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	Hiyasta Tablets 10 mg
Non-proprietary Name	Tucidinostat (JAN*)
Applicant	Huya Japan G.K.
Date of Application	September 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 10 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. Since only a limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a post-marketing drug use-results survey involving all Japanese patients treated with the product until data from a certain number of patients have been gathered in order to understand the characteristics of patients using the product and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

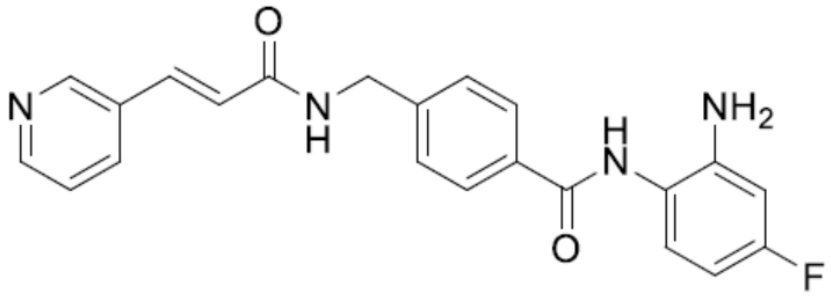
Review Report

May 11, 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	Hiyasta Tablets 10 mg
Non-proprietary Name	Tucidinostat
Applicant	Huya Japan G.K.
Date of Application	September 30, 2020
Dosage Form/Strength	Tablets: Each tablet contains 10 mg of tucidinostat.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{22}H_{19}FN_4O_2$

Molecular weight: 390.42

Chemical name: *N*-(2-Amino-4-fluorophenyl)-4-{[(2*E*)-3-(pyridin-3-yl)prop-2-enamido] methyl}benzamide

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 480 of 2020 [*R2 yaku*]; PSEHB/PED Notification No. 0817-5 dated August 17, 2020, issued by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has certain efficacy in the treatment of patients with relapsed or refractory adult T-cell leukemia/lymphoma, 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. Myelosuppression, infection, interstitial lung disease, and arrhythmia (including QT interval prolonged) needs to be further investigated through post-marketing surveillance.

Indication

Relapsed or refractory adult T-cell leukemia/lymphoma

Dosage and Administration

The usual adult dosage is 40 mg of tucidinostat administered orally once daily after a meal twice weekly (every 3 or 4 days). 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. Since only a limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a post-marketing drug use-results survey involving all Japanese patients treated with the product until data from a certain number of patients have been gathered in order to understand the characteristics of patients using the product and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Attachment

Review Report (1)

March 23, 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	Hiyasta Tablets 10 mg
Non-proprietary Name	Tucidinostat
Applicant	Huya Japan G.K.
Date of Application	September 30, 2020
Dosage Form/Strength	Tablets: Each tablet contains 10 mg of tucidinostat.
Proposed Indication	Relapsed or refractory adult T-cell leukemia/lymphoma

Proposed Dosage and Administration

The usual adult dosage is 40 mg of tucidinostat administered orally after a meal twice weekly.

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

Histone deacetylases (HDACs) represent a group of enzymes that catalyze the removal of an acetyl group from an acetylated lysine residue of proteins such as histones and transcription factors (deacetylation). Histone-deacetylation by these enzymes leads to the formation of condensed chromatins, resulting in the repression of gene transcription.

Tucidinostat is a small molecule HDAC inhibitor, which was discovered by Shenzhen Chipscreen Biosciences Co., Ltd. (China). Tucidinostat is considered to suppress tumor growth by inhibiting the deacetylation of histones, thereby inducing cell cycle arrest and apoptosis.

1.2 Development history etc.

A foreign phase I study (Study TG0702CDM) in patients with advanced solid tumor and patients with relapsed or refractory malignant lymphoma was initiated by Shenzhen Chipscreen Biosciences Co., Ltd. (China) in [redacted] 20[redacted].

As of February 2021, tucidinostat has been approved in 1 country[1)] but not approved for the treatment of relapsed or refractory adult T-cell leukemia/lymphoma (ATLL) in any country or region.

In Japan, a phase I study in patients with relapsed or refractory non-Hodgkin lymphoma (NHL) (Study HBI-8000-201 [Study 201]) and a phase IIb study in patients with relapsed or refractory ATLL (Study HBI-8000-210 [Study 210]) were initiated in June 2014 and November 2016, respectively.

An application for tucidinostat has been submitted based on the results of Study 210 as the pivotal study.

Tucidinostat was designated as an orphan drug for the intended indication of “relapsed or refractory adult T-cell leukemia/lymphoma” in August 2020 (Orphan Drug Designation No. 480 of 2020 [*R2 yaku*]).

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

2.1 Drug substance

2.1.1 Characterization

The drug substance occurs as a white powder. The general properties of the drug substance including description, solubility, melting point, acid dissociation constant, partition coefficient, thermal analysis, particle size, and hygroscopicity were determined. The drug substance has been found in at least 3 crystal forms (Forms A, B, and C), but [redacted] is mainly produced in the commercial production. The stability studies show that [redacted] remains unchanged.

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

1) Tucidinostat is approved in 1 country (China) for the treatment of peripheral T-cell lymphoma (PTCL) and breast cancer.

2.1.2 Manufacturing process

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

The quality control strategy was developed by the following investigations using quality by design (QbD) approaches (Table 1):

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

Table 1. Outline of control strategy for the drug substance

CQA	Control method
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] was identified as a critical step, and in-process control parameters and process control values are established for all the reaction and purification steps. In addition, [redacted] and crude drug substance are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR and liquid chromatography [LC]), purity ([redacted], related substances [LC], Impurity F [redacted], and residual solvents [gas chromatography (GC)]), water content, residue on ignition, microbial limit, and assay (LC).

2.1.4 Stability of drug substance

Table 2 shows major stability studies conducted on the drug substance. The drug substance was shown to be stable. Photostability testing showed that the drug substance was photostable.

Table 2. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 commercial-scale batches	25°C	60%RH	Low-density polyethylene bag + aluminum-laminated bag	12 months
Accelerated testing		40°C	75%RH		6 months

Based on the above findings, a retest period of [redacted] months was proposed for the drug substance when stored at room temperature in the low-density polyethylene bag and aluminum-laminated bag. The long-term testing will be continued for 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 (FC) tablets, each containing 10.0 mg of tucidinostat. Excipients included in the drug product contains are povidone, microcrystalline cellulose, lactose hydrate, sodium starch glycolate, talc, magnesium stearate, and Opadry II White [redacted].

2.2.2 Manufacturing process

The drug product is manufactured through the process comprising [redacted] to [redacted], packaging/labeling of bulk products, and printing and packaging/labeling.

[redacted] and [redacted] were identified as critical steps. Process controls have been established in steps for [redacted] and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (UV/VIS, LC and [redacted]), purity (related substances [LC] and ethanol [GC]), water content, uniformity of dosage units (content uniformity [LC]), microbial limit, dissolution (LC), and assay (LC).

2.2.4 Stability of drug product

Table 3 shows major stability studies conducted on the drug product. The drug product was stable. Photostability testing shows that the drug product was photostable.

Table 3. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 commercial-scale batches	25°C	60%RH	PTP ([redacted] and aluminum foil)	18 months
Accelerated		40°C	75%RH		6 months

Based on the above findings, a shelf life of 24 months was proposed for the drug product when stored at room temperature in a blister pack (press through package [PTP]) ([redacted] and aluminum foil) in accordance with the "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). The long-term study will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the quality of the drug substance and the drug product is adequately controlled.

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

3.1 Primary pharmacodynamics

3.1.1 HDAC inhibition (CTD 4.3-46, *Cancer Chemother Pharmacol.* 2012;69:901-9)

The inhibition of 11 HDAC isoforms (recombinant proteins) by tucidinostat was measured using a fluorescent substrate, which is released by enzymatic reaction. Table 4 shows the IC_{50} of tucidinostat against these HDAC isoforms.

Table 4. Inhibition of HDAC isoforms by tucidinostat

Isoform	IC_{50} (μmol/L)	Isoform	IC_{50} (μmol/L)
HDAC 1	0.095 ± 0.030	HDAC 7	>30
HDAC 2	0.160 ± 0.064	HDAC 8	0.733 ± 0.206
HDAC 3	0.067 ± 0.028	HDAC 9	>30
HDAC 4	>30	HDAC 10	0.078 ± 0.029
HDAC 5	>30	HDAC 11	0.432 ± 0.088
HDAC 6	>30		

Mean ± standard error (SE), n = 3

3.1.2 Inhibition of histone deacetylase activity (CTD 4.3-46, *Cancer Chemother Pharmacol.* 2012;69:901-9)

The ability of tucidinostat to inhibit histone deacetylase activity in human cervical cancer-derived cell line (HeLa cells) and human peripheral blood mononuclear cells (PBMCs) from healthy adult donors was investigated by Western blotting. In both cell types, tucidinostat inhibited deacetylation of histone H3.

3.1.3 Cell cycle arrest induction (CTD 4.3-30, *Cancer Sci.* 2016;107:1124-33)

The effects of tucidinostat on the expression of cell cycle inhibitor p21 in human ATLL-derived cell lines (KOB, LMY1, and KK1) were investigated by Western blotting. In all the cell lines, tucidinostat increased the expression of p21.

The cell cycle arrest induction of tucidinostat in human ATLL-derived cell lines (KOB, KK1, SO4, and ST1) was investigated by flow cytometry using propidium iodide (PI) stain as an indicator. In KK1, SO4, and ST1 cells, tucidinostat induced G1 cell cycle arrest.

3.1.4 Apoptosis induction (CTD 4.3-30, *Cancer Sci.* 2016;107:1124-33)

The effects of tucidinostat on the expression of pro-apoptotic protein Bim in primary cultured cells derived from 3 patients with ATLL as well as KOB and LMY1 cells were investigated by Western blotting. In all the cell types, tucidinostat increased the expression of Bim.

The apoptosis induction of tucidinostat in primary cultured cells derived from 6 patients with ATLL was investigated using double staining with annexin V and PI as an indicator. In all the cell types, tucidinostat induced apoptosis.

3.1.5 Growth inhibitory effect of tucidinostat on malignant tumor-derived cell lines

3.1.5.1 Effects on leukemia- and malignant lymphoma-derived cell lines

3.1.5.1.1 *In vitro* (CTD 4.3-30, *Cancer Sci.* 2016;107:1124-33; CTD 4.3-46, *Cancer Chemother Pharmacol.* 2012;69:901-9)

The growth inhibitory effect of tucidinostat on 3 human leukemia- and malignant lymphoma-derived cell lines was investigated based on viable cell-specific reductase activity. Table 5 shows the IC_{50} of tucidinostat against these cell lines.

Table 5. Growth inhibitory effect of tucidinostat on human leukemia- and malignant lymphoma-derived cell lines

Cell line	Origin	IC_{50} (μmol/L)
HL-60	Promyelocytic leukemia	0.4 ± 0.1
Jurkat	Acute T-cell leukemia	6.3 ± 0.9
Raji	Burkitt's lymphoma	4.0 ± 0.9

Mean ± SE, n ≥3

The growth inhibitory effect of tucidinostat on primary cultured cells from 10 patients with ATLL was investigated based on viable cell-specific reductase activity. Table 6 shows the IC_{50} of tucidinostat against these cells.

Table 6. Growth inhibitory effect of tucidinostat on primary cultured cells from patients with ATLL

	IC_{50} (μmol/L)		IC_{50} (μmol/L)
Patient 1	9.1	Patient 6	7.9
Patient 2	17.8	Patient 7	11.0
Patient 3	8.2	Patient 8	>20.0
Patient 4*	18.2, >20.0	Patient 9	>20.0
Patient 5	4.8	Patient 10	>20.0

n = 1

* Two types of ATLL cells were isolated from 1 patient.

3.1.5.2 Effects on malignant tumor-derived cell lines other than leukemia- and malignant lymphoma-derived ones

3.1.5.2.1 *In vitro* (CTD 4.3-46, *Cancer Chemother Pharmacol.* 2012;69:901-9)

The growth inhibitory effect of tucidinostat on 14 human malignant tumor-derived cell lines was investigated based on viable cell-specific reductase activity. Table 7 shows the IC_{50} of tucidinostat against these cell lines.

