BID, but no maximum tolerated dose (MTD) was reached.

Table 28 shows the results of response rate[58] by central assessment based on Revised RC (*J Clin Oncol.* 2007;25:579-86), the primary efficacy endpoint, in the efficacy analysis population of Cohorts 4 and 5 of the phase II part.

Table 28. Best overall response and response rate (central assessment, data cut-off August 9, 2019)

Best overall response	Number of patients (%)	
	Cohort 4 (*EZH2* gene mutation-positive) N = 45	Cohort 5 (*EZH2* gene mutation-negative) N = 54
CR	6 (13.3)	2 (3.7)
PR	25 (55.6)	17 (31.5)
SD	13 (28.9)	18 (33.3)
PD	1 (2.2)	12 (22.2)
Non-evaluable	0	5 (9.3)
Response (CR+PR)	31	19
Response rate [95% CI]*(%)	68.9 [53.4, 81.8]	35.2 [22.7, 49.4]

* Clopper-Pearson method

In patients with relapsed or refractory *EZH2* gene mutation-positive FL enrolled in Cohort 4, the centrally-assessed response rate [95% CI] was 83.3% [51.6%, 97.9%] (10 of 12) in patients with relapsed disease[59] and 63.6% [45.1%, 79.6%] (21 of 33) in patients with refractory disease.[60]

Death occurred in 29 of 396 patients during the treatment with tazemetostat or within 30 days after the end of treatment (phase I part, 4 patients in the dose escalation cohort [1 in the 200 mg BID group, 1 in the 400 mg BID group, 2 in the 1,600 mg BID group], 3 patients in the meal effect cohort; phase II part, 1 patient in Cohort 1, 6 patients in Cohort 2, 3 patients in Cohort 3, 1 patient in Cohort 4, and 11 patients in Cohort 6). The causes of death other than disease progression in 1 patient (Cohort 6 in the phase II part) were general physical condition decreased in 12 patients (1 each in the 200 mg and 1,600 mg BID groups in the dose escalation cohort and 2 in the meal effect cohort of the phase I part; 1 in Cohort 1, 2 in Cohort 2, and 5 in Cohort 6 of the phase II part), respiratory distress in 4 patients (1 each in the 400 mg BID group of dose escalation cohort and in the meal effect cohort in the phase I part; and 1 each in Cohort 2 and Cohort 3 of the phase II part), multiorgan failure in 2 patients (Cohort 6 of the phase II part), respiratory failure in 2 patients (1 each in Cohort 2 and Cohort 3 of the phase II part), septic shock in 1 patient (1,600 mg BID group in the dose escalation cohort of the phase I part), duodenal obstruction in 1 patient (Cohort 2 of the phase II part), mediastinal disorder in 1 patient (Cohort 2 of the phase II part), bronchopneumonia in 1 patient (Cohort 3 of the phase II part), chronic kidney disease in 1 patient (Cohort 4 of the phase II part), intestinal obstruction in 1 patient (Cohort 6 of the phase II part), death in 1 patient (Cohort 6 of the phase II part), and dyspnoea in 1 patient (Cohort 6 of the phase II part). A

58) The threshold response rate in Cohort 4, was determined as 20%, by referring to the threshold (20%) in the phase II study of idelalisib (unapproved in Japan) in patients with relapsed low malignant lymphoma (*N Eng J Med*. 2014;370:1008-18). According to a modified version of Green-Dahlberg design (*Statistics in Medicine*. 1992;11:853-62), the study was to be terminated for futility if only ≤1 of 10 patients responded in Stage 1, and if ≥2 patients responded, additional 35 patients were to be enrolled in Stage 2. In the final analysis, if ≥14 of 45 patients responded, the treatment was considered to have fulfilled the efficacy criteria. The type I error of the entire study conducted according to the above criteria was 0.0477.

59) Patients in Cohort 4 except patients with refractory disease

60) Patients without response in the prior treatment or patients who had PD within 6 months after the last dose.

causal relationship to tazemetostat could not be ruled out for intestinal obstruction and death in 1 patient each.

7.2 Reference data

7.2.1 Clinical pharmacology studies

The applicant submitted the data of the following 2 clinical pharmacological studies in patients with relapsed or refractory B cell lymphoma and patients with advanced solid tumor [see Sections 6.1 and 6.2]. In Study 105, death occurred in 4 of 32 patients (12.5%) during the treatment with tazemetostat or within 30 days after the end of the treatment. The causes of death were death caused by the primary disease in 3 patients and intestinal perforation in 1 patient. A causal relationship to tazemetostat was ruled out for all these events.

7.2.1.1 Foreign phase I study (CTD 5.3.1.1.1, Study 103 [ongoing since June 2018])

7.2.1.2 Foreign phase I study (CTD 5.3.4.4.1, Study 105 [ongoing since March 2017])

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

Recognizing that Cohort 4 of the phase II part in the foreign phase I/II study (Study 101) and Cohort 1 of the Japanese phase II study (Study 206) conducted in patients with relapsed or refractory *EZH2* gene mutation-positive FL had yielded the most important clinical study results for the efficacy and safety evaluation of tazemetostat in patients with relapsed or refractory *EZH2* gene mutation-positive FL, PMDA decided to place the main focus of the review on these studies.

7.R.2 Efficacy

As a result of the following review, PMDA concluded that the efficacy of tazemetostat had been demonstrated to a certain extent in patients with relapsed or refractory *EZH2* gene mutation-positive FL.

7.R.2.1 Efficacy endpoint and evaluation results

In Cohort 4 of the phase II part in Study 101, results of the centrally-assessed response rate based on Revised RC (*J Clin Oncol.* 2007;25:579-86), the primary endpoint, met the pre-specified efficacy criteria [see Section 7.1.2.1]. In Cohort 1 of Study 206, the lower limit of 90% CI of the centrally-assessed response rate based on Revised RC (*J Clin Oncol*. 2007;25:579-86), the primary endpoint, exceeded the pre-specified threshold response rate (10%) [see Section 7.1.1.2].

Figures 2 and 3 show the maximum rate of change in nodal/extranodal target lesion in Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206. In Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206, the secondary endpoint of the median response duration by the central assessment [95% CI] (months) was 10.9 [7.2, not estimated (NE)] and NE [11.0, NE], respectively.[61)]

[61)] The range of the response duration was 0 to 22.1 months in Cohort 4 of the phase II part in Study 101 and 0 to 13.8 months in Cohort 1 in Study 206.

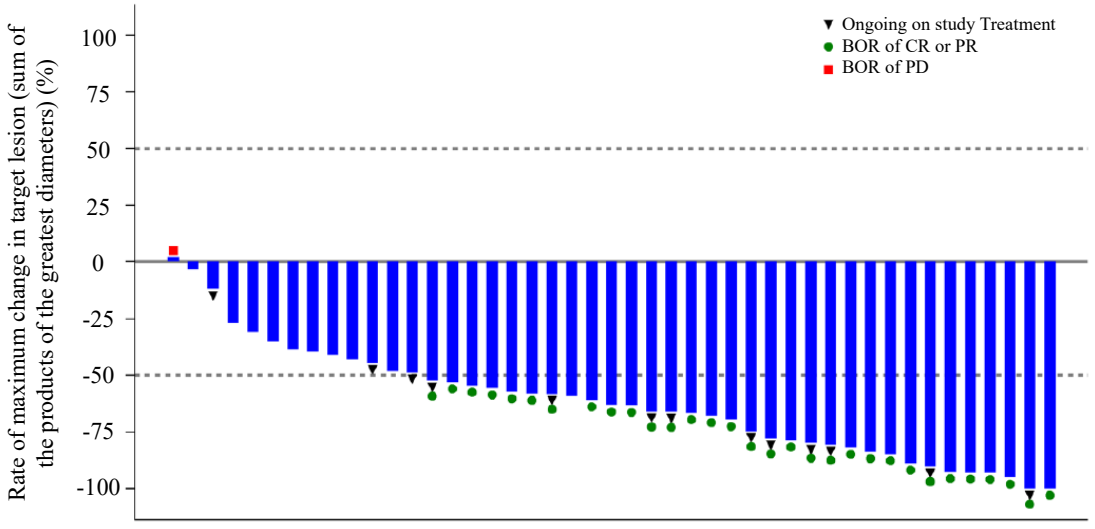

Figure 2. The rate of maximum change in nodal/extranodal target lesion (sum of the products of the greatest diameters) (Cohort 4 of the phase II part in Study 101, central assessment, efficacy analysis population)

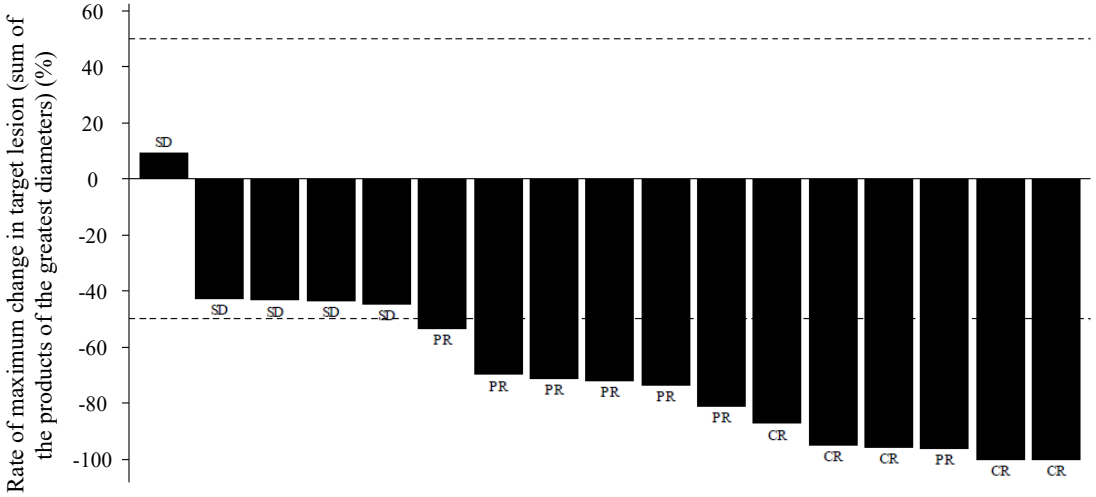

Figure 3. The rate of maximum change in nodal/extranodal target lesion (sum of the products of the greatest diameters) (Cohort 1 in Study 206, central assessment, efficacy analysis population)

The applicant's explanation about the response rate, the primary endpoint, in Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206:

There is no established standard treatment that prolongs overall survival (OS) of the patient population enrolled in Cohort 4 of the phase II part in Study 101 or in Cohort 1 in Study 206. These patients' responses indicate that the treatment will reduce tumor mass and improve clinical symptoms. Treatment with tazemetostat is thus expected to be of clinical significance.

PMDA's view:

The applicant's explanation about the efficacy endpoints is understandable. The above results demonstrated a certain level of efficacy of tazemetostat in the patient populations in Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206.