Table 7. Growth inhibitory effect of tucidinostat on human malignant tumor-derived cell lines

Cell line	Origin	IC_{50} (μmol/L)	Cell line	Origin	IC_{50} (μmol/L)
A549	NSCLC	8.2 ± 2.9	SK-N-SH	Neuroblastoma	>50
DU-145	Prostate cancer	25 ± 6.7	HCT-8	Colorectal cancer	7.2 ± 1.7
LNCaP		4.0 ± 1.2	SMMC	Hepatocellular carcinoma	16 ± 3.2
MCF-7	Breast cancer	5.0 ± 1.3	HepG2		4.0 ± 1.5
MB-231		7.9 ± 2.1	PANC-1	Pancreatic carcinoma	6.3 ± 2.1
SK-OV-3	Ovarian cancer	>50	SGC-7901	Gastric cancer	>50
HeLa	Cervix carcinoma	40 ± 8.3	U2OS	Osteosarcoma	2.0 ± 0.6

Mean ± SE, n ≥3

3.1.5.2.2 *In vivo* (CTD 4.2.1.1-3)

The tumor growth inhibitory effect of tucidinostat was investigated in nude mice subcutaneously transplanted with human colorectal cancer cell line HCT-8 (n = 10/group). Study treatment with tucidinostat was started 3 days after the transplantation (Day 1) in accordance with the following

regimens: Oral administration of tucidinostat at (a) 25 mg/kg QD; (b) 50 mg/kg once every 2 days; or (c) 50 mg/kg once every 3 days, for 20 days. Tumor weight was calculated on Day 20 or 21. Tucidinostat suppressed tumor growth with the regimens (a), (b) and (c) by 49.3%, 46.3%, and 41.2%,[2)] respectively, all showing a statistically significant tumor growth inhibition in comparison with the control (0.2% carboxymethylcellulose and 0.1% polysorbate 80) ($P < 0.001$, Student's t test).

3.2 Safety pharmacology

3.2.1 Effects on central nervous system

Four- and 13-week repeated oral dose toxicity studies in rats [see Section 5.2] were conducted to investigate the effects of tucidinostat on clinical signs and body weight. No effect of tucidinostat was observed.

Four- and 13-week repeated oral dose toxicity studies in dogs [see Section 5.2] were conducted to investigate the effects of tucidinostat on clinical signs and body weight. Tucidinostat was administered at 0.25, 0.75, or 1.25 mg/kg QD[3)] in the 4-week study and at 0.25, 0.75, or 1.25 mg/kg once every 2 days in the 13-week study. Animals treated with tucidinostat 0.75 or 1.25 mg/kg QD in the 4-week study showed inanimation, inappetence, and emaciation, and those at any dose in the 13-week study showed abnormal gait and limited use of limbs.

3.2.2 Effects on cardiovascular system

3.2.2.1 Effects on hERG potassium current (CTD 4.2.1.3-1)

Human *ether-a-go-go* related gene (hERG) was transfected into human fetal kidney-derived cell line HEK 293. The effect of tucidinostat 5 μmol/L on hERG potassium current was investigated using the cell line. Tucidinostat 5 μmol/L inhibited hERG potassium current by 2.5% ± 0.7% (mean ± standard error, n = 3). A statistically significant inhibition was observed in the tucidinostat group, compared with the control (HEPES buffered saline containing 1% dimethylsulfoxide [DMSO][4)]) group ($P < 0.05$, Dunnett's multiple comparison test).

3.2.2.2 Effects on heart rate and electrocardiogram

Four- and 13-week repeated oral dose toxicity studies in dogs [see Section 5.2] were conducted to investigate the effect of tucidinostat on the heart rate and electrocardiogram (RR, PR, QT, and QRS intervals). Tucidinostat was administered at 0.25, 0.75, or 1.25 mg/kg QD[3)] in the 4-week study and at 0.25, 0.75, or 1.25 mg/kg once every 2 days in the 13-week study. Tucidinostat 0.75 or 1.25 mg/kg QD prolonged QTc interval.

In addition to QT interval prolonged observed in the above toxicity study, electrocardiogram QT prolonged occurred in clinical studies [see Section 7.R.3.4]. The applicant, therefore, plans to appropriately advise healthcare professionals on such events through the package insert and other information materials.

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2) Tumor growth inhibition rate (%) = {(mean tumor weight in the control group - mean tumor weight in the tucidinostat group) / (mean tumor weight in the control group)} × 100

3) On Day 13 and thereafter, the once-every-2 days regimen was used.

4) 137 mmol/L sodium chloride, 4 mmol/L potassium chloride, 1.8 mmol/L calcium chloride, 1 mmol/L magnesium chloride, 10 mmol/L glucose, and 10 mmol/L HEPES (pH 7.4).

3.2.3 Effects on respiratory system

Four- and 13-week repeated oral dose toxicity studies in rats and dogs [see Section 5.2] were conducted to investigate the effects of tucidinostat on the respiratory system. No effect of tucidinostat was observed.

3.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about non-clinical pharmacology of tucidinostat is acceptable, except for the discussion presented in the following section.

3.R.1 Mechanism of action and efficacy of tucidinostat

The applicant's explanation about the mechanism of action of tucidinostat and its efficacy in the treatment of ATLL:

Tucidinostat inhibits histone deacetylation by inhibiting HDAC activity [see Sections 3.1.1 and 3.1.2], activates transcription by relaxing chromatin structure (*Cell.* 1996;87:5-8, etc.), and induces cell cycle arrest and apoptosis by modulating the expression of *p21*, *Bim*, and other genes [see Sections 3.1.3 and 3.1.4]. These actions of tucidinostat are considered to result in tumor growth inhibition [see Section 3.1.5].

Tucidinostat is expected to be effective in the treatment of ATLL because (i) tucidinostat inhibited the growth of primary cultured cells from patients with ATLL [see Section 3.1.5.1.1], and (ii) the increased expression of HDAC8 was observed in ATLL cells (*Blood.* 2013;121:3640-9).

The applicant's explanation about differences in pharmacological characteristics between tucidinostat and other HDAC inhibitors (vorinostat, panobinostat lactate [panobinostat], and romidepsin) approved in Japan:

These drugs commonly suppress tumor growth by inhibiting histone deacetylation mainly through the inhibition of Class I HDAC isoforms (HDAC1, 2, 3, and 8) and thereby inducing cell cycle arrest and apoptosis, though there are some differences in pharmacological characteristics among the HDAC inhibitors.

- The inhibition of Class IIb HDAC isoform (HDAC10) by tucidinostat, vorinostat, and panobinostat modulate autophagy-related factors, thereby contributing to tumor growth inhibition (*Proc Natl Acad Sci. USA* 2013;25:E2592-601, etc.). However, romidepsin hardly inhibited HDAC10 (*Nat Biotechnol.* 2011;29:255-65).
- Vorinostat, panobinostat, and romidepsin inhibit the deacetylation of non-histone proteins involved in tumorigenesis such as heat-shock protein (HSP) 90 and α-tubulin other than HDACs (*Oncol Ther.* 2016;4:73-89, *Expert Opin Investig Drugs.* 2015;24:965-79, etc.). However, tucidinostat has not been found to inhibit the deacetylation of the above non-histone proteins.

PMDA's view:

The above applicant's explanation is largely acceptable. Most of factors affected by tucidinostat as a HDAC inhibitor remain to be elucidated, and a direct relationship between the inhibition of HDAC activity by tucidinostat and the tumor growth inhibitory effect of tucidinostat is unclear. Because

information about factors affecting the efficacy of tucidinostat in patients with ATLL is potentially critical in predicting the efficacy of tucidinostat and identifying eligible patients in clinical settings, the applicant should continue collecting the information and appropriately inform healthcare professionals of new findings, if any.

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

The pharmacokinetics (PK) of tucidinostat was investigated in animals such as rats. Plasma protein binding, drug-metabolizing enzymes, transporters, etc. of tucidinostat were investigated using biomaterials of human or animal origins.

4.1 Absorption

4.1.1 Repeated-dose administration

Tucidinostat 9, 18, or 36 mg/kg was administered orally once every 2 days for 4 weeks to male and female rats in the fed state, and plasma concentrations of tucidinostat were determined (Table 8). Tucidinostat exposure was higher in females than in males. The applicant explained that this result was potentially attributable to sex differences in the expression of cytochrome P450 (CYP) isoforms in the rat liver (*Toxicol Lett.* 1992;64-65:661-7, etc.). Repeated doses of tucidinostat were found to have no clear impact on the exposure.

Table 8. PK parameters of tucidinostat* (male and female rats, 4-week repeated oral administration)

Day of blood sampling	Dose (mg/kg)	C_{max} (ng/mL)		t_{max} (h)		AUC_{48h} (ng·h/mL)		$t_{1/2}$ (h)	
		Male	Female	Male	Female	Male	Female	Male	Female
Day 1	9	438	712	0.5	0.5	2,610	3,600	6.5	8.8
	18	1,030	2,550	0.5	0.5	5,360	11,600	7.3	15.8
	36	2,520	4,410	0.5	0.5	12,800	16,200	10.2	8.5
Day 27	9	468	817	0.5	0.5	2,740	3,750	6.5	5.5
	18	2,270	2,470	0.5	0.5	6,390	8,980	9.0	8.2
	36	3,670	6,640	0.5	0.5	15,000	21,600	15.9	24.7

* PK parameters were calculated from mean plasma concentrations of tucidinostat at blood sampling (n = 3).

4.1.2 *In vitro* membrane permeability

Membrane permeability of tucidinostat was investigated using human colon cancer-derived cell line Caco-2. The apparent permeability in apical to basolateral direction ($P_{app\ A\rightarrow B}$) of tucidinostat 5 μmol/L was 0.36×10^{-6} cm/second. According to the applicant, tucidinostat has a medium membrane permeability in view of the above result and the fact that the $P_{app\ A\rightarrow B}$ of moderately membrane permeable atenolol 5 μmol/L was 0.24×10^{-6} cm/second.

4.2 Distribution

4.2.1 Tissue distribution

A single dose of ^{14}C-labeled tucidinostat (^{14}C-tucidinostat) 9 mg/kg was administered orally to male pigmented rats in the fasted state, and tissue distribution of the radioactivity was investigated by quantitative whole-body autoradiography. The radioactivity was extensively distributed in the tissues, and the radioactivity level peaked within 8 hours post-dose in most tissues including blood. The maximum radioactivity levels in the adrenal gland and kidney (2.40 and 2.33 μg Eq./g, respectively) were especially higher than that in blood (0.335 μg Eq./g). The radioactivity levels decreased to below the lower limit of quantitation (0.075 μg Eq./g) within 120 hours post-dose in the tissues except for the

uvea, in which the radioactivity was detected even at 840 hours post-dose. The applicant therefore explained that the above findings suggested the binding of tucidinostat or its metabolite to melanin.

4.2.2 Plasma protein binding

Plasma specimens from rats, dogs, and humans and tucidinostat (at concentrations of 0.3-3 μmol/L) were subjected to ultracentrifugation at 37°C for 2.5 hours to investigate the binding of tucidinostat to plasma protein. The plasma protein binding of tucidinostat ranged from 86.4% to 87.9% in rats, from 79.1% to 80.1% in dogs, and from 88.9% to 89.4% in humans.

4.2.3 Distribution in blood cells

Tucidinostat (at concentrations of 0.168, 0.56, and 1.68 μmol/L) was incubated with blood specimens from rats, dogs, and humans at 37°C for 1 hour to investigate the distribution of tucidinostat in blood cells. The distribution of tucidinostat in blood cells ranged from 48.1% to 52.8% in rats, from 52.5% to 57.8% in dogs, and from 59.2% to 76.0% in humans. The applicant explained that the results suggested the distribution of tucidinostat into blood cells.

4.2.4 Placental and fetal transfer

Placental and fetal transfer of tucidinostat was not investigated. According to the applicant, however, tucidinostat may possibly cross the placenta and be distributed in fetuses in light of its physicochemical properties of tucidinostat (molecular weight, 390.41; log P value, 2.3).

4.3 Metabolism

4.3.1 *In vitro*

Tucidinostat (at a concentration of 10 μmol/L) was incubated with rat and human hepatocytes at 37°C for 6 hours to investigate its metabolites. No human-specific metabolites were detected. Amide hydrolyzed metabolite (M1) and monoxide metabolite (M2) were detected in both rat and human hepatocytes.

Tucidinostat (at a concentration of 5 μmol/L) was incubated with human liver microsome at 37°C for 60 minutes in the presence and absence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), to investigate the metabolism of tucidinostat. In the presence of NADPH, tucidinostat was metabolized (residual rate of tucidinostat, 59%), while in the absence of NADPH, it was not metabolized.

The following investigations were conducted on CYP isoforms involved in the metabolism of tucidinostat in humans. The results show that CYP3A4 is the major CYP isoform that is responsible for the metabolism of tucidinostat, according to the applicant. CYP3A-mediated pharmacokinetic interactions of tucidinostat are described in “Section 6.R.3 Pharmacokinetic interactions mediated by CYP3A.”

- Tucidinostat (0.5 μmol/L) was incubated with recombinant human CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at 37°C for 120 minutes in the presence of NADPH. The residual rate of tucidinostat was 45.1% and 63.2% in the presence of CYP3A4 and CYP2D6, respectively, and ≥96.9% in the presence of other CYP isoforms.

- Tucidinostat (1 μmol/L) was incubated[5] with human liver microsome at 37°C for 3 minutes in the presence of inhibitors of CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A)[6] followed by further incubation at 37°C for 60 minutes in the presence of NADPH. Tucidinostat metabolism was inhibited in the presence of the CYP3A inhibitor, while it was almost not inhibited in the presence of inhibitors of other CYP isoforms investigated.

4.3.2 *In vivo*

A single dose of ^{14}C-tucidinostat 9 mg/kg was administered orally to bile duct-cannulated or non-cannulated male rats in the fasted state to investigate metabolites in plasma, urine, feces, and bile. The following results were obtained:

- In plasma collected within 24 hours post-dose from non-bile duct-cannulated male rats, unchanged tucidinostat was mainly detected (accounting for 66.3% of total radioactivity in plasma). In urine until 48hours post-dose and feces until 72 hours post-dose, unchanged tucidinostat was mainly detected (accounting for 18.9% and 30.1%, respectively, of the administered radioactivity).
- In bile collected within 48 hours post-dose from bile duct-cannulated male rats, 2 unidentified metabolites (3.46% and 0.86%) were mainly detected, and unchanged tucidinostat (0.53%) was also detected.

4.4 Excretion

4.4.1 Excretion in urine, feces, bile, and expired air

A single dose of ^{14}C-tucidinostat 9 mg/kg was administered orally to bile duct-cannulated or non-cannulated male rats in the fasted state to investigate urinary, fecal, and biliary excretion rates (percentage relative to the administered radioactivity). The urinary and fecal excretion rates of the radioactivity within 240 hours post-dose were 30.4% and 67.0%, respectively, in non-bile duct-cannulated male rats, and no radioactivity was detected in the expired air by 72 hours post-dose. The urinary, fecal, and biliary excretion rates of the radioactivity within 72 hours post-dose were 14.3%, 65.8%, and 9.49%, respectively, in bile duct-cannulated male rats. According to the applicant, the above results suggest that tucidinostat and its metabolite are mainly excreted in feces.

4.4.2 Excretion in milk

The excretion of tucidinostat in milk was not investigated. The applicant, however, explained that tucidinostat may possibly be excreted in milk in light of its physicochemical properties of tucidinostat (log P value, 2.3).

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[5] Incubation in the presence of CYP1A2 and CYP2A6 inhibitors was extended to 15 minutes.
[6] Inhibitors of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A used were furafylline, 8-methoxypsoralen, thiotepa, quercetin, sulfaphenazole, benzylnirvanol, quinidine, 4-methylpyrazole, and ketoconazole, respectively.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation:

In light of the following results and the steady-state C_{max} (0.1 μmol/L[7]) of unbound tucidinostat after administration of tucidinostat according to the proposed dosage regimen, tucidinostat may possibly cause CYP2C19 or CYP3A inhibition-mediated pharmacokinetic interactions in clinical settings.

- Tucidinostat (at concentrations of 0.0412-30.0 μmol/L) was incubated with human liver microsome in the presence of substrates[8] of CYP isoforms (CYP2C8 and CYP3A), followed by further incubation with NADPH, in order to investigate the inhibitory effect of tucidinostat on each CYP isoform. Tucidinostat inhibited the metabolism of the substrates of CYP2C8 and CYP3A with IC_{50} values of 12.7 and 1.47 μmol/L, respectively.
- Tucidinostat (at concentrations of 0.3-100 μmol/L[9]) was incubated with human liver microsome, followed by further incubation in the presence of substrates of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A)[10] and NADPH, in order to investigate the inhibitory effect of tucidinostat on each CYP isoform. Tucidinostat inhibited the metabolism of the substrates of CYP2C8, CYP2C19, and CYP3A with IC_{50} values of 11.7, 3.2,[11] and 5.08[12] μmol/L, respectively. On the other hand, tucidinostat did not show any clear inhibitory effect on the metabolism of the substrates of other CYP isoforms investigated.
- Tucidinostat (at concentrations of 0.3-100 μmol/L[9]) was incubated with human liver microsome in the presence of NADPH, followed by further incubation in the presence of the substrates[10] of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A), in order to investigate the time-dependent inhibitory effect of tucidinostat on each CYP isoform. Tucidinostat did not show a clear time-dependent inhibitory effect on the metabolism of the substrates of other CYP isoforms investigated.

4.5.2 Enzyme induction

Tucidinostat (at concentrations of 0.3-100 μmol/L) was incubated with human hepatocytes for 48 hours, and the expression level of the messenger ribonucleic acid (mRNA) of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A4) were determined. Tucidinostat at concentrations of 0.3 to 3 μmol/L increased the mRNA expression level of CYP1A2 in a concentration-dependent manner, and the mRNA expression induced by tucidinostat (at a concentration of 3 μmol/L) was 8% to 17% of that induced by the positive control.[13] Tucidinostat (at concentrations of 0.3-1 μmol/L) induced the mRNA expression of CYP2C8 and CYP3A4 to the largest extent (15%-45% and 10%-56%, respectively, of that induced by the positive control[14]) and also the mRNA expression of CYP2B6 was up to 19% of

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7) Calculated from C_{max} on Day 25 in Japanese patients with NHL who orally received tucidinostat 40 mg QD in the fed state twice weekly in Study 201 [see Section 6.2.1.1] and the plasma protein binding [see Section 4.2.2].
8) Substrates of CYP2C8 and CYP3A used were paclitaxel and testosterone, respectively.
9) Tucidinostat was used at concentrations of 0.001 to 10 μmol/L for CYP1A2, CYP2D6, and CYP3A.
10) Substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 used were phenacetin, bupropion, repaglinide, diclofenac, omeprazole, and dextromethorphan, respectively. In addition, substrates of CYP3A used were midazolam and testosterone.
11) IC_{50} determined by measuring 5-hydroxyomeprazole as a metabolite of omeprazole. For reference, IC_{50} determined by measuring desmethylomeprazole was 4.8 μmol/L.
12) IC_{50} determined by using midazolam as a substrate of CYP3A. For reference, IC_{50} determined by using testosterone as the substrate was 6.82 μmol/L.
13) Omeprazole (50 μmol/L) was used as a positive control for induction of CYP1A2 expression.
14) Phenobarbital (1,000 μmol/L) and rifampicin (10 μmol/L) were used as positive controls for induction of CYP2C8 and CYP3A4 expression, respectively.

that induced by the positive control.[15] Although the mRNA expression levels of CYP2B6, CYP2C8, and CYP3A4 increased in the presence of tucidinostat, the increases were not consistently concentration-dependent among human hepatocytes from different donors. Tucidinostat did not induce the mRNA expression of CYP2C9 in a concentration-dependent manner. The applicant explained that tucidinostat is unlikely to cause CYP induction-mediated pharmacokinetic interactions in clinical settings, in light of the above results and the steady-state C_{max} of unbound tucidinostat (0.1 μmol/L[7]) after administration of tucidinostat according to the proposed dosage regimen.

4.5.3 Transporters

The applicant's explanation:

The following results show that tucidinostat is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance associated protein (MRP)2, organic anion transporter (OAT)3, and multidrug and toxin extrusion (MATE)2-K. However, the concomitant use of an OAT3 or MATE2-K inhibitor with tucidinostat is unlikely to cause problems in clinical settings in light of the finding that the CL_r of tucidinostat in humans was <25% of CL [see Section 6.2.1.1]. P-gp-, BCRP-, or MRP2-medicated pharmacokinetic interactions of tucidinostat are described in Section "4.R.2 Pharmacokinetic interactions."

- P-gp-, BCRP-, or MRP2-mediated transport of tucidinostat (at a concentration of 5 μmol/L) was investigated using Caco-2 cells. The efflux ratio (the ratio of permeability coefficient in the secretary direction to that in the absorptive direction) of tucidinostat was 27.2 in the presence of a P-gp inhibitor (valspodar at a concentration of 1 μmol/L), 9.9 in the presence of a BCRP inhibitor (Ko143 at a concentration of 10 μmol/L), and 7.7 in the presence of an MRP2 inhibitor (MK-571 at a concentration of 30 μmol/L) while it was 79.8 in the absence of any inhibitor.
- Transporter-mediated transport of tucidinostat (at concentrations of 1-50 μmol/L[16]) was investigated using HEK293 cells expressing human organic anion transporting polypeptide (OATP)1B1, OATP1B3, OAT1, OAT3, and organic cation transporter (OCT)2 as well as Madin-Darby canine kidney cell line (MDCKII) expressing human MATE1 and MATE2-K. The ratios of uptake of tucidinostat in OAT3- and MATE2-K-expressing cells to that in the non-expressing cells were 2.30 and 2.90, respectively. The ratios of uptake of tucidinostat in OATP1B1-, OATP1B3-, OAT1-, OCT2-, and MATE1-expressing cells to that in the non-expressing cells were all <2.

In light of the following results and the steady-state C_{max} of unbound tucidinostat (0.1 μmol/L[7]) after administration of tucidinostat according to the proposed dosage regimen, tucidinostat is unlikely to cause P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K inhibition-mediated pharmacokinetic interactions in clinical settings.

- The inhibitory effect of tucidinostat (at concentrations of 0.412-100 μmol/L) on the transport of the substrates[17] of each transporter was investigated using MDCK cells expressing human P-gp and BCRP. Tucidinostat did not clearly inhibit the transport of the substrates of P-gp or BCRP.
- The inhibitory effect of tucidinostat (at concentrations of 0.07-50 μmol/L[18]) on the transport of the substrates[19] of each transporter was investigated using HEK293 cells expressing human OATP1B1,

[15] Phenobarbital (1,000 μmol/L) was used as a positive control for induction of CYP2B6.
[16] Tucidinostat was used at concentrations of 1-45 μmol/L for OATP1B1, 5 μmol/L for OAT3, and 1 μmol/L for OCT2 and MATE2-K.
[17] Digoxin (10 μmol/L) and cladribine (10 μmol/L) were used as substrates of P-gp and BCRP, respectively.

OATP1B3, OAT1, OAT3, and OCT2, and MDCKII cells expressing human MATE1 and MATE2-K. Tucidinostat inhibited the transport of the substrate of MATE2-K with IC_{50} of 18.31 μmol/L. At the highest concentration investigated, tucidinostat inhibited the transport of the substrates of OATP1B1, OATP1B3, OAT1, OAT3, and MATE1 by 34%, 37%, 29%, 23%, and 46%, respectively. Tucidinostat, on the other hand, did not clearly inhibit the transport of the substrate of OCT2.

4.R Outline of the review conducted by PMDA

Based on the submitted data and the results of review in the following section, PMDA concluded that the applicant's explanation about the non-clinical pharmacokinetics of tucidinostat is acceptable.

4.R.1 Tissue distribution

The submitted data show that tucidinostat or its metabolite binds to melanin [see Section 4.2.1]. PMDA asked the applicant to explain the safety of tucidinostat in melanin-containing tissues.

The applicant's response:

In light of the following results, tucidinostat is unlikely to cause any safety problems attributable to the distribution of tucidinostat or its metabolite into the melanin-containing tissues in clinical settings.

- In the repeated dose toxicity study in dogs, no toxicity was observed in the eyes or skin [see Section 5.2].
- In a Japanese phase I study (Study 201), a Japanese phase IIb study (Study 210), and a global phase IIb study (Study HBI-8000-203 [Study 203]), events coded to (a) eye disorders and events coded to (b) skin and subcutaneous tissue disorders were analyzed. The incidences of these events in Studies 201, 210, and 203 were as follows: (a) 0% (0 of 14 subjects), 4.3% (1 of 23 subjects), and 9.1% (5 of 55 subjects), respectively, and (b) 21.4% (3 of 14 subjects), 34.8% (8 of 23 subjects), and 41.8% (23 of 55 subjects), respectively. However, most of the events were Grade ≤2, raising no particular safety concerns.

PMDA accepted the applicant's explanation.

4.R.2 Pharmacokinetic interactions

The applicant's explanation about the metabolizing enzymes (CYP2C19 and CYP3A)- and transporters (P-gp, BCRP, and MRP2)-mediated pharmacokinetic interactions of tucidinostat:

The *in vitro* study results suggested that the CYP2C19-, CYP3A-, P-gp-, BCRP-, and MRP2-mediated pharmacokinetic interactions of tucidinostat may occur [see Sections 4.5.1 and 4.5.3].

However, the concomitant use of the substrate of CYP2C19 and CYP3A, and P-gp inhibitors with tucidinostat is unlikely to cause any problem in clinical settings because the substrates of CYP2C19 and CYP3A and P-gp inhibitors concomitantly used with tucidinostat did not raise any particular safety concerns in a Japanese phase I study (Study 201), a Japanese phase IIb study (Study 210), or a global phase IIb study (Study 203).