7.R.3 Safety [for adverse events, see Section "7.3 Adverse events, etc. observed in clinical studies"]

PMDA's view:

As a result of the following review, adverse events requiring particular attention in the use of tazemetostat are infection, bone marrow depression, secondary malignant tumor, and photosensitivity. These adverse events warrant attention in the use of tazemetostat.

Although the above-mentioned adverse events warrant attention in its use, tazemetostat will be well tolerable under the supervision of physicians with adequate knowledge and experience in the treatment of hematopoietic malignancy with appropriate measures, such as monitoring and controlling of adverse events, taken. Because of the extremely limited experience in the treatment of Japanese patients with tazemetostat, safety data should be further collected in the post-marketing setting [see Section 7.R.6].

7.R.3.1 Safety profile of tazemetostat and safety in Japanese patients

The applicant's explanation about the safety profile of tazemetostat in patients with relapsed or refractory, *EZH2* gene mutation-positive FL investigated in Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206:

Table 29 is the summary of safety in Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206.

Table 29. Summary of safety (Cohort 4 of the phase II part in Study 101 and Cohort 1 in Study 206)

	Number of patients (%)	
	Cohort 4 of phase II part in Study 101 n = 45	Cohort 1 in Study 206 n = 17
All adverse events	44 (97.8)	17 (100)
Events for which a causal relationship to tazemetostat could not be ruled out	38 (84.4)	17 (100)
Grade ≥3 adverse events	20 (44.4)	8 (47.1)
Adverse events resulting in death	1 (2.2)	0
Serious adverse events	11 (24.4)	6 (35.3)
Adverse events leading to discontinuation of tazemetostat	3 (6.7)	3 (17.6)
Adverse events leading to interruption of tazemetostat	11 (24.4)	9 (52.9)
Adverse events leading to dose reduction of tazemetostat	4 (8.9)	3 (17.6)

Table 30 shows adverse events with an incidence of ≥15% either in Cohort 4 of the phase II part in Study 101 or in Cohort 1 in Study 206.

Table 30. Adverse events with an incidence of ≥15% in either study (Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206)

SOC PT*	Number of patients (%)			
	Cohort 4 of phase II part in Study 101 n = 45		Cohort 1 in Study 206 n = 17	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	44 (97.8)	20 (44.4)	17 (100)	8 (47.1)
Blood and lymphatic system disorders				
Lymphopenia	0	0	5 (29.4)	2 (11.8)
Neutropenia	3 (6.7)	1 (2.2)	3 (17.6)	1 (5.9)
Thrombocytopenia	4 (8.9)	2 (4.4)	3 (17.6)	0
Gastrointestinal disorders				
Constipation	4 (8.9)	0	4 (23.5)	0
Diarrhoea	8 (17.8)	0	0	0
Nausea	9 (20.0)	0	3 (17.6)	0
Abdominal pain	7 (15.6)	0	1 (5.9)	0
Stomatitis	0	0	3 (17.6)	0
General disorders and administration site conditions				
Fatigue	8 (17.8)	1 (2.2)	1 (5.9)	0
Asthenia	7 (15.6)	1 (2.2)	0	0
Infections and infestations				
Nasopharyngitis	0	0	6 (35.3)	0
Upper respiratory tract infection	8 (17.8)	0	4 (23.5)	0
Investigations				
Blood CK increased	2 (4.4)	0	5 (29.4)	0
Weight decreased	1 (2.2)	0	3 (17.6)	0
Nervous system disorders				
Dysgeusia	6 (13.3)	0	9 (52.9)	0
Skin and subcutaneous tissue disorders				
Alopecia	10 (22.2)	0	2 (11.8)	0
Rash	4 (8.9)	0	3 (17.6)	0

* Medical Dictionary for Regulatory Activities (MedDRA) ver.18.1 in Study 101 and MedDRA ver.22.0 in Study 206.

In Cohort 4 of the phase II part in Study 101, serious adverse events observed were empyema, herpes zoster, *Pneumocystis jirovecii* pneumonia, sepsis, osmotic demyelination syndrome, post herpetic neuralgia, syncope, transient global amnesia, acute myeloid leukemia (AML), malignant melanoma, hypoxia, pleural effusion, chronic kidney disease, femoral artery occlusion, and subclavian vein thrombosis in 1 patient (2.2%) each. A causal relationship to tazemetostat could not be ruled out for transient global amnesia in 1 patient. Adverse events leading to discontinuation of tazemetostat were oral fungal infection, oral herpes, weight decreased, AML, and chronic kidney disease in 1 patient (2.2%) each. Adverse events leading to interruption of tazemetostat in ≥2 patients were thrombocytopenia and diarrhoea in 2 patients (4.4%) each, and the adverse event leading to dose reduction of tazemetostat in ≥2 patients was alopecia in 3 patients (6.7%).

In Cohort 1 in Study 206, serious adverse events observed were mechanical ileus, atypical pneumonia, *Pneumocystis jirovecii* pneumonia, pneumonia, traumatic intracranial haemorrhage, non-small cell lung cancer, pneumonia aspiration, and upper respiratory tract inflammation in 1 patient (5.9%) each. A causal relationship to tazemetostat could not be ruled out for atypical pneumonia, *Pneumocystis jirovecii* pneumonia, pneumonia, and upper respiratory tract inflammation in 1 patient each. Adverse events leading to discontinuation of tazemetostat were atypical pneumonia, traumatic intracranial haemorrhage, non-small cell lung cancer, and muscle spasticity in 1 patient (5.9%) each. Adverse events leading to interruption of tazemetostat in ≥2 patients were influenza and dysgeusia in 2 patients (11.8%) each. There were no adverse events leading to dose reduction of tazemetostat in ≥2 patients.

The applicant's explanation about the difference in the safety of tazemetostat between Japanese and non-Japanese patients:
Adverse events with a ≥10% higher incidence in Cohort 1 in Study 206 than in Cohort 4 of the phase II part in Study 101 were dysgeusia (9 Japanese patients [52.9%], 5 non-Japanese patients [11.1%]), nasopharyngitis (6 patients [35.3%], 4 patients [8.9%]), blood creatine phosphokinase (CK) increased (5 patients [29.4%], 2 patients [4.4%]), lymphopenia (5 patients [29.4%], 0), constipation (4 patients [23.5%], 4 patients [8.9%]), weight decreased (3 patients [17.6%], 1 patients [2.2%]), neutropenia (3 patients [17.6%], 3 patients [6.7%]), stomatitis (3 patients [17.6%], 0 patients), herpes simplex (2 patients [11.8%], 0), pneumonia (2 patients [11.8%], 0), ALT increased (2 patients [11.8%], 0), AST increased (2 patients [11.8%], 0), and eczema (2 patients [11.8%], 0). The Grade ≥3 adverse event reported in ≥2 Japanese patients with a higher incidence in Japanese patients than in non-Japanese patients was lymphopenia (2 patients [11.8%], 0). Adverse events leading to treatment interruption in ≥2 Japanese patients with a higher incidence in Japanese patients than in non-Japanese patients were ~~i~~nfluenza (2 patients [11.8%], 0) and dysgeusia (2 patients [11.8%], 0). There were no adverse events resulting in death, serious adverse events, adverse events leading to discontinuation of tazemetostat, or adverse events leading to dose reduction of tazemetostat in ≥2 Japanese patients with a higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:
Extra caution is warranted against serious adverse events and Grade ≥3 adverse events observed in Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206. The occurrence of these events should be appropriately communicated to healthcare professionals via the package insert, etc.

Because of the limited number of patients investigated in the clinical studies, it is difficult to draw a definite conclusion on the difference in the safety of tazemetostat between Japanese and non-Japanese patients. Nevertheless, adverse events occurring at a higher incidence in Japanese patients than in non-Japanese patients require close attention. The occurrence of these adverse events should be appropriately communicated to healthcare professionals. Also, relevant data should be further collected in the post-marketing setting and new findings should be appropriately provided to healthcare professionals as soon as available.

The following subsections summarize discussions focusing on infection and bone marrow depression, which are serious adverse events for which a causal relationship to tazemetostat could not be ruled out, and secondary malignant tumor and photosensitivity, which are considered related to toxicity findings (carcinogenicity and phototoxicity) of safety concerns in clinical use, based on the safety results mainly in Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206. Because of the extremely limited number of patients with relapsed or refractory *EZH2* gene mutation-positive FL treated with tazemetostat, the occurrence of relevant Grade ≥3 adverse events, deaths, and serious adverse events were also investigated in patients with relapsed or refractory *EZH2* gene mutation-negative FL in Cohort 5 in the phase II part of Study 101, patients with relapsed or refractory DLBCL in Cohorts 1 to 3 and 6 in the phase II part of Study 101, and those with relapsed or refractory *EZH2* gene mutation-positive DLBCL in Cohort 2 of Study 206.

7.R.3.2 Infection

The applicant's explanation about the incidence of infection associated with tazemetostat:
Adverse events related to infection were tabulated by preferred terms (PTs) falling under the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) of "Infections and infestations."

Table 31 shows the incidences of infections in Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206.

Table 31. Incidences of infections occurring in ≥2 patients at an incidence of ≥5% in either study (Cohort 4 of the phase II part in Study 101 and Cohort 1 in Study 206)

MedDRA PT*	Number of patients (%)			
	Cohort 4 of phase II part in Study 101 n = 45		Cohort 1 in Study 206 n = 17	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infection	27 (60.0)	4 (8.9)	14 (82.4)	2 (11.8)
Upper respiratory tract infection	8 (17.8)	0	4 (23.5)	0
Bronchitis	6 (13.3)	0	1 (5.9)	0
Nasopharyngitis	4 (8.9)	1 (2.2)	0	0
Urinary tract infection	4 (8.9)	1 (2.2)	1 (5.9)	0
Respiratory tract infection	3 (6.7)	0	0	0
Sinusitis	3 (6.7)	0	0	0
Nasopharyngitis	0	0	6 (35.3)	0
Herpes simplex	0	0	2 (11.8)	0
Influenza	1 (2.2)	0	2 (11.8)	0
Pneumonia	0	0	2 (11.8)	1 (5.9)

* MedDRA ver.18.1 in Study 101, MedDRA ver.22.0 in Study 206

In Cohort 4 of the phase II part in Study 101, serious infection was observed in 4 patients (8.9%; sepsis, empyema, herpes zoster, and *Pneumocystis jirovecii* pneumonia in 1 patient each). A causal relationship to tazemetostat was ruled out for all events. Infection leading to discontinuation of tazemetostat was observed in 1 patient (2.2%) and infection leading to interruption of tazemetostat in 1 patient (2.2%). There was no infection resulting in death or leading to dose reduction of tazemetostat.