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[18] Tucidinostat was used at concentrations of 0.06 to 45 μmol/L for OATP1B1 and OAT3

[19] The following substrates were used: (a) Estradiol 17β-D-glucuronide (1 μmol/L) for OATP1B1, (b) cholecystokinin-8 (0.1 μmol/L) for OATP1B3, (c) tenofovir (5 μmol/L) for OAT1, (d) estrone-3-sulfate (1 μmol/L) for OAT3, and (e) metformin (10 μmol/L) for OCT2, MATE1, and MATE2-K.

In contrast, none of the BCRP and MRP2 inhibitors were concomitantly used with tucidinostat in the clinical studies. It is difficult to draw a clear conclusion on whether the concomitant use of these inhibitors with tucidinostat may raise any clinical concern about BCRP- and MRP2-mediated pharmacokinetic interactions. The investigation, however, revealed that tucidinostat is a substrate of BCRP and MRP2 *in vitro*, and this is an important finding. The relevant information will be appropriately communicated to healthcare professionals.

PMDA's view:
PMDA largely accepted the explanation of the applicant. The information about CYP2C19-, CYP3A-, P-gp-, BCRP-, and MRP2-mediated pharmacokinetic interactions of tucidinostat is critical for the proper use of tucidinostat. The relevant information should be provided to healthcare professionals through the package insert. Further, additional information should be collected continuously, and any useful findings should be communicated appropriately to healthcare professionals.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted results from single-dose toxicity, repeated-dose toxicity, genotoxicity, and phototoxicity studies as data on the toxicity of tucidinostat.

Unless otherwise specified, the vehicles used in *in vivo* studies were a deionized water (pH 2.5) containing 10% hydroxypropyl-β-cyclodextrin and 10% propylene glycol and those used in *in vitro* studies were DMSO.

5.1 Single-dose toxicity

A single oral dose crossover study in dogs and oral dose-ranging studies in rats and dogs were conducted to evaluate the acute toxicity of tucidinostat (Table 9).

Table 9. Single-dose toxicity studies

Test system	Route of administration	Dose	Major findings	Approximate lethal dose	Attached document CTD
Male dogs (beagle)	Oral	10 mg, 1.25 mg/kg[a)]	No findings requiring special mention	>10 mg, >1.25 mg/kg	4.2.3.1-1 Reference
Male and female rats (Sprague Dawley)	Oral (repeated for 21 days)	10, 20, 40 mg/kg/day (once every other day [QOD])	Death: 40 mg/kg (3 of 5 males, on Days 20 and 21) ≥20 mg/kg: Low body weight gain, loose stool, piloerection 40 mg/kg: Decreased body weight (male)	Not applicable[b)]	4.2.3.2-1 Reference
Male dogs (beagle)	Oral (repeated for 19 days)	1, 1.5, 2, 2.5 mg/kg/day[c)]	Death or moribund euthanasia: 1 animal treated at 1, 2, and 2.5 mg/kg (died 3 days after dose increase to 2.5 mg/kg), 1 animal treated at 1, 1.5, and 2 mg/kg (moribund euthanized 3 days after dose increase to 2 mg/kg), blood in stool and associated dehydration	Not applicable[d)]	4.2.3.2-4 Reference

a) The dose was 10 mg on Days 1 and 8 as well as 1.25 mg/kg on Day 15.
b) Animals were considered to be intolerable at 40 mg/kg.
c) The dose was 1 mg/kg between Days 1 and 8; 1, 1.5, or 2 mg/kg between Days 9 and 13; and 1.5, 2, or 2.5 mg/kg between Days 14 and 19.
d) Animals were considered to be intolerable at 2 mg/kg.

5.2 Repeated-dose toxicity

Four- and 13-week repeated-dose toxicity studies were conducted in rats and dogs (Table 10). Major findings in these studies include reduced body weight gain associated with decreased food consumption, gastrointestinal toxicity, low erythrocytic and leukocytic parameter values associated with bone marrow depression, atrophic changes of lymphoid tissues, low globulin and albumin values, QTc interval prolonged potentially attributable to low serum potassium and calcium values (dogs), inflammatory changes in the lungs, hemorrhagic findings in the heart (rats), and atrophic tissue changes in the male and female reproductive system.

In terms of tucidinostat exposure, C_{max} and $AUC_{0\text{-}24}$ at the no observed adverse effect level (NOAEL) (3 mg/kg/day in rats and 0.25 mg/kg/day in dogs in the 13-week repeated-dose toxicity studies) were (a) 1.76 ng/mL and 7.00 ng·h/mL in male rats, (b) 6.61 ng/mL and 34.2 ng·h/mL in female rats, (c) 22.0 ng/mL and 55.6 ng·h/mL in male dogs, and (d) 38.1 ng/mL and 79.0 ng·h/mL in female dogs, and these exposures were (a) 0.005 and 0.001 times, (b) 0.017 and 0.006 times, (c) 0.057 and 0.009 times, (d) 0.099 and 0.013 times, respectively, the exposure in humans at the clinical dose.[20)] When compared with the human exposure to tucidinostat, the non-clinical exposure (C_{max} and $AUC_{0\text{-}24}$) at doses resulting in a moribund condition in some of the animals treated (27 mg/kg/day in rats and 1.25 mg/kg/day in dogs) does not have an adequate safety margin, although the dosing frequency differed.

Table 10. Repeated-dose toxicity studies

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	4-week study + 4-week recovery	0, 9, 18, 36 (QOD)	Death: 9 mg/kg (1 of 15 males),[a)] 18 mg/kg (1 of 15 males)[a)] ≥9 mg/kg: Decreased food consumption and body weight; low Ht level (male); low reticulocyte count; low white blood cell, neutrophil, and lymphocyte counts; low total protein (male); low calcium level; low kidney weight (male); low thymus and pituitary gland weights; low submandibular gland weight (female); inflammatory finding in the spleen ≥18 mg/kg: Low Hb level (female), low Ht level, low platelet count (female), low total protein, low albumin value (female), low globulin level, high BUN level, low kidney weight, low submandibular gland weight, bone marrow hypoplasia, thymic atrophy, lymphocyte depletion in the lymphoid tissue 36 mg/kg: Low red blood cell count (male), low Hb level, low platelet count, low albumin level, high GGT level (male), high bilirubin level (male), small thymus (male) Reversibility: Yes[b)]	<9	4.2.3.2-2
Male and female rats (Sprague Dawley)	Oral	13-week study + 4-week recovery	0, 3, 9, 27 (QOD)	Moribund euthanasia: 3 mg/kg (1 of 15 females),[a)] 27 mg/kg (1 of 15 females),[c)] decreased activity, dehydration, hunchback position, etc. ≥3 mg/kg: Decreased food consumption, high MCHC level (male), low prostate gland weight, bone marrow hypoplasia (male) ≥9 mg/kg: Low body weight, high MCHC, low reticulocyte count, low white blood cell and lymphocyte counts (male), low neutrophil count, high BUN level (male), low total protein level, low globulin and albumin levels (female), low calcium level, low pituitary gland weight (male), dark mesenteric lymph node (male), pale spleen foci (male), small thymus (male), dark gastric foci	3	4.2.3.2-3

[20)] C_{max} and $AUC_{0\text{-}t}$ on Day 25 in Japanese patients with NHL who orally received tucidinostat 40 mg QD twice weekly in Study 201 were 385 ng/mL and 6,010 ng·h/mL, respectively [see Section 6.2.1.1].

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
				(female), bone marrow hypoplasia, monocytic inflammation and fibrosis in the spleen (male), anterior pituitary gland atrophy (male), decreased thymic lymphocytes (male), thyroid follicular dilatation, decreased lymph node lymphocytes (male), mammary gland atrophy (male) 27 mg/kg: Low MCH and MCV levels; low white blood cell and lymphocyte counts; low platelet count; high GGT and BUN levels; low globulin and albumin levels; low potassium level; low thymus and pituitary gland weights; dark mesenteric lymph node; splenic adhesion (male); small thymus; dark foci in the lung (male); dark foci in the stomach; dark jejunum and ileum (male); dark foci in the cecum (female); pale pituitary gland and thyroid (male); myocardial hemorrhage and inflammation; alveolar hemorrhage and perivascular edema and fibrosis (male); intraalveolar histiocyte accumulation; gastric hemorrhage (female); jejunal hemorrhage (male); ileal and cecal hemorrhage (female); decreased lymphocytes in the thymus; decreased lymphocytes in the lymph node; mammary gland atrophy Reversibility: Yes[d)]		
Male and female dogs (beagle)	Oral	4-week study + 4-week recovery	0, 0.25, 0.75, 1.25 (QOD on and after Day 13)	Moribund euthanasia: 1.25 mg/kg (3 of 5 males, 1 of 5 females)[e)] ≥0.25 mg/kg: Low thymus weight, thymic atrophy (male) ≥0.75 mg/kg: Low food consumption and body weight; decreased activity (female); inappetence; emaciation; watery, mucous, and discolored feces; QTc interval prolonged; low erythroid parameters; low lymphocyte count; low total protein and albumin levels, and low A/G ratio, abnormal electrolytes (Na, K, Cl, Ca, P); small thymus (female); bone marrow hypoplasia (male); thymus atrophy 1.25 mg/kg: Decreased activity, APTT prolonged, low creatinine level, troponin I positive (female), low spleen weight, small spleen (male), bone marrow hypoplasia, lymphocyte depletion in the spleen, lymphocyte depletion in the mandibular and mesenteric lymph nodes Reversibility: Yes[f)]	0.25	4.2.3.2-5
Male and female dogs (beagle)	Oral	13-week study + 4-week recovery	0, 0.25, 0.75, 1.25 (QOD)	≥0.25 mg/kg: Abnormal gait (male), limited use of limbs (male), low lymphocyte count (male) ≥0.75 mg/kg: Low food consumption (male); hunchback position (female); decreased erythroid parameters; low lymphocyte count; low weights of testis, epididymis, prostate gland, ovary, and uterus; dark red lung with patchy discoloration, etc.; alveolar inflammation; epididymis, prostate gland, ovary, and uterus atrophies; lymphocyte depletion in the gut-associated lymphoid tissue 1.25 mg/kg: Low body weight (male); limited use of limbs; high BUN level; high globulin level; low albumin level; low A/G ratio; low thyroid weight (male); low thymus weight (male); small testis, epididymis, prostate gland, ovary, and uterus; small thymus (female), foreign matter deposition in the thymus; small spleen (male); dark mediastinal lymph node (female); foreign matter deposition in the subcutaneous tissue (male); alveolar hemorrhage; nodal hyperplasia in the spleen (male); seminiferous tubule, uterine cervix, and vagina atrophies; lymphocyte depletion in the thymus; lymphocyte depletion in the mesenteric lymph node; polycythemia in the mediastinal lymph node (female); follicle atrophy in the thyroid (male) Reversibility: Yes[g)]	0.25	4.2.3.2-6

a) None of the findings were considered related to tucidinostat.
b) The following findings remained: low body weight, low white blood cell and lymphocyte counts, low total protein and globulin levels, low thymus weight, and bone marrow hypoplasia.
c) Bacterial infection was suspected from the findings.
d) The following findings remained: high mean corpuscular hemoglobin concentration (MCHC), low white blood cell, neutrophil, and lymphocyte counts, inflammation and fibrosis in the spleen, intraalveolar histiocyte accumulation, gastric edema, anterior pituitary gland atrophy, and thyroid follicular dilatation.

e) All of the findings were considered attributable to pneumonia associated with lymphocyte depletion.
f) Decreased activity and watery, mucous, and discolored feces remained.
g) The following findings remained: high lung weight; low testis, epididymis, and prostate gland weights; alveolar inflammation and fibrosis; seminiferous tubule, epididymis, prostate gland, ovary, uterus, uterine cervix, and vagina atrophies; lymphocyte depletion in the gut-associated lymphoid tissue; and polycythemia in the mediastinal and mandibular lymph nodes.

5.3 Genotoxicity

Genotoxicity studies conducted included *in vitro* studies (bacterial reverse mutation assay and chromosomal aberration assay in cultured cells) and an *in vivo* study (rat micronucleus assay) (Table 11). The applicant explained that results from all the studies were negative, showing tucidinostat to be non-genotoxic.

Table 11. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Result	Attached document CTD
In vitro	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2 *uvrA*	S9−	0, 50, 158, 500, 1,581, 5,000	Negative	4.2.3.3.1-1
			S9+	0, 50, 158, 500, 1,581, 5,000		
	Chromosomal aberration assay in cultured cells	Cultured human peripheral blood lymphocytes	S9− (4 hours)	0, 100, 200, 390	Negative	4.2.3.3.1-2
			S9+ (4 hours)	0, 100, 200, 390[a)]	Negative	
			S9+ (21 hours)	0, 100, 200, 390	Negative	
In vivo	Rat micronucleus assay	Male and female rats (Sprague Dawley) Bone marrow		0, 10, 20, 40 (oral, 2 days)	Negative	4.2.3.3.2-1

a) Precipitates were found in the cultured medium at the end of treatment.