In Cohort 1 of Study 206, there was no infection resulting in death. Serious infection was observed in 2 patients (11.8%; atypical pneumonia, *Pneumocystis jirovecii* pneumonia, and pneumonia in 1 patient each [including multiple events per patient]), but a causal relationship to tazemetostat could not be ruled out for all events. Infection leading to discontinuation of tazemetostat was observed in 1 patient (5.9%), infection leading to interruption of tazemetostat in 4 patients (23.5%), and infection leading to dose reduction of tazemetostat in 1 patient (5.9%).

In Cohorts 1, 2, 3, 5, and 6 of the phase II part in Study 101, Grade ≥3 infection was observed in 30 patients (10.4%; events observed in ≥2 patients were pneumonia in 5 patients, sepsis and bronchopneumonia in 3 patients each, urinary tract infection, lower respiratory tract infection, lung infection, and staphylococcal infection in 2 patients each). Infection led to a death in 1 patient (0.3%; bronchopneumonia), but its causal relationship to tazemetostat was ruled out. Serious infection was observed in 29 patients (10.1%; events observed in ≥2 patients were sepsis and pneumonia in 4 patients each, lung infection in 3 patients, bronchitis, bronchopneumonia, lower respiratory tract infection, and

urinary tract infection in 2 patients each). A causal relationship to tazemetostat could not be ruled out for urinary tract infection in 2 patients and bronchopneumonia and pneumonia in 1 patient each.

In Cohort 2 in Study 206, there was no Grade ≥3 infection, infection resulting in death, or serious infection.

PMDA asked the applicant to explain the progress in Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206, i.e., (a) screening and monitoring for opportunistic infection (including viral reactivation) and hepatitis B virus (HBV) infection, and (b) the occurrence of opportunistic infection and HBV infection and the progress in prophylactic administration.

The applicant's explanation:
(a) In Study 101, no screening or monitoring for HBV infection was conducted. In Study 206, patients with active HBV infection were excluded, and patients who were positive for anti-hepatitis B core antibody (anti-HBc antibody) or anti-hepatitis B surface antibody (anti-HBs antibody) and negative for hepatitis B surface antigen (HBs antigen) were enrolled if they were confirmed to be negative for HBV-deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) at the screening. No monitoring was conducted.

(b) Studies 101 and 206 did not specify particular rules for prophylactic administration against opportunistic infection or HBV infection. The occurrence of opportunistic infection and HBV infection in Cohort 4 of the phase II part in Study 101 and in Study 206 and the progress in prophylactic administration were as follows:

- Prophylactic treatment for HBV infection[62)] was not given either in Cohort 4 of the phase II part in Study 101 or in Cohort 1 in Study 206. HBV infection was not observed in either study.
- Prophylactic treatment for cytomegalovirus (CMV) infection[63)] was given to 2 of 45 patients (4.4%) in Cohort 4 of the phase II part in Study 101 and to 1 of 17 patients (5.9%) in Cohort 1 in Study 206. CMV infection was not observed in either study.
- Prophylactic treatment for tuberculosis infection[64)] was not given either in Cohort 4 of the phase II part in Study 101 or in Cohort 1 in Study 206. No tuberculosis infection was observed in either study.
- Prophylactic treatment for *Pneumocystis jirovecii* infection[65)] was given to 5 of 45 patients (11.1%) in Cohort 4 of the phase II part in Study 101 and to 8 of 17 patients (47.1%) in Cohort 1 in Study 206. *Pneumocystis jirovecii* infection was not observed in any patient who had received the prophylactic treatment in either study. Among patients without prophylaxis, 1 of 40 patients (2.5%) in Cohort 4 of the phase II part in Study 101 and 1 of 9 patients (11.1%) in Cohort 1 in Study 206 experienced *Pneumocystis jirovecii* infection.

62) MedDRA PTs of "Acute hepatitis B," "Chronic hepatitis B," "Hepatitis B," or Hepatitis B reactivated" were tabulated.
63) MedDRA PTs under the HLT of "Cytomegaloviral infections" were tabulated.
64) MedDRA PTs under the HLT of "Tuberculous infections" were tabulated.
65) MedDRA PTs under the HLT of "*Pneumocystis* infections" were tabulated.

- Prophylactic treatment for varicella zoster virus (VZV) infection[66] was given to 8 of 45 patients (17.8%) in Cohort 4 of the phase II part in Study 101 and to 2 of 17 patients (11.8%) in Cohort 1 in Study 206. VZV infection was observed in none of the patients who had received prophylaxis. Among patients without prophylaxis, 1 of 37 patients (2.7%) in Cohort 4 of the phase II part in Study 101 had VZV infection, whereas none in Cohort 1 in Study 206 had the infection.

PMDA's view:
Cohort 4 of the phase II part in study 101 and in Cohort 1 in Study 206 showed high incidences of tazemetostat-associated infection, and multiple patients in Cohort 1 in Study 206 experienced serious infection (including opportunistic infection) for which a causal relationship to tazemetostat could not be ruled out. Therefore, caution should be exercised against infection in the use of tazemetostat. Accordingly, information on the incidence of infection, including opportunistic infection, in clinical studies should be appropriately provided to healthcare professionals via the package insert, etc. Also, the safety measures, such as prophylaxis of infection, taken in the clinical studies should be appropriately communicated to healthcare professionals, using materials, etc.

7.R.3.3 Bone marrow depression

The applicant's explanation about the incidence of bone marrow depression associated with tazemetostat:
Events associated with bone marrow depression were tabulated by PTs falling under the MedDRA standard MedDRA queries (SMQ) of "Haematopoietic cytopenias," except those falling under the MedDRA SOC of "Infections and infestations."

Table 32 shows the incidence of bone marrow depression in Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206.

Table 32. Incidences of bone marrow depression occurring in ≥2 patients at an incidence of ≥5% in either study
(Cohort 4 of the phase II part in Study 101 and in Cohort 1 in Study 206)

MedDRA PT*	Number of patients (%)			
	Cohort 4 of phase II part in Study 101 n = 45		Cohort 1 in Study 206 n = 17	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Bone marrow depression	6 (13.3)	3 (6.7)	8 (47.1)	3 (17.6)
Thrombocytopenia	4 (8.9)	2 (4.4)	3 (17.6)	0
Anaemia	3 (6.7)	2 (4.4)	2 (11.8)	0
Neutropenia	3 (6.7)	1 (2.2)	3 (17.6)	1 (5.9)
Lymphopenia	0	0	5 (29.4)	2 (11.8)

* MedDRA ver.18.1 in Study 101, MedDRA ver.22.0 in Study 206

In Cohort 4 of the phase II part in Study 101, bone marrow depression led to the interruption of tazemetostat in 2 patients (4.4%) and to the dose reduction of tazemetostat in 1 patient (2.2%). There

[66] Tabulated MedDRA PTs were "Varicella post vaccine," "Bleeding varicella syndrome," "Herpes zoster," "Herpes zoster pharyngitis," "Herpes zoster necrotising retinopathy," "Herpes zoster meningitis," "Herpes zoster meningoradiculitis," "Herpes zoster meningomyelitis," "Herpes zoster meningoencephalitis," "Disseminated herpes zoster," "Disseminated herpes zoster virus vaccine infection," "Varicella," "Varicella zoster virus infection," "Varicella zoster pneumonia," "Varicella zoster gastritis," "Varicella zoster oesophagitis," "Varicella keratitis," "Disseminated skin herpes zoster," "Herpes zoster ophthalmic," "Herpes zoster infection neurological," and "Genital herpes zoster."

was no bone marrow depression resulting in death, serious bone marrow depression, or bone marrow depression leading to discontinuation of tazemetostat.

In Cohort 1 in Study 206, bone marrow depression led to the interruption of tazemetostat in 1 patient (5.9%) and to the dose reduction of tazemetostat in 1 patient (5.9%). There was no bone marrow depression resulting in death, serious bone marrow depression, or bone marrow depression leading to discontinuation of tazemetostat.

In Cohorts 1, 2, 3, 5, and 6 of the phase II part in Study 101, serious bone marrow depression was observed in 39 patients (13.5%, neutropenia in 19, thrombocytopenia in 16, anaemia in 8, febrile neutropenia in 4, lymphopenia in 2, and pancytopenia in 1 [including multiple events per patient]). A causal relationship to tazemetostat could not be ruled out for neutropenia in 15 patients, thrombocytopenia in 8 patients, anaemia in 4 patients, febrile neutropenia in 2 patients, and pancytopenia in 1 patient. There was no bone marrow depression resulting in death.

In Cohort 2 in Study 206, there was no Grade ≥3 bone marrow depression, bone marrow depression resulting in death, or serious bone marrow depression.

PMDA's view:
Caution should be exercised against bone marrow depression, given the high incidence of bone marrow depression in Cohort 1 in Study 206, and multiple patients in the phase II part of Study 101 experienced serious bone marrow depression for which a causal relationship to tazemetostat could not be ruled out. Accordingly, the occurrence of bone marrow depression in the clinical studies should be communicated to healthcare professionals in an appropriate manner. Also, healthcare professionals should be advised appropriately via the package insert, etc. to perform hematological tests periodically during the treatment with tazemetostat and to take appropriate measures such as the interruption or dose reduction of tazemetostat in case of any abnormality.

7.R.3.4 Secondary malignant tumor

The applicant's explanation about the incidence of secondary malignant tumor associated with tazemetostat:
Adverse events associated with secondary malignant tumor were tabulated by MedDRA PT falling under the MedDRA SOC of "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" except for "Benign neoplasm of retina," "Relapsed DLBCL," "Fibroma," "Metastases to lung," "Seborrhoeic keratosis," "Skin papilloma," "Tumour pain," "Pericardial effusion malignant," "Tumour haemorrhage," "Malignant neoplasm progression," "Tumour associated fever," "Cancer pain," or "Oncologic complication."

Table 33 shows the details of patients who had secondary malignant tumor after tazemetostat administration in the clinical studies submitted for the present application.

Table 33. Secondary malignant tumor observed in clinical studies submitted for the present application

Study	Age	Sex	Disease type of NHL	Event	Time to onset of the event*	Grade	Severity	Causal relationship	Outcome
Phase II part in Study 101	6[redacted]	M	FL	AML	786	4	Serious	Not related	Not resolved
	6[redacted]	F	FL	Malignant melanoma	353	4	Serious	Not related	Resolved
				Malignant melanoma	401	4	Serious	Not related	Resolved
	6[redacted]	F	FL	Thyroid neoplasm	85	1	Non-serious	Not related	Not resolved
	6[redacted]	M	FL	MDS	465	3	Serious	Related	Not resolved
	6[redacted]	M	FL	Basal cell carcinoma	29	2	Non-serious	Not related	Resolved
	6[redacted]	M	FL	Myelofibrosis	665	1	Non-serious	Not related	Not resolved
	8[redacted]	M	FL	Squamous cell carcinoma	680	3	Non-serious	Not related	Not resolved
	7[redacted]	F	DLBCL	Basal cell carcinoma	308	1	Non-serious	Not related	Not resolved
	8[redacted]	F	DLBCL	Basal cell carcinoma	161	1	Non-serious	Not related	Resolved
	7[redacted]	F	DLBCL	Basal cell carcinoma	72	1	Non-serious	Not related	Resolved
	7[redacted]	F	DLBCL	Basal cell carcinoma	98	1	Non-serious	Not related	Not resolved
	8[redacted]	M	DLBCL	Squamous cell carcinoma of skin	455	1	Non-serious	Not related	Resolved
Study 106	7[redacted]	F	FL	Squamous cell carcinoma of the tongue	204	3	Serious	Not related	Resolved
Cohort 1 in Study 206	6[redacted]	M	FL	Non-small cell lung cancer	308	2	Serious	Not related	Not resolved

* The day of starting tazemetostat administration was taken as Day 1.