5.4 Carcinogenicity

Because tucidinostat is an antineoplastic agent intended for the treatment of advanced cancer, no carcinogenicity study was conducted in accordance with the ICH S9 guideline.

5.5 Reproductive and developmental toxicity

No reproductive and developmental toxicity study was conducted because (i) tucidinostat is an antineoplastic agent intended for treatment of advanced cancer and (ii) from its pharmacological action, tucidinostat is inferred to affect embryo-fetal development.

The applicant's explanation:

In view of the following points, tucidinostat potentially affect fertility and early embryonic development to implantation as well as embryo-fetal development, and thus its use will be contraindicated in pregnant women or women who may be pregnant:

- In the repeated-dose toxicity studies in rats and dogs [see Section 5.2], atrophy was observed in the male and female reproductive organ systems, suggesting that tucidinostat may affect fertility.
- Tucidinostat is considered to be potentially toxic to embryo-fetal development because literature has reported developmental toxicity, including teratogenicity, attributable to HDAC inhibition which is the mechanism of action of tucidinostat (*Curr Pharm Des.* 2014;20:5438-42, etc.).

5.6 Other studies

5.6.1 Toxicity of impurities

A reverse mutation test of Impurity F, a potential impurity in the drug substance, was conducted (Table 12). The result was positive. The applicant explained that the amount will be controlled to meet the acceptance limit ([redacted] ppm), which is below the acceptable intake specified in the "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" (PSEHB/ELD Notification No. 1110-3 dated November 10, 2015) (ICH M7 guideline).

Table 12. Toxicity study of impurities

Impurity name	Type of study	Concentration (μg/plate)	Result	Attached document CTD
Impurity F	Ames test	0, 15-5,000	Positive	4.2.3.7.6-1 Reference

5.6.2 Phototoxicity

An *in vitro* phototoxicity test was conducted using a mouse fibroblast cell line BALB/c 3T3 (Table 13). The applicant explained that tucidinostat is not phototoxic.

Table 13. Phototoxicity study

Type of study	Test system	Test method	Major findings	Attached document CTD
In vitro Phototoxicity	3T3 NRU method	Cells were treated with tucidinostat at concentrations of 0[a)]-10 μg/mL for 90 minutes, followed by UVA irradiation at 5 J/cm^2 and UVB irradiation at 23-25 mJ/cm^2.	Not phototoxic	4.2.3.7.7-1

a) Phosphate-buffered saline containing 1% DMSO

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the toxicity of tucidinostat is acceptable.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Oral formulations of tucidinostat are available in uncoated tablets and FC tablets, and the PK, etc. of tucidinostat was investigated using these formulations (Table 14). The proposed commercial formulation is FC tablets 10 mg. The bioequivalence between the uncoated 10-mg tablets[21)] and FC 10-mg tablets was confirmed by the dissolution test performed in accordance with the "Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 67 dated February 14, 2000).

[21)] [redacted] is contained. The formulation was used in the Japanese phase IIb study (Study 210) and other studies.

Table 14. Formulations used in each clinical study

Formulation	Study
Uncoated tablets*1 (2.5, 5, and 10 mg)	Foreign phase I studies (Studies TG0702CDM*3 and 101*4), foreign phase II study (Study TG0902CDM*5)
Uncoated tablets*2 (5 and 10 mg)	Japanese phase I study (Study 201), Japanese phase IIb study (Study 210*6), global phase IIb study (Study 203*6), foreign phase Ib/II study (Study 302*6)
FC tablets (10 mg)	Foreign phase I study (Study 304)

*1 [redacted] is not contained.
*2 [redacted] is contained.
*3 [redacted] was used.
*4 [redacted] was used.
*5 [redacted] was used.
*6 [redacted] was used.

6.1.1 Assay

Tucidinostat in human plasma and urine were determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS), and the lower limit of quantitation was 1.00 ng/mL for both specimens.

6.1.2 Foreign clinical study

6.1.2.1 Foreign phase I study (CTD 5.3.1.1-1, Study HBI-8000-304 [Study 304], [redacted] to [redacted])

A 2-treatment, 3-period crossover study was conducted in 16 healthy adults (16 subjects evaluable for PK analysis) to investigate the food effect and the effect of itraconazole on the PK of tucidinostat. On Days 1 and 11, tucidinostat 20 mg was administered orally in the fasted state[22] or 30 minutes after a high-fat meal (lipids accounting for 50% of total calorie [800-1,000 kcal]); on Days 17 to 24, itraconazole 200 mg was administered orally QD[23]; and on Day 21, tucidinostat 20 mg was administered orally in the fasted state.[22] The results on Days 1 and 11 were used to investigate the food effect on the PK of tucidinostat. The effect of itraconazole on the PK of tucidinostat is discussed in "Section 6.2.4.1 Drug interaction study with itraconazole."

The geometric mean ratios [90% confidence interval (CI)] of the C_{max} and AUC_{inf} of tucidinostat after a high-fat meal to those in the fasted state were 0.757 [0.615, 0.932] and 1.09 [0.968, 1.24], respectively. The median t_{max} of tucidinostat was 2.0 hours in the fasted state and 4.5 hours after a high-fat meal. The applicant explained that the decreased C_{max} and delayed t_{max} of tucidinostat after a high-fat meal were considered attributable to a decreased gastric emptying rate.

6.1.3 Effect of gastric pH on the PK of tucidinostat

The applicant's explanation:

A dissolution test was conducted using the proposed commercial formulation. The dissolution of tucidinostat was shown to be ≥[redacted]% in 15 minutes at any pH ranging from [redacted] to [redacted]. In light of this result and other findings, increased gastric pH associated with the use of proton pump inhibitors, etc. was unlikely to affect the PK of tucidinostat.

[22] Tucidinostat was administered after a ≥10-hour fasting period, followed by a ≥4-hour fasting period.
[23] Tucidinostat was administered after a meal except for Day 21, on which it was administered after a ≥10-hour fasting period, followed by a ≥4-hour fasting period.

6.2 Clinical pharmacology

The PK of tucidinostat in healthy adults and patients with cancer was investigated for the administration of tucidinostat alone or in combination with itraconazole.

6.2.1 Japanese clinical study

6.2.1.1 Japanese phase I study (CTD 5.3.3.2-1, Study 201, June 2014 to October 2016)

An open-label, uncontrolled study was conducted in 14 patients with relapsed or refractory NHL (14 patients evaluable for PK analysis) to investigate the PK and other aspects of tucidinostat. In a 28-day treatment cycle, subjects received tucidinostat 30 or 40 mg QD orally twice weekly (Days 1, 4, 8, 11, 15, 18, 22, and 25) in the fed state to determine plasma and urinary concentrations of tucidinostat.

Table 15 shows the PK parameters of tucidinostat. An accumulation ratio of tucidinostat[24)] was 1.24 when it was administered at 40 mg. Unchanged tucidinostat excreted into urine within 72 hours after the first dose of tucidinostat 40 mg accounted for 25.2% of the dose.

Table 15. PK parameters of tucidinostat

Dose (mg)	Day of administration (Day)	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{tau} (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	CL_r (L/h)
30	1	7	199 ± 105	3.98 (2.50, 11.9)	3,740 ± 1,210	17.1 ± 3.15	8.33 ± 2.89	1.88 ± 0.936
	25	6	240 ± 79.6	5.00 (2.47, 12.0)	4,870 ± 1,320	21.6 ± 5.27	6.62 ± 2.04	1.71 ± 1.21*2
40	1	7	590 ± 464	2.42 (1.52, 5.95)	6,760 ± 3,650	19.4 ± 6.51	7.41 ± 5.12	1.75 ± 0.735
	25	4	385 ± 218	4.19 (0.78, 12.0)	6,010 ± 3,500	18.7 ± 2.05	8.97 ± 6.01	1.69 ± 0.627

Mean ± standard deviation (SD); *1 Median (range), *2 n = 5

6.2.2 Global clinical study

6.2.2.1 Global phase IIb study (CTD 5.3.5.4-1, Study 203, ongoing since March 2017 [data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in 55 patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) (26 patients evaluable for PK analysis) to investigate the PK, etc. of tucidinostat. Subjects received tucidinostat 40 mg QD orally twice weekly in the fed state to determine plasma concentrations of tucidinostat.

Table 16 shows the PK parameters of tucidinostat after the first dose.

Table 16. PK parameters of tucidinostat

Population	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{tau} (ng·h/mL)	$t_{1/2}$ (h)
Japanese patients	10	297 ± 149	5.78 (1.83, 7.00)	5,620 ± 1,590	19.6 ± 3.61
Non-Japanese patients*2	16	217 ± 125	6.75 (2.08, 24.1)	4,480 ± 1,590*3	17.2 ± 2.92*4

Mean ± SD; *1 Median (range); *2 Korean; *3 n = 14; *4 n = 13

6.2.3 Foreign clinical studies

6.2.3.1 Foreign phase Ib/II study (CTD 5.3.5.4-2, Study HBI-8000-302 [Study 302], phase Ib cohort, ongoing since August 2016 [data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study[25)] was conducted in 17 patients with advanced solid tumor (17 patients evaluable for PK analysis) to investigate the PK and other aspects of tucidinostat. Subjects

24) Ratio of AUC_{tau} on Day 25 to that on Day 1

received tucidinostat 20 to 40 mg QD orally twice weekly in the fed state, in combination with nivolumab (genetical recombination) (hereinafter referred to as "nivolumab"),[26] to determine plasma concentrations of tucidinostat.

Table 17 shows the PK parameters of tucidinostat after the first dose of tucidinostat.[27]

Table 17. PK parameters of tucidinostat

Dose (mg)	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{24h} (ng·h/mL)
20	3	108 ± 34.5	6.58 (5.00, 6.67)	1,637 ± 489.5
30	7	123 ± 38.4	6.50 (3.13, 26.2)	1,794 ± 497.4
40	7	307 ± 190	4.83 (1.00, 6.58)	4,129 ± 2,154

Mean ± SD; * Median (range)

6.2.4 Drug-drug interaction

6.2.4.1 Drug interaction study with itraconazole (CTD 5.3.1.1-1, Study 304, [redacted] to [redacted] 20[redacted])

A 2-treatment, 3-period crossover study was conducted in 16 healthy adults (16 subjects evaluable for PK analysis) to investigate the food effect and the effect of itraconazole (potent CYP3A inhibitor) on the PK of tucidinostat. Subjects received oral doses of tucidinostat 20 mg in the fasted or fed state on Days 1 and 11; oral doses of itraconazole 200 mg QD on Days 17 to 24; and an oral dose of tucidinostat 20 mg in the fasted state on Day 21. Based on the data of tucidinostat administered in the fasted state, the effect of itraconazole on the PK of tucidinostat was investigated.

The geometric mean ratios [90% CI] of the C_{max} and AUC_{inf} of tucidinostat co-administered with itraconazole to those of tucidinostat alone were 1.41 [1.02, 1.94] and 1.46 [1.23, 1.72], respectively.

6.2.5 Use of tucidinostat in patients with renal impairment

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

The applicant's explanation:
Dose adjustment of tucidinostat is not necessary in patients with renal impairment, in light of the following findings:

- Results from the Japanese phase I study (Study 201) suggest that renal excretion contributes only minimally to the elimination of tucidinostat [see Section 6.2.1.1].
- In the 40 mg cohort of the Japanese phase I study (Study 201) as well as the Japanese phase IIb study (Study 210) and the global phase IIb study (Study 203), analyses were made for Grade ≥3 adverse events and serious adverse events in patients with normal renal function (20 patients), mild renal impairment (31 patients), or moderate renal impairment (34 patients).[28] In patients with normal renal function, those with mild renal impairment, and those with moderate renal impairment, the incidences of Grade ≥3 adverse events were 70.0%, 83.9%, and 88.2%, respectively, and the

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25) Conducted in the US.
26) Nivolumab 240 mg was intravenously administered Q2W.
27) One patient in the 40 mg cohort had remarkably high exposure (C_{max}, 679 ng/mL; AUC_{24h}, 8,170 ng·h/mL). C_{max} and AUC_{24h} (mean ± SD) in the 40 mg cohort excluding the patient were 245 ± 105 ng/mL and 3,455 ± 1,325 ng·h/mL, respectively.
28) Renal function was classified according to the following criteria: normal renal function, CrCL ≥90 mL/min; mild impairment, CrCL ≥60 mL/min and <90 mL/min; and moderate impairment, CrCL ≥30 mL/min and <60 mL/min.

incidences of serious adverse events were 25.0%, 19.4%, and 32.4%, respectively, showing no clear differences in the incidences of adverse events between patients with normal renal function and those with mild or moderate renal impairment.