Other unlisted clinical studies[67] reported secondary malignant tumor observed in 8 patients (squamous cell carcinoma of skin and second primary malignancy in 2 each,[68] malignant melanoma, AML, MDS, and squamous cell carcinoma in 1 each). A causal relationship to tazemetostat could not be ruled out for second primary malignancy in 2 patients and MDS in 1 patient.

PMDA's view:

In light of the limited number of cases with secondary malignant tumor and no consistent trend in its type or onset timing, currently available data preclude a definite conclusion on a relationship between tazemetostat and secondary malignant tumor. However, serious secondary malignant tumor for which a causal relationship to tazemetostat could not be ruled out was observed in the clinical studies, and results of nonclinical studies suggest that tazemetostat is carcinogenic [see Section 5.R.1], warranting caution against secondary malignant tumor in the use of tazemetostat. Accordingly, the occurrence of secondary malignant tumor in the clinical studies should be communicated via the package insert, etc. Such information should be further collected in the post-marketing setting.

7.R.3.5 Photosensitivity

The applicant's explanation about the occurrence of photosensitivity associated with tazemetostat:

Adverse events associated with photosensitivity falling under the MedDRA PT of "Photosensitivity reaction" were tabulated.

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67) Study EZH-102 (Study 102) in patients with synovial sarcoma, etc., Study 202 in patients with epithelioid sarcoma, etc., Study 203 in patients with mesothelioma malignant, and Study EZH-501 which was an extension study of other studies

68) One patient was a [redacted]-year old black girl with poorly differentiated chordoma. On Day 420, unilateral facial puffiness occurred. On Day 425, the patient visited the emergency room for mild cough that worsened at night, unilateral facial puffiness persisting for 2 weeks, nasal congestion, chest pain after coughing, abdominal pain, and shortness of breath. Abnormalities such as mediastinal lymphadenopathy was found. T-LBL was confirmed based on the bone-marrow examination on Day 430 and on lymph node biopsy on Day 431. Tazemetostat administration was completed on Day 425 and, from Day 432, treatment for T-LBL was started. Another patient was a 7[redacted]-year-old Caucasian man with DLBCL. On Day 834, Grade 1 anemia, Grade 2 leukopenia, and Grade 3 thrombocytopenia occurred. On Day 836, tazemetostat administration was discontinued because of thrombocytopenia. On Day 843, the patient was diagnosed as having low-risk MDS with chromosomal abnormalities consisting of 5q deletion and 17p rearrangement. On Day 988, MDS progressed to AML and, the patient died of AML on Day 1,041, despite treatment given.

In clinical studies submitted in the present application, photosensitivity (Grade 1, nonserious) was observed in 1 patient in Cohort 4 of the phase II part in Study 101, for which causal relationship to tazemetostat could not be ruled out. In response to the phototoxicity of tazemetostat suggested by a non-clinical study [see Section 5.6.2], clinical study protocols stipulated that participants in the clinical studies of tazemetostat should avoid long-term exposure to sunlight, requiring preventive measures against exposure to ultraviolet light (e.g., sunscreen, sunglasses).

PMDA's view:
The extremely limited number of cases with photosensitivity in the clinical studies of tazemetostat precludes a definite conclusion on a relationship between tazemetostat and development of photosensitivity. However, phototoxicity of tazemetostat was suggested in an *in vitro* phototoxicity testing using a mouse fibroblast strain [see Section 5.6.2], and the clinical studies were conducted with preventive measures taken against exposure to ultraviolet light as recommended. Accordingly, the occurrence of photosensitivity in the clinical studies should be communicated to healthcare professionals via the package insert, and information about the occurrence of photosensitivity should be further collected in the post-market setting.

7.R.4 Clinical positioning and indication

The proposed indication for tazemetostat was "relapsed or refractory *EZH2* gene mutation-positive follicular lymphoma (excluding treatment-naïve patients)." The "Precautions Concerning Indication" section was proposed as follows:

- Tazemetostat should be administered to patients who have been confirmed to have *EZH2* gene mutation by a highly experienced pathologist or at a laboratory facility, using an approved *in vitro* diagnostics.
- The efficacy and safety of tazemetostat have not been established in the first-line therapy of patients with relapsed or refractory FL.
- Physicians should have a full understanding of the efficacy and safety of tazemetostat with adequate knowledge from the "Clinical Studies" section. Before deciding the use of tazemetostat, other treatment options should also be considered carefully for each patient.

As a result of discussions in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following subsections, PMDA concluded that the indication be "relapsed or refractory *EZH2* gene mutation-positive follicular lymphoma (limited to those refractory to standard treatments)," the descriptions in "Precautions Concerning Indication" section be modified as follows.

- Tazemetostat should be administered to patients who have been confirmed to have *EZH2* gene mutation by a highly experienced pathologist or at a laboratory facility, using an approved *in vitro* diagnostics or medical device.
- Treatment with tazemetostat should be performed in patients who are non-responsive to at least 2 standard treatments or who have had a relapse after treatment.
- Physicians should have a full understanding of the efficacy and safety of tazemetostat with adequate knowledge from the "Clinical Studies" section. Before deciding the use of tazemetostat, other treatment options should also be considered carefully for each patient.

7.R.4.1 Clinical positioning and indication of tazemetostat

Japanese and foreign clinical practice guidelines and leading hematology textbooks describe tazemetostat in the treatment of relapsed or refractory FL as follows:

Clinical practice guidelines

- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-cell Lymphomas (NCCN Guideline) (v.4.2020): Tazemetostat is recommended as a treatment option for the following patients (Category 2A[69]); (a) patients with relapsed or refractory *EZH2* gene-mutation positive FL with ≥2 prior treatment regimens, and (b) patients with relapsed or refractory *EZH2* gene-mutation negative FL without any other suitable treatment option

The applicant's explanation about the clinical positioning of tazemetostat:
Relapsed or refractory *EZH2* FL with ≥2 prior treatment regimens is rare, and there is no established standard treatment method for the disease, with only limited treatment options available (Practical Guidelines for Hematological Malignancies, 2018 revised version [edited by Japan Society of Hematology]). In this situation, the clinical benefits of tazemetostat was demonstrated in Cohort 4 of the phase II part in Study 101 in patients with relapsed or refractory *EZH2* gene mutation-positive FL with ≥2 prior treatment regimens [see Sections 7.R.2 and 7.R.3]. Also, tazemetostat was shown to be clinically useful in Cohort 1 in Study 206 in patients with relapsed or refractory *EZH2* gene mutation-positive FL with ≥1 prior treatment regimen and have no standard treatment option available [see Sections 7.R.2 and 7.R.3]. In addition, the results in the subpopulation with ≥2 prior treatment regimens were similar to those in the entire population.[70] These suggest that tazemetostat can potentially be recognized as one of the treatment options for patients with relapsed or refractory *EZH2* gene mutation-positive FL with ≥2 prior treatment regimens.

In Japan, other antineoplastic agents indicated for relapsed or refractory FL include (a) lenalidomide hydrate (lenalidomide) used in combination with rituximab and (b) obinutuzumab used in combination with bendamustine hydrate (bendamustine). Both drugs achieved a statistically significant prolongation of PFS as compared to the control in confirmatory studies, the former in patients with relapsed or refractory FL with ≥1 prior treatment and the latter in patients with relapsed or refractory rituximab-resistant FL with ≥1 prior treatment (*J Clin Oncol.* 2019;37:1188-99, etc.). Therefore, these treatments will be prioritized over tazemetostat. Besides these antineoplastic agents administered to patients with relapsed or refractory FL who have ≥2 prior treatment, a regimen that includes bendamustine achieved a response rate of 77.8%, and while that of the other regimen without bendamustine was 40.0% (*Ann Hematol.* 2020;99:2133-9). These results suggest that tazemetostat provides equal or greater clinical benefit than other antineoplastic agents for patients with relapsed or refractory FL who have ≥2 prior treatments. However, there are no clinical study data comparing the clinical benefit between tazemetostat and the approved antineoplastic agents. Cohort 4 of the phase II part in Study 101 and Cohort 1 in Study 206 investigated the efficacy and safety of tazemetostat in an exploratory manner. Given these facts, a decision of whether to use tazemetostat should be made after due consideration of

[69] Based on relatively low-level evidence, there is a uniform consensus of National Comprehensive Cancer Network (NCCN) that the intervention is appropriate.
[70] In the subpopulation with ≥2 prior treatment regimens in Cohort 1 in Study 206, the response rate [90% CI] by the central assessment based on Revised RC (*J Clin Oncol*. 2007;25:579-86) was 73.3% [48.9%, 90.3%] (11 of 15).

other treatment options for each patient. The extremely limited number of patients with 1 prior treatment regimen enrolled in Study 206 indicates that the efficacy and safety of tazemetostat as the first-line treatment for patients with relapsed or refractory FL have not been established at present.

Based on the above, the indication for tazemetostat was proposed as "relapsed or refractory *EZH2* gene mutation-positive follicular lymphoma (excluding treatment-naïve patients)" with the following descriptions provided in the "Precautions Concerning Indication" section.

- The efficacy and safety of tazemetostat have not been established in the first-line therapy of patients with relapsed or refractory FL.
- Physicians should have a full understanding of the efficacy and safety of tazemetostat with adequate knowledge from the "Clinical Studies" section. Before deciding the use of tazemetostat, other treatment options should also be considered carefully for each patient.

PMDA's view:

The applicant explains that tazemetostat can be recognized as a treatment option for patients with relapsed or refractory *EZH2* gene mutation-positive FL who have ≥2 prior treatments, which is considered reasonable to a certain extent. However, in Japan, there are some antineoplastic agents that were approved based on confirmatory studies in patients with relapsed or refractory FL, and in contrast, there are no clinical study data verifying the clinical benefit of tazemetostat at present. Given this situation, the indication should clearly state that tazemetostat is intended for patients with relapsed or refractory *EZH2* gene mutation-positive FL that is incurable with a standard therapy with clinically proven efficacy.

Based on the above, the indication for tazemetostat should be "relapsed or refractory *EZH2* gene mutation-positive follicular lymphoma (limited to those refractory to standard treatments)."

Precautions Concerning Indication

- Treatment with tazemetostat should be performed in patients who are non-responsive to at least 2 standard treatments or who have had a relapse after treatment.
- Physicians should have a full understanding of the efficacy and safety of tazemetostat with adequate knowledge from the "Clinical Studies" section. Before deciding the use of tazemetostat, other treatment options should also be considered carefully for each patient.

7.R.4.2 Test on *EZH2* gene

The applicant's explanation about the test for the identification of eligible patients eligible for tazemetostat treatment:

In the phase II part in Study 101, tumor tissue samples were tested for *EZH2* gene mutation at the central laboratory using "cobas EZH2 Mutation Test," a PCR method developed by Roche Molecular Systems, Inc. In this study, tazemetostat was shown to be highly effective in *EZH2* gene mutation-positive patients as compared with negative patient [see Section 7.1.2.1]. Based on the results of the phase II part in Study 101, Study 206 enrolled only patients found to be *EZH2* gene mutation-positive identified by the "cobas EZH2 Mutation Test" at the central laboratory, and the clinical benefit of tazemetostat was demonstrated in these patients [see Sections 7.R.2 and 7.R.3]. The "cobas EZH2 Mutation Test" used in the phase II

part in Study 101 and in Cohort 1 in Study 206 has been proposed as companion diagnostics (CDx) for the complementary use in eligibility assessment for tazemetostat.

Thus, in using tazemetostat for patients with relapsed or refractory *EZH2* gene mutation-positive FL, eligible patients should be identified by "cobas EZH2 Mutation Test." Accordingly, the "Precautions Concerning Indication" section will advise that the *EZH2* gene mutation test should be performed by an adequately experienced pathologist or at a laboratory facility using approved *in vitro* diagnostics.

Currently, there are no efficacy and safety data of tazemetostat in Japanese patients with relapsed or refractory *EZH2* gene mutation-negative FL from clinical studies. Therefore, tazemetostat is not recommended for this patient population.

PMDA's view:
PMDA accepted the applicant's explanation. The description about the test on *EZH2* gene in the "Precautions Concerning Indication" section should be modified as follows to raise caution:

- Tazemetostat should be administered to patients who have been confirmed to have *EZH2* gene mutation by a highly experienced pathologist or at a laboratory facility, using an approved *in vitro* diagnostic or medical device.

7.R.5 Dosage and administration

The dosage and administration of tazemetostat was proposed as "the usual adult dosage is 800 mg of tazemetostat administered orally twice daily. The dose may be reduced according to the patient's condition." In the "Precautions Concerning Dosage and Administration" section, the criteria for dose adjustment in concomitant use with CYP3A-inhibiting drugs were once proposed but removed after submission because of the lack of clinical data on the efficacy and safety of tazemetostat based on these criteria. Instead, the following precautions were presented in the "Precautions Concerning Dosage and Administration" section.

Precautions Concerning Dosage and Administration

- The efficacy and safety of tazemetostat in combination with other antineoplastic agents have not been established.
- Criteria for dose adjustment of tazemetostat in case of adverse drug reactions

As a result of discussion in the Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the discussion in the following sections, PMDA concluded that the dosage and administration should be defined as proposed by the applicant, along with modified descriptions of the "Precautions Concerning Dosage and Administration" section as follows:

Precautions Concerning Dosage and Administration

- The efficacy and safety of tazemetostat in combination with other antineoplastic agents have not been established.
- If any adverse drug reaction of tazemetostat occurs during treatment, tazemetostat should be interrupted, continued at a reduced dose, or discontinued according to the following criteria.

Level of tazemetostat dose reduction

Level	Dose
Usual dose	800 mg twice daily
1-level lower dose	600 mg twice daily
2-level lower dose	400 mg twice daily
3-level lower dose	Discontinue

Criteria for interruption, dose reduction, and discontinuation of tazemetostat

Adverse drug reaction	Grade*	Measures to be taken
Neutropenia	Neutrophil count <750/mm^3	Interrupt tazemetostat until neutrophil count recovers to ≥750/mm^3. After recovery, tazemetostat may be resumed at a 1-level lower dose.
Other adverse drug reactions	Either of the following (except clinically insignificant laboratory abnormalities) • Intolerable Grade 2 • Grade 3	Interrupt tazemetostat until the symptom recovers to Grade ≤1 or baseline (In case of nausea, vomiting, or diarrhea, take appropriate measures. Interrupt tazemetostat if the symptom cannot be controlled). After recovery, tazemetostat may be resumed at a 1-level lower dose.
	Grade 4 (non-life-threatening laboratory abnormalities are handled as Grade 3)	Discontinue tazemetostat.

* Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

7.R.5.1 Dosage and administration of tazemetostat

The applicant's explanation about the dosage regimen of tazemetostat:

In Cohort 4 of the phase II Part in Study 101 and in Cohort 1 in Study 206, oral tazemetostat 800 mg was administered BID daily, taking account of the following:

- Tazemetostat was tolerated up to 1,600 mg BID in the phase I part of Study 101.
- In the phase I part of Study 101, tazemetostat 800 mg administered BID achieved blood tazemetostat concentration which is expected to inhibit EZH2, and the response rate suggested the efficacy of tazemetostat.

Results of studies in Cohort 4 of the phase II part in Study 101 and Cohort 1 of Study 206 demonstrated the clinical benefit of tazemetostat [see Sections 7.R.2 and 7.R.3]. Accordingly, the proposed dosage and administration for tazemetostat was determined based on the dosage regimen used in these studies.

PMDA accepted the applicant's explanation.

7.R.5.2 Dose adjustment of tazemetostat

The applicant's explanation about dose adjustment of tazemetostat in case of any adverse drug reaction:

In Cohort 4 of the phase II part in Study 101 and in Cohort 1 of Study 206, the criteria were set for interruption, dose reduction, and discontinuation of tazemetostat following the onset of any adverse event. The clinical benefit of tazemetostat was demonstrated in patients who had adhered to the criteria.

Thus, the "Precautions Concerning Dosage and Administration" section provides the dose adjustment criteria of tazemetostat according to the criteria employed in Cohort 1 of Study 206 in Japanese patients.

PMDA's view:
PMDA accepted the applicant's explanation. The dose adjustment criteria of tazemetostat following an adverse drug reaction should be presented as follows:

Precautions Concerning Dosage and Administration

- If any adverse drug reaction of tazemetostat occurs during treatment, tazemetostat should be interrupted, continued at a reduced dose, or discontinued according to the following criteria.

Level of tazemetostat dose reduction

Level	Dose
Usual dose	800 mg twice daily
1-level lower dose	600 mg twice daily
2-level lower dose	400 mg twice daily
3-level lower dose	Discontinue

Criteria for interruption, dose reduction, and discontinuation of tazemetostat

Adverse drug reaction	Grade*	Measures to be taken
Neutropenia	Neutrophil count <750/mm^3	Interrupt tazemetostat until neutrophil count recovers to ≥750/mm^3. After recovery, tazemetostat may be resumed at a 1-level lower dose.
Other adverse drug reactions	Either of the following (except clinically insignificant laboratory abnormalities) • Intolerable Grade 2 • Grade 3	Interrupt tazemetostat until the symptom recovers to Grade ≤1 or baseline (In case of nausea, vomiting, or diarrhea, take appropriate measures. Interrupt tazemetostat if the symptom cannot be controlled). After recovery, tazemetostat may be resumed at a 1-level lower dose.
	Grade 4 (non-life-threatening laboratory abnormalities are handled as Grade 3)	Discontinue tazemetostat.

* Graded defined according to NCI-CTCAE v4.03.

7.R.5.3 Concomitant use with other antineoplastic agents

The applicant's explanation:
There are no clinical data on the efficacy and safety of tazemetostat used in combination with other antineoplastic agents in patients with relapsed or refractory *EZH2* gene mutation-positive FL. This will be stated in the "Precautions Concerning Dosage and Administration" section to raise caution.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation about their post-marketing investigation plan:
In order to investigate the safety, etc. of tazemetostat in clinical use after the market launch, the applicant plans to conduct a post-marketing surveillance involving all patients treated with tazemetostat.

The safety specification for the surveillance will include thrombocytopenia, neutropenia, anemia, lymphopenia, and infection, taking account of the occurrence of these adverse events in the phase II part of Study 101, Study 106, and Study 206.

The planned sample size is 145 patients, based on the incidence of the events specified in the safety specification in the phase II part of Study 101.

The follow-up period is 52 weeks, based on time-to-onset of the events specified in the safety specification in the phase II part of study 101, Study 106, and Study 206.

PMDA's view:
Because of extremely limited information about the safety of tazemetostat in Japanese patients treated, the surveillance should cover all patients receiving tazemetostat and be implemented for a certain post-marketing period to collect safety data in a prompt and unbiased manner. Obtained safety information should be provided to healthcare professionals without delay.

The safety specification in the surveillance, based on the review in Section "7.R.3 Safety," should include infection, bone marrow depression, secondary malignant tumor, and photosensitivity.

The planned sample size and the follow-up period should be reconsidered based on the occurrence of the events specified in the surveillance safety specification in the clinical studies.

7.3 Adverse events, etc. observed in clinical studies

Deaths reported in the safety evaluation data are described in Sections "7.1 Evaluation data" and "7.2 Reference data." The following subsections summarize major adverse events other than death.

7.3.1 Japanese phase I study (Study 106)

Adverse events occurred in 7 of 7 patients (100%). Adverse events for which a causal relationship to tazemetostat could not be ruled out occurred in 6 of 7 patients (85.7%). Adverse events with an incidence of ≥20% were nasopharyngitis in 5 patients (71.4%), thrombocytopenia, constipation, dysgeusia, and muscle spasms in 3 patients (42.9%) each, anaemia, leukopenia, neutropenia, dry eye, stomatitis, fatigue, influenza, blood creatinine increased, insomnia, dry skin, and rash in 2 patients (28.6%) each.

Serious adverse events occurred in 2 of 7 patients (28.6%). The events observed were intestinal perforation and squamous cell carcinoma of the tongue in 1 patient (14.3%) each, and their causal relationship to tazemetostat was ruled out.

An adverse event, squamous cell carcinoma of the tongue, led to the discontinuation of tazemetostat in 1 of 7 patients (14.3%) and, its causal relationship to tazemetostat was ruled out.

7.3.2 Japanese phase II study (Study 206)

Adverse events occurred in 17 of 17 patients (100%) in Cohort 1 (patients with FL) and in 3 of 3 patients (100%) in Cohort 2 (patients with DLBCL). Adverse events for which a causal relationship to tazemetostat could not be ruled out occurred in 17 of 17 patients (100%) in Cohort 1 (patients with FL) and in 3 of 3 patients (100%) in Cohort 2 (patients with DLBCL). Adverse events with an incidence of ≥20% were dysgeusia in 9 patients (52.9%), nasopharyngitis in 6 patients (35.3%), lymphopenia and blood CK increased in 5 patients (29.4%) each, constipation and upper respiratory tract infection in 4 patients (23.5%) each in Cohort 1 (patients with FL); and fatigue, nasopharyngitis, electrocardiogram

QT prolonged, dysgeusia, alopecia, supraventricular tachycardia, non-cardiac chest pain, arthralgia, back pain, and dizziness in 1 patient (33.3%) each in Cohort 2 (patients with DLBCL).