6.2.6 Relationship between exposure and change in QT/QTc interval

Plasma concentrations of tucidinostat at the time of electrocardiography were measurable in 14 subjects in the phase Ib cohort of a foreign phase Ib/II study (Study 302) Based on the data, a relationship between plasma tucidinostat concentrations and change in Fridericia-corrected QT interval (QTcF) from baseline (ΔQTcF) was investigated using a mixed-effects model. No clear relationship was observed between plasma tucidinostat concentration and ΔQTcF. Further, the upper limit of 90% CI of ΔQTcF was estimated to be <10 milliseconds at C_{max} (geometric mean, 259.3 ng/mL) after a single oral dose of tucidinostat 40 mg in the fed state. Data on QT interval prolonged in clinical studies and review on precautionary advice on QT interval prolonged based on the above data are presented in "Section 7.R.3.4 Cardiac disorder."

6.2.7 PPK analysis

A population pharmacokinetic (PPK) analysis was performed using the non-liner mixed-effects model (software, NONMEM Version 7.3), based on the PK data of tucidinostat (1,052 sampling points in 65 patients) obtained from a Japanese phase I study (Study 201), a global phase IIb study (Study 203), and a foreign phase Ib/II study (Study 302). The PK of tucidinostat was described by a 2-compartment model with first order absorption process through 3 transit compartments and linear elimination process.

Possible covariates for (a) CL/F, (b) Vc/F and Vp/F, and (c) MTT of tucidinostat were (a) body weight, sex, age, race (Asian, Caucasian, and non-Caucasian American), carcinoma, region (Japan, South Korea, and the US), albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, CrCL, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and use of concomitant medications[29]; (b) body weight, sex, age, race (Asian, Caucasian, and non-Caucasian American), carcinoma, region (Japan, South Korea, and the US), albumin, and ECOG PS; and (c) body weight, sex, age, race (Asian, Caucasian, and non-Caucasian American), carcinoma, region (Japan, South Korea, and the US), and ECOG PS. CrCL and sex were selected as significant covariates for CL/F and Vc/F, respectively. According to the applicant, these results suggests that CrCL and sex are unlikely to have clinically significant effects on the PK of tucidinostat in light of the following findings:

- The decreased CrCL was inferred to result in increased AUC of tucidinostat at steady state, but no clear differences in the incidence of adverse events were observed between patients with normal renal function and patients with mild or moderate renal impairment [see Section 6.2.5].
- The C_{max} of tucidinostat at steady state was inferred to be higher in female patients than in male patients, but there was no clear sex difference in the efficacy or safety of tucidinostat.

[29] CYP3A inhibitors and inducers, CYP2D6 inhibitors as well as drugs affecting gastric pH

6.2.8 Relationship between exposure and efficacy or safety

6.2.8.1 Relationship between exposure and efficacy

The data from the global phase IIb study (Study 203) were analyzed to investigate a relationship between steady-state tucidinostat exposure [30)] (C_{max}, C_{min}, and AUC) and response. No clear relationship was observed between tucidinostat exposure and response.

6.2.8.2 Relationship between exposure and safety

The data from the Japanese phase I study (Study 201), the global phase IIb study (Study 203), and the foreign phase Ib/II study (Study 302) were analyzed to investigate relationships between steady-state tucidinostat exposure[30)] (C_{max}, C_{min}, and AUC) and the risks of thrombocytopenia, neutropenia, and lymphopenia. No clear relationship was observed between tucidinostat exposure and the risks of the above adverse events.

6.2.9 Difference in PK of tucidinostat between Japanese and non-Japanese patients

The applicant's explanation:

No clear difference was observed in the PK of tucidinostat between Japanese and non-Japanese patients in light of the following observations:

- No clear difference was observed in the PK of tucidinostat between Japanese and non-Japanese patients [see Section 6.2.2.1].
- Neither race nor region was selected as a significant covariate for the PK parameters of tucidinostat by the PPK analysis [see Section 6.2.7].

6.R Outline of the review conducted by PMDA

Based on the submitted data and review in the following section, PMDA concluded that the applicant's explanation about findings on the clinical pharmacology of tucidinostat is acceptable.

6.R.1 Timing of administration of tucidinostat

The applicant's explanation about the timing of administration of tucidinostat:

Because a foreign phase II study (Study 0901/0902PK[31)]) using the clinical formulation (uncoated tablets[32)]) suggested that the C_{max} and AUC_{inf} of tucidinostat in the fed state were higher than those in the fasted state, the Japanese phase IIb study (Study 210) was designed to employ the administration of tucidinostat in the fed state. The study demonstrated the clinical benefit of tucidinostat. The foreign phase I study (Study 304) later conducted using the proposed commercial formulation (FC tablets) did not show a clear difference in the AUC_{inf} of tucidinostat between administration after a high-fat meal and administration in the fasted state, but suggested that the C_{max} of tucidinostat in the fasted state was 1.32 times higher than that after a high-fat meal [see Section 6.1.2.1]. In addition, because safety information obtained from patients with cancer who received tucidinostat 40 mg in the fasted state was very limited, the proposed Dosage and Administration section includes a precautionary statement that tucidinostat should be administered after a meal.

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30) Estimated by the PPK analysis [see Section 6.2.7].

31) The study was conducted to investigate the food effect on the PK of tucidinostat as a study accompanying Studies TG0901CDM and TG0902CDM in patients with PTCL and those with cutaneous T-cell lymphoma (CTCL).

32) 5-mg tablets not containing [redacted]. The bioequivalence between the clinical formulation and proposed commercial formulation has not been investigated.

PMDA accepted the applicant's explanation. The applicant's explanation and PMDA's conclusion about the dosage regimen are described in "Section 7.R.5.1 Dosage and administration of tucidinostat."

6.R.2 Use of tucidinostat in patients with hepatic impairment

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

The applicant's explanation about the use of tucidinostat in patients with hepatic impairment:
Because tucidinostat is mainly eliminated through hepatic metabolism [see Sections 4.3.1 and 6.2.1.1], hepatic impairment may affect the PK of tucidinostat. In a foreign phase Ib/II study (Study 302), however, there was no clear difference in the incidence of adverse events between patients with normal hepatic function (83 patients) and patients with mild hepatic impairment[33)] (6 patients), and thus the dose adjustment of tucidinostat is not necessary for patients with mild hepatic impairment. In contrast, tucidinostat has not been used in patients with moderate or severe hepatic impairment. The applicant will advise healthcare professionals that the use of tucidinostat in such patients needs due attention. The 40 mg cohort of the Japanese phase I study (Study 201), the Japanese phase IIb study (Study 210), and the global phase IIb study (Study 203) did not include patients with hepatic impairment.

PMDA's view:
The applicant's explanation is largely acceptable. However, tucidinostat is mainly eliminated through hepatic metabolism, and information on the safety of tucidinostat in patients with hepatic impairment (including mild hepatic impairment) is extremely limited. Therefore, the use of tucidinostat in patients with hepatic impairment needs due attention, irrespective of the severity of hepatic impairment, and this precautionary statement should be included in the package insert. The information on the PK of tucidinostat in patients with hepatic impairment is critical for the proper use of tucidinostat, and the relevant information should be collected continuously. New findings should be appropriately communicated to healthcare professionals, if any.

6.R.3 Pharmacokinetic interactions mediated by CYP3A

The applicant's explanation about the concomitant use of tucidinostat with a CYP3A inhibitor or inducer:
In the foreign phase I study (Study 304), tucidinostat exposure was increased by the concomitant use of tucidinostat with a potent CYP3A inhibitor [see Section 6.2.4.1]. For this reason, healthcare professionals should be advised to pay attention to the concomitant use of a potent CYP3A inhibitor. This precautionary statement will be included in the package insert.

Although the concomitant use of tucidinostat with a potent CYP3A inducer may decrease tucidinostat exposure, there was no clear relationship between tucidinostat exposure and response [see Section 6.2.8.1]. Based on this and other findings, such concomitant use is unlikely to raise any concern about the use of tucidinostat in clinical settings.

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

PMDA's view:
PMDA accepted the applicant's explanation about the concomitant use of a CYP3A inhibitor.

In addition, the concomitant use of tucidinostat with a potent CYP3A inhibitor increased tucidinostat exposure in a foreign phase I study (Study 304) [see Section 6.2.4.1], suggesting some contribution of CYP3A to the metabolism of tucidinostat. Given the above result, the concomitant use of tucidinostat with a potent CYP3A inducer may decrease tucidinostat exposure. No clinical studies evaluating the interaction of tucidinostat with potent CYP3A inducers, however, have been conducted, leaving it unknown to what extent concomitant potent CYP3A inducers would decrease tucidinostat exposure. At present, it is difficult to draw a clear conclusion on whether the decrease in tucidinostat exposure would pose concerns about the use of tucidinostat in clinical settings. Accordingly, the applicant should inform healthcare professionals of the involvement of CYP3A4 in the metabolism of tucidinostat [see Section 4.3.1] through the package insert. In addition, the applicant should continuously collect information about the pharmacokinetic interactions of tucidinostat with CYP3A inducers, and should appropriately communicate useful findings to healthcare professionals, if any.

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 2 clinical studies, a Japanese phase I study and a Japanese phase IIb study (Table 18). The applicant also submitted the results from a total of 6 clinical studies, 1 global phase IIb study, 3 foreign phase I studies, 1 foreign phase Ib/II study, and 1 foreign phase II study (Table 18) as reference data.

Table 18. List of clinical studies for efficacy and safety

Data category	Region	Study ID	Phase	Study population	Number of participants	Dosage regimen	Major endpoints
Evaluation	Japan	201	I	Patients with relapsed or refractory NHL	14 (a) 7 (b) 7	Oral dose of tucidinostat (a) 30 or (b) 40 mg QD in the fed state twice weekly (Days 1, 4, 8, 11, 15, 18, 22, and 25)	Safety PK
		210	IIb	Patients with relapsed or refractory ATLL	23	Oral dose of tucidinostat 40 mg QD in the fed state twice weekly*[1]	Efficacy Safety
Reference	Global	203	IIb	Patients with relapsed or refractory PTCL	55	Oral dose of tucidinostat 40 mg QD in the fed state twice weekly*[1]	Efficacy Safety PK
	Foreign	304	I	Healthy adults	16	A single oral dose of tucidinostat 20 mg in the fasted state or after a high-fat meal on Day 1, followed by crossover treatment on Day 11, and then a single oral dose of tucidinostat 20 mg in combination with itraconazole in the fasted state.	PK
		101	I	Patients with advanced solid tumor and patients with relapsed or refractory malignant lymphoma	25	In a 4-week cycle, oral dose of tucidinostat 5-25 mg QD in the fed state 3 times weekly (Days 1, 3, 5, 8, 10, 12, 15, 17, and 19).	Safety PK
		TG0702CDM	I	Patients with advanced solid tumor and patients with relapsed or refractory malignant lymphoma	31	In a 6-week cycle, oral dose of tucidinostat 5-50 mg QD twice weekly or 32.5 or 50 mg QD 3 times weekly in the fed state from Weeks 1 to 4.	Safety PK
		302	Ib/II	Patients with advanced solid tumor*[2]	89 (a) 17 (b) 72	(a) Oral dose of tucidinostat 20, 30, or 40 mg QD twice weekly in the fed state, in combination with intravenous nivolumab 240 mg Q2W (b) Oral dose of tucidinostat 30 mg QD in the fed state twice weekly, in combination with nivolumab*[3]	Efficacy Safety PK
		TG0902CDM	II	Patients with relapsed or refractory PTCL	102 (a) 19 (b) 83	(a) In a 6-week cycle, oral dose of tucidinostat 30 or 50 mg QD in the fed state twice weekly at Weeks 1, 2, 4, and 5. (b) In a 6-week cycle, oral dose of tucidinostat 30 mg QD in the fed state twice weekly.	Efficacy Safety

*[1] Doses were given every 3 or 4 days.
*[2] Patients with malignant melanoma, renal cell carcinoma, or non-small cell lung cancer (NSCLC) were included in the study.
*[3] Nivolumab was administered in accordance with the package insert and institutional procedures.

Each clinical study is summarized in the sections below. The major adverse events other than death observed in each clinical study are described in Section "7.3 Adverse events 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 study

7.1.1.1 Japanese phase I study (CTD 5.3.3.2-1, Study 201, June 2014 to October 2016)

An open-label, uncontrolled study was conducted at 8 study sites in Japan to investigate the safety, PK, and other aspects of tucidinostat in patients with relapsed or refractory NHL (target sample size, up to 18 subjects).

Subjects received oral doses of tucidinostat 30 or 40 mg QD in the fed state twice weekly (Days 1, 4, 8, 11, 15, 18, 22, and 25). Subjects continued the treatment until any of the treatment discontinuation criteria was met.

Of 22 patients enrolled in the study, 14 patients (7 in 30 mg cohort, 7 in 40 mg cohort) received tucidinostat[34] and were included in the safety analysis population. Of those included in the safety analysis population, 12 patients[35] were included in dose limiting toxicity (DLT) evaluation.

During the DLT evaluation period of 28 days after the start of treatment, DLT was observed in 2 of 6 patients in the 40 mg cohort (Grade 3 ALT increased and Grade 4 neutropenia in 1 patient each). The Grade 3 ALT increased was asymptomatic and resolved immediately after discontinuation of tucidinostat, and the Grade 4 neutropenia resolved immediately after administration of a granulocyte colony stimulating factor (G-CSF) preparation. In light of the above findings, the maximum tolerated dose (MTD) of tucidinostat was centrally determined to be 40 mg QD twice weekly.

No deaths occurred during treatment with tucidinostat or within 35 days after the end of treatment.

7.1.1.2 Japanese phase IIb study (CTD 5.3.5.2-1, Study 210, ongoing since November 2016 [data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 20 study sites in Japan to investigate the efficacy and safety of tucidinostat in patients with relapsed or refractory ATLL[36] (target sample size, 22 subjects).

Subjects received oral doses of tucidinostat 40 mg QD in the fed state twice weekly (at intervals of 3 or 4 days). Subjects continued the treatment until any of the treatment discontinuation criteria was met.

Of 29 patients enrolled in the study,[37] 23 patients received tucidinostat and were included in the efficacy and safety analysis populations.

The primary endpoint in the study was the response rate centrally accessed according to the partially modified version of the criteria proposed by the International Conference on Human Retrovirology (*J Clin Oncol.* 2009;27:453-9) (Table 19).

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34) Of the patients who did not receive tucidinostat, 6 patients failed to meet the inclusion criteria and 2 patients withdrew the informed consent.

35) Of the patients excluded from the DLT evaluation, 1 patient in the 30 mg cohort was found to have not met the inclusion criteria after receiving tucidinostat and 1 patient in the 40 mg cohort received tucidinostat at a reduced dose owing to adverse events other than DLT.

36) The study included patients with relapsed or refractory ATLL who were classified as acute type, lymphoma type, or chronic type ATLL with poor prognostic factors and who had been previously treated with mogamulizumab (genetical recombination) (hereinafter "mogamulizumab") or were intolerable to mogamulizumab

37) Of the patients, 6 patients failed to meet the inclusion criteria.

Table 19. Modified Criteria of International Conference on Human Retrovirology

Overall response	Sum of the products of the greatest diameters of target lesion	Non-target lesion		Hepatomegaly, splenomegaly	Skin lesion (mSWAT)*[1]	Peripheral blood image	Bone marrow tumor cell infiltration	New lesion
		Nodal	Extranodal					
CR*[2]	Normal	Normal	Disappeared	Disappeared	No skin lesion	Abnormal lymphocyte count <5% of white blood cell count, and lymphocyte count <4000/μL	Negative	Not found
CRu*[2]	≥75% decrease	Normal	Disappeared	Disappeared	No skin lesion	Same as above	Negative	Not found
PR*[2]	≥50% decrease	No increase	No increase	No aggravation	≥50% decrease	≥50% decrease	Unchanged (untested)	Not found
SD*[2]	<50% decrease or increase	No increase	No increase	No aggravation	Neither PR nor PD	Unchanged	Unchanged (untested)	Not found
PD	≥50% increase	Increase	Increase	Aggravated	≥25% increase or new mass*[3]	≥50% increase from nadir, and lymphocyte count ≥4000/μL	Positive after negative conversion	Found

*[1] Skin lesion was assessed according to modified Severity Weighted Assessment Tool (mSWAT) (*Arch Dermatol.* 2002;138:42-8).
*[2] ≥4 weeks of maintenance is not required.
*[3] Increase in mSWAT score in patients achieving complete response (CR) or partial response (PR) is greater than a 50% increase from the sum of nadir and baseline.

Table 20 shows the response rate[38] centrally assessed according to the Modified Criteria of the International Conference on Human Retrovirology, which was the primary endpoint.

Table 20. Best overall response and response rate (central assessment, efficacy analysis population, data cut-off on [redacted], 20[redacted])

Best overall response	n (%) N = 23
CR	1 (4.3)
CRu	0
PR	6 (26.1)
SD	5 (21.7)
PD	11 (47.8)
Response (CR, CRu, or PR) (response rate [95% CI] [%]*)	7 (30.4 [13.2, 52.9])

* Exact confidence interval based on binomial distribution

The centrally assessed response rate [95% CI] in patients with relapsed[39] ATLL was 38.9% [17.3, 64.3] (7 of 18 patients), and that in patients with refractory[40] ATLL was 0% [0, 52.2] (0 of 5 patients).

Deaths occurred in 2 of 23 patients (8.7%) during treatment with tucidinostat or within 30 days after the end of treatment due to disease progression for both.

7.2 Reference data

7.2.1 Clinical pharmacology

The applicant submitted results from a clinical pharmacology study in healthy adults shown below [see Sections 6.1.2.1 and 6.2.4.1]. In the study, no deaths occurred during treatment with tucidinostat or within 10 days after the end of treatment.

38) The threshold clinically meaningful for patients with relapsed or refractory ATLL was specified at 5% in view of the response rate to conventional treatment in such patients (*Oncology* 2009;14:1250-6 and *J Clin Oncol* 2012;30:837-42).
39) Patients who achieved at least stable disease (SD) after the last treatment
40) Patients who experienced progressive disease (PD) after the last treatment

7.2.1.1 Foreign phase I study (CTD 5.3.1.1-1, Study 304, [redacted] to [redacted] 20[redacted])

7.2.2 Global study

7.2.2.1 Global phase IIb study (CTD 5.3.5.4-1, Study 203, ongoing since March 2017 [data cut-off on [redacted] [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 31 study sites in 2 countries including Japan to investigate the efficacy, safety, and PK of tucidinostat in patients with relapsed or refractory PTCL (target sample size, 50-60 subjects).

Of 74 patients enrolled in the study, 55 patients (including 39 Japanese patients) received tucidinostat and were included in the safety analysis population.

Death occurred in 1 of 55 patients (1.8%, pneumonia) during treatment with tucidinostat or within 30 days after the end of treatment, but its causal relationship to tucidinostat was ruled out (none of the Japanese patients died).

7.2.3 Foreign clinical studies

7.2.3.1 Foreign phase I study (CTD 5.3.3.2-2, Study HBI-8000-101 [Study 101], [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted at 2 study sites overseas to investigate the safety and PK of tucidinostat in patients with advanced solid tumor or patients with relapsed or refractory malignant lymphoma (target sample size, 17-30 subjects).

All of 25 patients[41)] enrolled in the study (1 in the 5 mg cohort, 2 in the 10 mg cohort, 3 in the 20 mg cohort, and 6 in the 25 mg cohort for administration of tucidinostat in the fasted state; 3 in the 20 mg cohort, 5 in the 25 mg, and 5 in the 30 mg cohorts for administration of tucidinostat in the fed state) received tucidinostat and were included in the safety analysis population.

Deaths occurred in 2 of 25 patients (8.0%) during treatment with tucidinostat or within 35 days after the end of treatment due to cardio-respiratory arrest in 1 patient each in the 25 mg cohort in the fasted state and 30 mg cohort in the fed state. A causal relationship to tucidinostat could not be ruled out for cardio-respiratory arrest in the 25 mg cohort in the fasted state.

7.2.3.2 Foreign phase I study (CTD 5.3.3.2-3, Study TG0702CDM, [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted at a single study site overseas to investigate the safety and PK of tucidinostat in patients with advanced solid tumor or patients with relapsed or refractory malignant lymphoma (target sample size, 24-40 subjects).

All of 31 patients enrolled in the study received tucidinostat and were included in the safety analysis population.

41) Only patients with solid tumor were enrolled, and patients with malignant lymphoma were not.

No deaths occurred during treatment with tucidinostat or within 28 days after the end of treatment.

7.2.3.3 Foreign phase Ib/II study (CTD 5.3.5.4-2, Study 302, ongoing since August 2016 [data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 6 study sites overseas to investigate the efficacy, safety, and PK of tucidinostat in combination with nivolumab in patients with advanced solid tumor (target sample size, up to 18 subjects in phase Ib, up to 100 subjects in phase II).

All of 89 patients enrolled in the study (17 in phase Ib [3 in the 20 mg cohort, 7 in the 30 mg cohort, 7 in the 40 mg cohort], 72 in phase II) received the study drug and were included in the safety analysis population.

Deaths occurred in 1 of 3 patients (33.3%, pneumonia) in the 20 mg cohort, 1 of 7 patients (14.3%, hepatic failure/acute kidney injury/septic shock/acidosis) in the 30 mg cohort, and 1 of 7 patients (14.3%, pulmonary embolism) in the 40 mg cohort in the phase Ib part and 3 of 72 patients (4.2%, cardiac failure congestive, aortic valve disease, and cardiac arrest in 1 patient each) in the phase II part during the study drug treatment or within 30 days after the end of treatment. A causal relationship to the study drug could not be ruled out for the death due to hepatic failure/acute kidney injury/septic shock/acidosis in 1 patient in the 30 mg cohort in the phase Ib part.

7.2.3.4 Foreign phase II study (CTD 5.3.5.4-3, Study TG0902CDM, May 2009 to September 2012)

An open-label, uncontrolled study was conducted at 13 study sites overseas for the exploratory part and 15 study sites overseas for the pivotal part to investigate the efficacy and safety of tucidinostat in patients with relapsed or refractory PTCL (target sample size, 26 subjects in exploratory part, 79 subjects in pivotal part).

All of 102 patients enrolled in the study (19 in the exploratory part, 83 in the pivotal part) received tucidinostat and were included in the safety analysis population.

Deaths occurred in 3 of 83 patients (3.6%) in the pivotal part during treatment with the study drug or within 1 month after the end of treatment, and the causes of the deaths were sudden cardiac death (1 patient), intestinal perforation (1 patient), and lactic acidosis/hepatic function abnormal (1 patient). A causal relationship to the study drug could not be ruled out for sudden cardiac death (1patient) and hepatic function abnormal (1 patient).[42)]

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA considered that, among the evaluation data submitted, the Japanese phase IIb study (Study 210) conducted in patients with relapsed or refractory ATLL was the pivotal clinical study for evaluating the efficacy and safety of tucidinostat, and decided to evaluate the submitted data focusing on this study.

[42)] A causal relationship between the hepatic function abnormal and the study drug was considered to be unclassifiable.

7.R.2 Efficacy

As a result of the following review, PMDA concluded that the efficacy of tucidinostat in patients with relapsed or refractory ATLL had been demonstrated to a certain extent.

7.R.2.1 Efficacy endpoint and evaluation results

In Study 210, the lower limit of 95% CI of the response rate centrally accessed according to the Modified Criteria of International Conference on Human Retrovirology, the primary endpoint, exceeded the predetermined response threshold (5%) [see Section 7.1.1.2].