Serious adverse events occurred in 6 of 17 patients (35.3%) in Cohort 1 (patients with FL), but not in Cohort 2 (patients with DLBCL). Serious adverse events observed were mechanical ileus, atypical pneumonia, *Pneumocystis jirovecii* pneumonia, pneumonia, traumatic intracranial haemorrhage, non-small cell lung cancer, pneumonia aspiration, and upper respiratory tract inflammation in 1 patient (5.9%) each. A causal relationship to tazemetostat could not be ruled out for atypical pneumonia, *Pneumocystis jirovecii* pneumonia, pneumonia, and upper respiratory tract inflammation in 1 patient each.

Adverse events led to the discontinuation of tazemetostat in 3 of 17 patients (17.6%) in Cohort 1 (patients with FL) and in 1 of 3 patients (33.3%) in Cohort 2 (patients with DLBCL). The events observed were atypical pneumonia, traumatic intracranial haemorrhage, non-small cell lung cancer, and muscle spasticity in 1 patient (5.9%) each in Cohort 1 (patients with FL) and dysgeusia in 1 patient (33.3%) in Cohort 2 (patients with DLBCL). A causal relationship to tazemetostat could not be ruled out for atypical pneumonia and muscle spasticity in 1 patient each in Cohort 1 (patients with FL) and for dysgeusia in 1 patient in Cohort 2 (patients with DLBCL).

7.3.3 Foreign phase I/II study (Study 101)

7.3.3.1 Phase I part

7.3.3.1.1 Dose escalation cohort

Adverse events occurred in 6 of 6 patients (100%) in the tazemetostat 100 mg group, 3 of 3 patients (100%) in the tazemetostat 200 mg group, 3 of 3 patients (100%) in the tazemetostat 400 mg group, 6 of 6 patients (100%) in the tazemetostat 800 mg group, and 6 of 6 patients (100%) in the tazemetostat 1,600 mg group. Adverse events for which a causal relationship to tazemetostat could not be ruled out occurred in 6 of 6 patients (100%) in the 100 mg group, 2 of 3 patients in (66.7%) in the 200 mg group, 6 of 6 patients (100%) in the 800 mg group, and 6 of 6 patients (100%) in the 1,600 mg group (none in the tazemetostat 400 mg group). Adverse events with an incidence of ≥20% were asthenia in 4 patients (66.7%), diarrhoea and muscle spasms in 2 patients (33.3%) each in the 100 mg group; vomiting, asthenia, general physical health deterioration, catheter site infection, herpes zoster, thermal burn, wound secretion, decreased appetite, hypertriglyceridaemia, headache, dysuria, pollakiuria, pelvic pain, and hair growth abnormal in 1 patient (33.3%) each in the 200 mg group; anaemia, asthenia, oedema peripheral, blood creatinine increased, blood urea increased, decreased appetite, musculoskeletal chest pain, tumour pain, dyspnoea, pulmonary embolism, and respiratory distress in 1 patient (33.3%) each in the 400 mg group; asthenia in 6 patients (100%), muscle spasms in 3 patients (50.0%), anaemia, thrombocytopenia, lacrimation increased, influenza, bronchitis, cough, dyspnoea exertional, hypertension, dry skin in 2 patients (33.3%) each in the 800 mg group; and nausea, asthenia, pyrexia, and dysgeusia in 3 patients (50.0%) each, anaemia, thrombocytopenia, dry mouth, sepsis, muscle spasms, depression, cough, and dyspnoea exertional in 2 patients (33.3%) each in the 1,600 mg group.

Serious adverse events occurred in 1 of 6 patients (16.7%) in the 100 mg group, 1 of 3 patients (33.3%) in the 200 mg group, 2 of 3 patients (66.7%) in the 400 mg group, and 2 of 6 patients (33.3%) in the

1,600 mg group (none in the 800 mg group). The events observed were pulmonary embolism in 1 patient (16.7%) in the 100 mg group; general physical health deterioration in 1 patient (33.3%) in the 200 mg group; anaemia, pulmonary embolism, and respiratory distress in 1 patient (33.3%) each in the 400 mg group; and sepsis and thrombocytopenia in 2 patients (33.3%) each, anaemia, general physical health deterioration, empyema, and septic shock in 1 patient (16.7%) each in the 1,600 mg group. A causal relationship to tazemetostat could not be ruled out for anaemia and thrombocytopenia in the 1,600 mg group.

Adverse events led to the discontinuation of tazemetostat in 1 of 6 patients (16.7%) in the 100 mg group, 1 of 6 patients (16.7%) in the 800 mg group, and 1 of 6 patients (16.7%) in the 1,600 mg group (none in the 200 mg and 400 mg groups). The events observed were pulmonary embolism in 1 patient (16.7%) in the 100 mg group, biliary dilatation in 1 patient (16.7%) in the 800 mg group, empyema and sepsis in 1 patient (16.7%) each in the 1,600 mg group. A causal relationship to tazemetostat could not be ruled out for biliary dilatation in 1 patient in the 800 mg group.

7.3.3.1.2 Dose expansion cohort

Adverse events occurred in 7 of 8 patients (87.5%) in the tazemetostat 800 mg group and in 6 of 6 patients (100%) in the tazemetostat 1,600 mg group. Adverse events for which a causal relationship to tazemetostat could not be ruled out occurred in 5 of 8 patients (62.5%) in the 800 mg group and in 5 of 6 patients (83.3%) in the 1,600 mg group. Adverse events with an incidence of ≥20% were asthenia in 4 patients (50.0%), vomiting and muscle spasms in 3 patients (37.5%) each, neutropenia, abdominal pain, diarrhoea, decreased appetite, anxiety, and night sweats in 2 patients (25.0%) each in the 800 mg group; and nausea in 3 patients (50.0%), asthenia and dyspnoea in 2 patients (33.3%) each in the 1,600 mg group.

Serious adverse events occurred in 2 of 8 patients (25.0%) in the 800 mg group and in 3 of 6 patients (50.0%) in the 1,600 mg group. The events observed were neutropenia, lung infection, anxiety, acute respiratory distress syndrome, and dyspnoea in 1 patient (12.5%) each in the 800 mg group; and febrile neutropenia, abdominal pain, asthenia, pyrexia, decreased appetite, musculoskeletal pain, tumour pain, depression, renal colic, acute kidney injury, and pain management in 1 patient (16.7%) each in the 1,600 mg group. A causal relationship to tazemetostat could not be ruled out for neutropenia in 1 patient in the 800 mg group.

An adverse event led to the discontinuation of tazemetostat in 1 of 8 patients (12.5%) in the 800 mg group (none in the 1,600 mg group). The event was neutropenia, and its causal relationship to tazemetostat could not be ruled out.

7.3.3.1.3 Meal effect cohort

Adverse events occurred in 5 of 13 patients (38.5%) in the tazemetostat 200 mg high-fat fed group, in 3 of 13 patients (23.1%) in the tazemetostat 200 mg fasted group, and in 11 of 12 patients (91.7%) in the tazemetostat 400 mg group. Adverse events for which a causal relationship to tazemetostat could not be ruled out occurred in 2 of 13 patients (15.4%) in the 200 mg high-fat fed group, in 2 of 13 patients (15.4%) in the 200 mg fasted group, and in 6 of 12 patients (50.0%) in the 400 mg group. Adverse events

with an incidence of ≥20% were asthenia in 5 patients (41.7%) and decreased appetite in 3 patients (25.0%) in the 400 mg group (none in the 200 mg high-fat fed and tazemetostat 200 mg fasted groups).

Serious adverse events occurred in 1 of 13 patients (7.7%) in the 200 mg fasted group and in 5 of 12 patients (41.7%) in the 400 mg group (none in the 200 mg high-fat fed group). The events observed were abdominal pain in 1 patient (7.7%) in the 200 mg fasted group; and general physical health deterioration in 2 patients (16.7%), asthenia, device related infection, decreased appetite, tumour pain, neuralgia, respiratory distress, pain management, and orthostatic hypotension in 1 patient (8.3%) each in the 400 mg group. A causal relationship to tazemetostat was ruled out for all events.

An adverse event led to the discontinuation of tazemetostat in 1 of 13 patients (7.7%) in the 200 mg high-fat fed group (none in the 200 mg fasted or 400 mg group). The event observed was thrombocytopenia, and its causal relationship to tazemetostat was ruled out.

7.3.3.1.4 Drug interaction cohort

Adverse events occurred in 0 of 13 patients in the midazolam group, 9 of 13 patients (69.2%) in the tazemetostat group, and 12 of 13 patients (92.3%) in the midazolam/tazemetostat group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 7 of 13 patients (53.8%) in the tazemetostat group and in 8 of 13 patients (61.5%) in the midazolam/tazemetostat group (none in the midazolam group). Adverse events with an incidence of ≥30% were anaemia in 4 patients (30.8%) in the tazemetostat group, asthenia in 5 patients (38.5%) and anaemia in 4 patients (30.8%) in the midazolam/tazemetostat group (none in the midazolam group).

Serious adverse events occurred in 2 of 13 patients (15.4%) in the midazolam/tazemetostat group (none in the midazolam group or the tazemetostat group). These events were pancreatitis and cervicobrachial syndrome in 1 patient (7.7%) each, and their causal relationship to the study drug was ruled out.

No adverse events leading to discontinuation of the study drug occurred in any groups.

7.3.3.2 Phase II part

Adverse events occurred in 37 of 37 patients (100%) in Cohort 1, 61 of 62 patients (98.4%) in Cohort 2, 58 of 64 patients (90.6%) in Cohort 3, 44 of 45 patients (97.8%) in Cohort 4, 54 of 54 patients (100%) in Cohort 5, and 68 of 71 patients (95.8%) in Cohort 6. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 26 of 37 patients (70.3%) in Cohort 1, 35 of 62 patients (56.5%) in Cohort 2, 37 of 64 patients (57.8%) in Cohort 3, 38 of 45 patients (84.4%) in Cohort 4, 42 of 54 patients (77.8%) in Cohort 5, and 34 of 71 patients (47.9%) in Cohort 6. Adverse events with an incidence of ≥20% were nausea and pyrexia in 11 patients (29.7%) each, diarrhoea in 10 patients (27.0%), vomiting and fatigue in 9 patients (24.3%) each, cough and thrombocytopenia in 8 patients (21.6%) each in Cohort 1; thrombocytopenia in 18 patients (29.0%), cough in 15 patients (24.2%), and nausea in 14 patients (22.6%) in Cohort 2; nausea and anaemia in 13 patients (20.3%) each in Cohort 3; alopecia in 10 patients (22.2%) and nausea in 9 patients (20.0%) in Cohort 4; nausea in 14 patients (25.9%), asthenia in 12 patients (22.2%), cough and anaemia in 11 patients (20.4%) each in Cohort 5;

and thrombocytopenia in 17 patients (23.9%), anaemia in 16 patients (22.5%), and asthenia in 15 patients (21.1%) in Cohort 6.

Serious adverse events occurred in 22 of 37 patients (59.5%) in Cohort 1, 34 of 62 patients (54.8%) in Cohort 2, 30 of 64 patients (46.9%) in Cohort 3, 11 of 45 patients (24.4%) in Cohort 4, 16 of 54 patients (29.6%) in Cohort 5, and 49 of 71 patients (69.0%) in Cohort 6. Serious adverse events observed in ≥2 patients in each cohort were abdominal pain in 4 patients (10.8%) and neutropenia in 2 patients (5.4%) in Cohort 1; neutropenia in 4 patients (6.5%), general physical condition decreased in 3 patients (4.8%), anaemia, oedema peripheral, hyperglycaemia, back pain, cancer pain, and neuralgia in 2 patients (3.2%) each in Cohort 2; neutropenia and general physical condition decreased in 6 patients (9.4%) each, thrombocytopenia in 5 patients (7.8%), and lung infection in 2 patients (3.1%) in Cohort 3; anaemia and general physical condition decreased in 2 patients (3.7%) each in Cohort 5; and thrombocytopenia and general physical condition decreased in 8 patients (11.3%) each, neutropenia in 6 patients (8.5%), anaemia, febrile neutropenia, pyrexia, and pneumonia in 3 patients (4.2%) each, multi-organ failure, non-cardiac chest pain, sepsis, lower respiratory tract infection, back pain, cancer pain, dyspnoea, lung disorder, and cough in 2 patients (2.8%) each in Cohort 6 (none in Cohort 4). A causal relationship to the study drug could not be ruled out for neutropenia in 2 patients and abdominal pain in 1 patient in Cohort 1; neutropenia in 4 patients and anaemia and oedema peripheral in 1 patient each in Cohort 2; neutropenia in 4 patients and thrombocytopenia in 2 patients in Cohort 3; and thrombocytopenia and neutropenia in 4 patients each, anaemia in 2 patients, febrile neutropenia and pneumonia in 1 patient each in Cohort 6.

Adverse events leading to discontinuation of the study drug occurred in 4 of 37 patients (10.8%) in Cohort 1, 3 of 62 patients (4.8%) in Cohort 2, 4 of 64 patients (6.3%) in Cohort 3, 3 of 45 patients (6.7%) in Cohort 4, 5 of 54 patients (9.3%) in Cohort 5, and 8 of 71 patients (11.3%) in Cohort 6. There were no adverse events leading to discontinuation of the study drug occurring in ≥2 patients in any cohort.

7.3.4 Foreign phase I study (Study 103)

Adverse events occurred in 3 of 3 patients (100%). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 3 of 3 patients (100%). Adverse events observed in ≥2 patients were diarrhoea, nausea, vomiting, cellulitis, headache, lethargy, fatigue, and cough in 2 patients (66.7%) each.

Serious adverse events occurred in 3 of 3 patients (100%), which included cellulitis in 2 patients (66.7%), neutropenic sepsis and neck mass in 1 patient (33.3%) each. A causal relationship to the study drug could not be ruled out for cellulitis and neutropenic sepsis in 1 patient each.

An adverse event, neck mass, led to the discontinuation of the study drug occurred in 1 of 3 patients (33.3%). The causal relationship to the study drug was ruled out.

7.3.5 Foreign phase I study (Study 105)

7.3.5.1 Part A

Adverse events occurred in 8 of 16 patients (50.0%) in the tazemetostat 400 mg group, 5 of 14 patients (35.7%) in the fluconazole/tazemetostat group, and 11 of 14 patients (78.6%) in the tazemetostat 800 mg group. A causal relationship to the study drug could not be ruled out in 4 of 16 patients (25.0%) in the tazemetostat 400 mg group, 3 of 14 patients (21.4%) in the fluconazole/tazemetostat group, and 7 of 14 patients (50.0%) in the tazemetostat 800 mg group. Adverse events with an incidence of ≥10% were nausea, vomiting, abdominal pain, fatigue, and hypercalcaemia in 2 patients (12.5%) each in the tazemetostat 400 mg group; nausea and diarrhoea in 2 patients (14.3%) each in the fluconazole/tazemetostat group; and fatigue in 4 patients (28.6%), nausea, diarrhoea, and dizziness in 3 patients (21.4%) each, and vomiting and herpes zoster in 2 patients (14.3%) each in the tazemetostat 800 mg group.

Serious adverse events occurred in 3 of 16 patients (18.8%) in the tazemetostat 400 mg group and in 2 of 14 patients (14.3%) in the tazemetostat 800 mg group (none in the fluconazole/tazemetostat group). The events observed were abdominal pain in 2 patients (12.5%) and hypercalcaemia in 1 patient (6.3%) in the tazemetostat 400 mg group; and death and herpes zoster in 1 patient (7.1%) each in the tazemetostat 800 mg group. A causal relationship to the study drug could not be ruled out for herpes zoster in 1 patient in the tazemetostat 800 mg group.

No adverse events led to the discontinuation of the study drug in any group.

7.3.5.2 Part B

Adverse events occurred in 2 of 15 patients (13.3%) in the repaglinide/omeprazole group, 9 of 16 patients (56.3%) in the tazemetostat group, 7 of 15 patients (46.7%) in the tazemetostat/repaglinide/omeprazole group, and 14 of 16 patients (87.5%) in the tazemetostat/omeprazole group. Their causal relationship to the study drug could not be ruled out in 5 of 16 patients (31.3%) in the tazemetostat, 6 of 15 patients (40.0%) in the tazemetostat/repaglinide/omeprazole group, and 6 of 16 patients (37.5%) in the tazemetostat/omeprazole group (none in the repaglinide/omeprazole group). Adverse events with an incidence of ≥10% were constipation and fatigue in 2 patients (12.5%) each in the tazemetostat group; fatigue in 3 patients (20.0%) and white blood cell count decreased in 2 patients (13.3%) in the tazemetostat/repaglinide/omeprazole group; and anaemia in 4 patients (25.0%), diarrhoea and platelet count decreased in 3 patients (18.8%) each, vomiting, death, pyrexia, upper respiratory tract infection, fall, incision site pain, and nasal congestion in 2 patients (12.5%) each in the tazemetostat/omeprazole group (none in the repaglinide/omeprazole group).

Serious adverse events occurred in 1 of 16 patients (6.3%) in the tazemetostat group and 7 of 16 patients (43.8%) in the tazemetostat/omeprazole group (none in the repaglinide/omeprazole or tazemetostat/repaglinide/omeprazole group). These events were sepsis in 1 patient (6.3%) in the tazemetostat group; and death in 2 patients (12.5%), anaemia, faecal incontinence, intestinal perforation, small intestinal obstruction, appendicitis, bronchitis, peritonitis bacterial, subdural haematoma, hypocalcaemia, tumour pain, pleural effusion, pneumonia aspiration, and respiratory failure in 1 patient

(6.3%) each in the tazemetostat/omeprazole group. A causal relationship to the study drug could not be ruled out for anaemia in 1 patient in the tazemetostat/omeprazole group.

Death led to the discontinuation of the study drug in 1 of 16 patients (6.3%) in the tazemetostat/omeprazole group (none in the repaglinide/omeprazole, tazemetostat, or tazemetostat/repaglinide/omeprazole group), and its causal relationship to the study drug was ruled out.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2.6) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that tazemetostat has efficacy in the treatment of patients with relapsed or refractory *EZH2* gene mutation-positive FL (limited to those who are refractory or intolerant to standard treatments), and that tazemetostat has acceptable safety in view of its benefits. Tazemetostat is a drug with a new active ingredient that inhibits EZH2 methylation, inducing cell cycle arrest and apoptosis, and thereby leading to tumor growth suppression. Tazemetostat is thus expected to have a clinical significance as a treatment option for patients with relapsed or refractory *EZH2* gene mutation-positive FL. The clinical positioning and indications, etc. of tazemetostat should be further evaluated.

PMDA has concluded that tazemetostat may be approved if tazemetostat is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

April 27, 2021

Product Submitted for Approval

Brand Name	Tazverik Tablets 200 mg
Non-proprietary Name	Tazemetostat Hydrobromide
Applicant	Eisai Co., Ltd.
Date of Application	June 30, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008)

1.1 Efficacy

As a result of its discussion in Section "7.R.2 Efficacy" in the Review Report (1), PMDA concluded that a certain level of efficacy of tazemetostat had been demonstrated in patients with relapsed or refractory *EZH2* gene mutation-positive FL, based on the following results obtained in 2 clinical studies in patients with this disease (Cohort 4 of the phase II part in Study 101 and Cohort 1 in Study 206):

- In Cohort 4 of the phase II part in Study 101, the primary endpoint of the centrally-assessed response rate based on Revised RC (*J Clin Oncol*. 2007;25:579-86) met the pre-defined efficacy criteria.
- In Cohort 1 in Study 206, the lower limit of 90% CI of the centrally-assessed response rate based on Revised RC (*J Clin Oncol.* 2007;25:579-86), the primary efficacy endpoint, was greater than the pre-specified threshold response rate (10%).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of the review in Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that adverse events warranting attention in the use of tazemetostat are infection, bone marrow depression, secondary malignant tumor, and photosensitivity.

PMDA also concluded that although caution should be exercised against these adverse events during treatment, tazemetostat is tolerable when monitoring and controlling of adverse events or other

appropriate measures are taken by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancy.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication

As a result of its review on Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA concluded that tazemetostat should be indicated for patients with relapsed or refractory *EZH2* gene mutation-positive FL that is refractory to the standard therapy with clinically proven efficacy, based on the following:

- Tazemetostat is expected to be recognized as a treatment option for patients with relapsed or refractory *EZH2* gene mutation-positive FL who have ≥2 prior treatments.
- In Japan, while there are antineoplastic agents approved based on confirmatory studies in patients with relapsed or refractory FL, no clinical study data have demonstrated the clinical benefit of tazemetostat until now.

Based on the above review, PMDA concluded that the indication for tazemetostat should be "relapsed or refractory *EZH2* gene mutation-positive follicular lymphoma (limited to those refractory to standard treatments)," with the following advice provided in the "Precautions Concerning Indication" section.

Precautions Concerning Indication

- Tazemetostat should be administered to patients who have been confirmed to have *EZH2* gene mutation by a highly experienced pathologist or at a laboratory facility, using approved *in vitro* diagnostic or medical device.
- Treatment with tazemetostat should be performed in patients who are non-responsive to at least 2 standard treatments or who have had a relapse after treatment.
- Physicians should have a full understanding of the efficacy and safety of tazemetostat with adequate knowledge from the "Clinical Studies" section. Before deciding the use of tazemetostat, other treatment options should also be considered carefully for each patient.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Accordingly, PMDA instructed the applicant to finalize the descriptions in the "Indication" and "Precautions Concerning Indication" sections as above. The applicant agreed.

1.4 Dosage and administration

After the discussion in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections should be specified as follows:

Dosage and Administration

The usual adult dosage is 800 mg of tazemetostat administered orally twice daily. The dose may be reduced according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of tazemetostat in combination with other antineoplastic agents have not been established.
- If any adverse drug reaction of tazemetostat occurs during treatment, tazemetostat should be interrupted, continued at a reduced dose, or discontinued according to the following criteria.

Level of tazemetostat dose reduction

Level	Dose
Usual dose	800 mg twice daily
1-level lower dose	600 mg twice daily
2-level lower dose	400 mg twice daily
3-level lower dose	Discontinue

Criteria for interruption, dose reduction, and discontinuation of tazemetostat

Adverse drug reaction	Grade*	Measures to be taken
Neutropenia	Neutrophil count <750/mm^3	Interrupt tazemetostat until neutrophil count recovers to ≥750/mm^3. After recovery, tazemetostat may be resumed at a 1-level lower dose.
Other adverse drug reactions	Either of the following (except clinically insignificant laboratory abnormalities) • Intolerable Grade 2 • Grade 3	Interrupt tazemetostat until the symptom recovers to Grade ≤1 or baseline (In case of nausea, vomiting, or diarrhea, take appropriate measures. Interrupt tazemetostat if the symptom cannot be controlled). After recovery, tazemetostat may be resumed at a 1-level lower dose.
	Grade 4 (non-life-threatening laboratory abnormalities are handled as Grade 3)	Discontinue tazemetostat.

* Graded according to NCI-CTCAE v4.03.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to finalize the descriptions in the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as above. The applicant agreed.

1.5 Risk management plan (draft)

In order to investigate the safety, etc. of tazemetostat in post-marketing clinical use, the applicant plans to conduct a post-marketing surveillance covering all patients treated with tazemetostat, with the planned sample size of 145 and the follow-up period of 52 weeks.

As a result of the review in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA concluded that the surveillance should be conducted for a certain post-approval period, covering all patients receiving tazemetostat to collect safety information promptly in an unbiased manner, and safety information should be provided to healthcare professionals as soon as available.

PMDA further concluded as follows:

- The surveillance safety specification should include infection, bone marrow depression, secondary malignant tumor, and photosensitivity.

- The planned sample size and the follow-up period should be reconsidered based on the incidences of events which were observed in the clinical studies and are included in safety specification of the surveillance.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above discussion, PMDA instructed the applicant to revise the surveillance plan.

The applicant's response:
- The safety specification will include infection, bone marrow depression, secondary malignant tumor, and photosensitivity.
- The planned sample size and the follow-up period will be 145 patients and 52 weeks, respectively, taking account of the occurrence of events which occurred in the clinical studies and are included in safety specification of the surveillance.

PMDA accepted the response of the applicant.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for tazemetostat should include the safety specification presented in Table 34, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 35 and 36.

Table 34. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infection • Bone marrow depression	• Secondary malignant tumor • Photosensitivity	• Use in patients with hepatic impairment • Drug interactions with CYP3A inhibitors
Efficacy specification		
Not applicable		

Table 35. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance) • Post-marketing clinical study (extension of Study 206)	Not applicable	• Information provision based on the early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals

Table 36. Outline of use-results survey (draft)

Objective	To investigate the safety of tazemetostat in the post-marketing clinical use
Survey method	All-case surveillance
Population	All patients receiving tazemetostat
Follow-up period	52 weeks
Planned sample size	145
Main survey items	Safety specification: Infection, bone marrow depression, secondary malignant tumor, and photosensitivity Other main survey items: Patient characteristics (age, sex, diagnosis, clinical stage, past illness, comorbidity, etc.), prior treatments, status of tazemetostat administration, concomitant drugs, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that tazemetostat may be approved for the modified indication and dosage regimen shown below and with the following approval conditions, presupposing the provision of appropriate cautionary advice and information through the package insert in the post-marketing setting as well as the adherence to the proper use of tazemetostat under the supervision of physicians with adequate knowledge and experience in treating hematopoietic malignancy and at medical institutions capable of emergency response. Tazemetostat is a drug with a new active ingredient, and the re-examination period is thus 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Relapsed or refractory *EZH2* gene mutation-positive follicular lymphoma (limited to those refractory to standard treatments)

Dosage and Administration

The usual adult dosage is 800 mg of tazemetostat administered orally twice daily. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of extremely limited data from Japanese clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product in the post-marketing setting until data are available from a certain number of patients, to understand the characteristics of patients using the product and to collect safety and efficacy data promptly so that necessary measures are taken to ensure proper use of the product.

Warning

The product should be administered only to patients found to be eligible for the treatment, under the supervision of a physician with adequate knowledge and experience in treatment of hematopoietic malignancies and at a medical institution capable of emergency response. Prior to treatment, patients or their family must be thoroughly informed of the potential risks and benefits of the treatment and provide consent.

Contraindication

Patients with a history of hypersensitivity to any ingredients of the product

Precautions Concerning Indication

1. Tazemetostat should be administered to patients who have been confirmed to have *EZH2* gene mutation by a highly experienced pathologist or at a laboratory facility, using approved *in vitro* diagnostic or medical device.
2. Treatment with tazemetostat should be performed in patients who are non-responsive to at least 2 standard treatments or who have had a relapse after treatment.
3. Physicians should have a full understanding of the efficacy and safety of tazemetostat with adequate knowledge from the "Clinical Studies" section. Before deciding the use of tazemetostat, other treatment options should also be considered carefully for each patient.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of tazemetostat in combination with other antineoplastic agents have not been established.
2. If any adverse drug reaction occurs during treatment, tazemetostat should be interrupted, continued at a reduced dose, or discontinued according to the following criteria.

Level of tazemetostat dose reduction

Level	Dose
Usual dose	800 mg twice daily
1-level lower dose	600 mg twice daily
2-level lower dose	400 mg twice daily
3-level lower dose	Discontinue

Criteria for interruption, dose reduction, and discontinuation of tazemetostat

Adverse drug reaction	Grade*	Measures to be taken
Neutropenia	Neutrophil count <750/mm^3	Interrupt tazemetostat until neutrophil count recovers to ≥750/mm^3. After recovery, tazemetostat may be resumed at a 1-level lower dose.
Other adverse drug reactions	Either of the following (except clinically insignificant laboratory abnormalities) • Intolerable Grade 2 • Grade 3	Interrupt tazemetostat until the symptom recovers to Grade ≤1 or baseline (In case of nausea, vomiting, or diarrhea, take appropriate measures. Interrupt tazemetostat if the symptom cannot be controlled). After recovery, tazemetostat may be resumed at a 1-level lower dose.
	Grade 4 (non-life-threatening laboratory abnormalities are handled as Grade 3)	Discontinue tazemetostat.

* Grade was defined according to NCI-CTCAE v4.03.

List of Abbreviations

ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
application	marketing approval application
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BA	bioavailability
BCRP	breast cancer resistance protein
Bendamustine	Bendamustine hydrate
BID	bis in die
BOR	best overall response
BSEP	bile salt export pump
BUN	blood urea nitrogen
CDx	companion diagnostics
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisolone/prednisone/methylprednisolone
CI	confidence interval
CK	creatine phosphokinase
CMV	cytomegalovirus
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CrCL	creatinine clearance
CVP	cyclophosphamide, vincristine, prednisolone/prednisone/methylprednisolone
Cyclophosphamide	Cyclophosphamide hydrate
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
efflux ratio	the ratio of permeability coefficient in the secretory direction to that in the absorptive direction
ELISA	enzyme-linked immunosorbent assay
EZH2	enhancer of zeste homolog 2
FL	follicular lymphoma
FRET	fluorescence resonance energy transfer
GC	gas chromatography
GCB	germinal-center B-cell-like
HBc antibody	anti-hepatitis B core antibody
HBs antibody	hepatitis B surface antibody
HBs antigen	hepatitis B surface antigen
HBV	hepatitis B virus
hERG	human *ether-a-go-go*-related gene
HMT	histone methyltransferase
H3K4	histone H3 lysine 4
H3K9	histone H3 lysine 9
H3K27	histone H3 lysine 27
H3K27me3	histone H3 lysine 27 trimethylation
H3K36	histone H3 lysine 36
H3K79	histone H3 lysine 79

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E Guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH Q3A Guideline	"Revision of the Guideline on Impurities in New Drug Substances" (PFSB/ELD Notification No. 1216001, dated December 16, 2002)
ICH Q3B Guideline	"Revision of the Guideline on Impurities in New Drug Products" (PFSB/ELD Notification No. 0624001, dated June 24, 2003)
IR	infrared absorption spectrum
k_a	absorption rate constant
LC	liquid chromatography
LC-MS/MS	liquid chromatography/tandem mass spectrometry
Lenalidomide	Lenalidomide hydrate
LIW Feeder	loss in weight feeder
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPE	mean photo effect
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN	National Comprehensive Cancer Network
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-cell Lymphomas
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NE	not estimated
NHL	non-Hodgkin lymphoma
NMR	nuclear magnetic resonance spectrum
NOD/SCID mouse	non-obese diabetic/severe combined immunodeficient mouse
NZW	New Zealand White
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
Obinutuzumab	Obinutuzumab (genetical recombination)
OCT	organic cation transporter
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
P-gp	P-glycoprotein
PI	propidium iodide
PIF	photo irritation factor
PK	pharmacokinetics
pKa	Acid dissociation constant
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PRC2	polycomb-repressive complex 2
PRDM1	PR domain zinc finger protein 1
PSL	prednisolone/prednisone/methylprednisolone
PT	preferred term

QbD	quality by design
QD	quaque die
Revised RC	Revised Response Criteria for Malignant Lymphoma
Rituximab	Rituximab (genetical recombination)
RNA	ribonucleic acid
SCID mouse	severe combined immunodeficient mouse
SD	stable disease
SMARCA2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member2
SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member4
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member1
SMQ	standard MedDRA queries
SOC	system organ class
Study 101	Study E7438-G000-101
Study 102	Study EZH-102
Study 103	Study EZH-103
Study 105	Study EZH-105
Study 106	Study E7438-J081-106
Study 202	Study EZH-202
Study 203	Study EZH-203
Study 206	Study E7438-J081-206
T-ALL	acute lymphoblastic leukemia
Tazemetostat	Tazemetostat hydrobromide
TID	ter in die
T-LBL	T cell lymphoblastic lymphoma
TP53INP1	tumor protein p53 inducible nuclear protein1
TUNEL	terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
VZV	varicella zoster virus
ΔQTcI	Individual-corrected QT interval
^{14}C-tazemetostat	^{14}C-labeled tazemetostat