Figure 1 shows the maximum percent change in overall tumor size (sum of the products of the greatest diameters) of nodal and extranodal target lesions in patients who had measurable lesions at baseline. The median [95% CI] (months) of the duration of centrally assessed response, the secondary endpoint, was 6.5 [2.6, -].[43)]

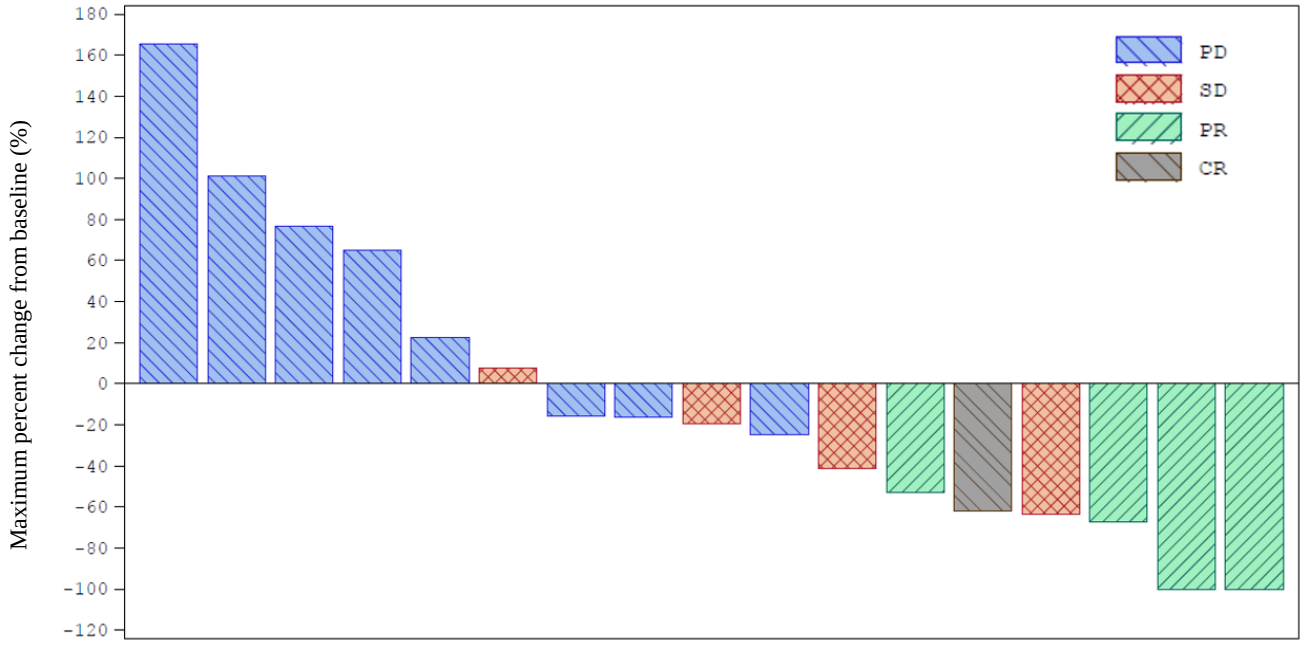

Figure 1. Maximum percent change in overall tumor size (sum of the products of the greatest diameters) of nodal and extranodal target lesions
(Modified Criteria of International Conference on Human Retrovirology, Study 210, efficacy analysis population, central assessment)

In Study 210, the response rate for each disease type assessed according to the Modified Criteria of International Conference on Human Retrovirology was 46.2% (6 of 13 patients) for acute type, 12.5% (1 of 8 patients) for lymphomatous type, and 0% (0 of 2 patients) for chronic type with poor prognostic factors.[44)]

43) The duration of response ranged from 0 to 9.3 months.
44) Defined as the presence of at least one of serum albumin <3.5 g/dL, lactate dehydrogenase (LDH) >300 U/L, and blood urea nitrogen (BUN) >25 mg/dL

The applicant's explanation about the response rate assessed according to the Modified Criteria of International Conference on Human Retrovirology, the primary endpoint of Study 210:
Patients with relapsed or refractory ATLL has poor prognosis, and there is no established standard treatment that prolongs overall survival (OS). Patients with ATLL have serious disease-related symptoms such as generalized swollen lymph nodes and skin eruption, which adversely affect their quality of life. Treatment response in such patients represents a decrease in tumor size, which is expected to alleviate accompanying symptoms, delay disease progression, and extend time to the next treatment, and thus it is considered clinically meaningful.

PMDA's view:
The applicant's explanation about the efficacy endpoints is understandable. Based on the above results, tucidinostat was shown to be effective in patients with relapsed or refractory ATLL to a certain extent. The applicant also should appropriately provide information about the efficacy of tucidinostat for each disease type to healthcare professionals using information materials.

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

PMDA's view:
As a result of the review presented in the subsections below, the following adverse events requiring due attention during treatment with tucidinostat were identified: myelosuppression, infection, interstitial lung disease (ILD), and arrhythmia (including QT interval prolonged). Patients should be carefully monitored for the risk of these adverse events during treatment with tucidinostat.

Although the above-mentioned adverse events require due attention during treatment, tucidinostat will be well tolerable if physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies take appropriate measures such as monitoring and controlling of these adverse events and dose interruption, dose reduction, and discontinuation of tucidinostat. Clinical experience with the use of tucidinostat in Japanese patients, however, is extremely limited, and thus post-marketing safety information should be further collected [see Section 7.R.6].

7.R.3.1 Safety profile of tucidinostat

The applicant's explanation about the safety profile of tucidinostat:
Table 21 shows the summary of safety in Study 210 and the 40 mg cohort of Study 201.

Table 21. Summary of safety (Study 210 and 40 mg cohort of Study 201)

	n (%)	
	Study 210 N = 23	40 mg cohort of Study 201 N = 7
Any adverse event	23 (100)	7 (100)
Events for which a causal relationship to tucidinostat cannot be ruled out	23 (100)	7 (100)
Grade ≥3 adverse events	18 (78.3)	6 (85.7)
Adverse event leading to death	0	0
Serious adverse events	7 (30.4)	1 (14.3)
Adverse events leading to treatment discontinuation	9 (39.1)	4 (57.1)
Adverse events leading to dose interruption	10 (43.5)	3 (42.9)
Adverse events leading to dose reduction	4 (13.0)	2 (28.6)

Table 22 shows all-Grade adverse events occurring in ≥20% of patients in either Study 210 or the 40 mg cohort of Study 201.

Table 22. Adverse events occurring in ≥20% of patients in either study (Study 210 and 40 mg cohort of Study 201)

SOC PT*	n (%)			
	Study 210 N = 23		40 mg cohort of Study 201 N = 7	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	23 (100)	18 (78.3)	7 (100)	6 (85.7)
Blood and lymphatic system disorders				
Anaemia	8 (34.8)	4 (17.4)	0	0
Thrombocytopenia	3 (13.0)	3 (13.0)	4 (57.1)	2 (28.6)
Neutropenia	1 (4.3)	1 (4.3)	2 (28.6)	2 (28.6)
Gastrointestinal disorders				
Diarrhoea	6 (26.1)	0	1 (14.3)	0
Nausea	3 (13.0)	0	2 (28.6)	0
General disorders and administration site conditions				
Malaise	7 (30.4)	0	0	0
Pyrexia	3 (13.0)	0	2 (28.6)	1 (14.3)
Infections and infestations				
Nasopharyngitis	0	0	2 (28.6)	0
Investigations				
Platelet count decreased	15 (65.2)	9 (39.1)	3 (42.9)	0
Neutrophil count decreased	11 (47.8)	9 (39.1)	0	0
White blood cell count decreased	9 (39.1)	7 (30.4)	1 (14.3)	1 (14.3)
Weight decreased	4 (17.4)	1 (4.3)	2 (28.6)	0
Musculoskeletal and connective tissue disorders				
Back pain	4 (17.4)	0	2 (28.6)	0
Metabolism and nutrition disorders				
Decreased appetite	8 (34.8)	0	2 (28.6)	0
Hypocalcaemia	0	0	3 (42.9)	0

* Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) ver.21.1 applied to Study 210, and MedDRA/J ver.19.1 to Study 201

Serious adverse events reported in Study 210 were platelet count decreased in 2 patients (8.7%), neutrophil count decreased, palpitations, *Pneumocystis jirovecii* pneumonia, urinary tract infection, acute respiratory failure, and ILD in 1 patient each (4.3%, some patients had more than one event). A causal relationship to tucidinostat could not be ruled out for any of the above events except for acute respiratory failure. Adverse events leading to discontinuation of tucidinostat in ≥2 patients were platelet count decreased and neutrophil count decreased in 3 patients each (13.0%), and a causal relationship to tucidinostat could not be ruled out for the two events. Adverse events leading to dose interruption of tucidinostat in ≥2 patient were neutrophil count decreased in 5 patients (21.7%) and

platelet count decreased in 4 patients (17.4%). Adverse events leading to dose reduction of tucidinostat in ≥2 patient were platelet count decreased in 2 patients (8.7%). No adverse events led to death.

Serious adverse events in the 40 mg cohort of Study 201 were abdominal pain and enterocolitis in 1 patient each (14.3%, some patients had more than one event). A causal relationship to tucidinostat could not be ruled out for abdominal pain. Adverse events leading to interruption of tucidinostat in ≥2 patient were platelet count decreased in 2 patients (28.6%). There was no adverse event leading to death or adverse events leading to discontinuation or dose reduction of tucidinostat in ≥2 patient.

PMDA's view:
Patients should be carefully monitored during treatment with tucidinostat for the risk of serious adverse events, Grade ≥3 adverse events, and adverse events leading to discontinuation of tucidinostat reported in Study 210, the 40 mg cohort of Study 201, and a global phase IIb study in patients with relapsed or refractory PTCL (Study 203) [see Section 7.3.8]. Information on the incidence of these events should be appropriately provided to healthcare professionals using the package insert.

In the following subsection, PMDA conducted a review with the focus on serious adverse events for which a causal relationship to tucidinostat could not be ruled out and adverse events listed in the warnings and precautions section of the foreign labels, mainly based on the safety results in Study 210, and also checked the incidences of serious adverse events and Grade ≥3 adverse events in Studies 201 and 203. Because clinical experience with the use of tucidinostat is extremely limited, other submitted clinical study data and foreign post-marketing information were checked for the uncommonly reported events.

7.R.3.2 Myelosuppression

The applicant's explanation about myelosuppression associated with the use of tucidinostat:
Myelosuppression-related adverse events were tabulated based on preferred terms (PTs) coded to the Medical Dictionary for Regulatory Activities (MedDRA), standardized MedDRA queries (SMQ) "Haematopoietic cytopenias (broad)."

Table 23 shows the incidences of myelosuppression in Study 210.

Table 23. Incidences of myelosuppression in ≥2 patient (Study 210)

PT (MedDRA/J ver.21.1)	n (%) N = 23	
	All Grades	Grade ≥3
Myelosuppression	19 (82.6)	16 (69.6)
Platelet count decreased	15 (65.2)	9 (39.1)
Neutrophil count decreased	11 (47.8)	9 (39.1)
White blood cell count decreased	9 (39.1)	7 (30.4)
Anaemia	8 (34.8)	4 (17.4)
Thrombocytopenia	3 (13.0)	3 (13.0)
Lymphocyte count decreased	2 (8.7)	1 (4.3)

In Study 210, serious myelosuppression occurred in 2 patients (8.7%, platelet count decreased in 2 patients, neutrophil count decreased in 1 patient [some patients had more than one event]). A causal relationship to tucidinostat could not be ruled out for any of the events. Myelosuppression leading to

discontinuation of tucidinostat was observed in 5 patients (21.7%), myelosuppression leading to dose interruption in 15 patients (65.2%), and myelosuppression leading to dose reduction in 1 patient (4.3%). There was no fatal myelosuppression.

In Study 201, Grade ≥3 myelosuppression occurred in 4 patients (57.1%, neutrophil count decreased in 2 patients; neutropenia, anaemia, lymphocyte count decreased, and white blood cell count decreased in 1 patient each [some patients had more than one event]) in the 30 mg cohort and 3 patients (42.9%, neutropenia and thrombocytopenia in 2 patients each; white blood cell count decreased in 1 patient [some patients had more than one event]) in the 40 mg cohort. There was no fatal myelosuppression or serious myelosuppression.

In Study 203, Grade ≥3 myelosuppression occurred in 41 patients (74.5%; events reported by ≥5% of patients were platelet count decreased in 17 patients, neutrophil count decreased in 15 patients, thrombocytopenia in 11 patients, anaemia in 9 patients, white blood cell count decreased in 9 patients each, lymphocyte count decreased in 8 patients, neutropenia in 5 patients, lymphopenia in 4 patients, and febrile neutropenia in 3 patients [some patients had more than one event]). Serious myelosuppression occurred in 3 patients (5.5%, febrile neutropenia in 2 patients, aplastic anaemia in 1 patient). A causal relationship to tucidinostat could not be ruled out for any of the events. There was no fatal myelosuppression.

PMDA's view:
In Japanese and foreign clinical studies, Grade ≥3 myelosuppression associated with the use of tucidinostat commonly occurred, and serious myelosuppression for which a causal relationship to tucidinostat could not be ruled out occurred in multiple patients. Taking account of the above results, patients should be carefully monitored for the risk of myelosuppression during treatment with tucidinostat. Thus, the applicant should provide healthcare professionals with information on the incidence of myelosuppression in the clinical studies. In addition, the package insert should include a precautionary statement that appropriately advises healthcare professionals to perform periodical hematological tests in patients during treatment with tucidinostat and then take measures such as dose interruption, dose reduction, and discontinuation of tucidinostat, if any abnormality is found.

7.R.3.3 Infection

The applicant's explanation about infection associated with the use of tucidinostat:
Adverse events related to infection were tabulated by PTs coded to the MedDRA system organ class (SOC) "Infections and infestations."

Table 24 shows the incidences of infection in Study 210.

Table 24. Incidences of infection (Study 210)

PT (MedDRA/J ver.21.1)	n (%) N = 23	
	All Grades	Grade ≥3
Infection	7 (30.4)	3 (13.0)
Urinary tract infection	1 (4.3)	1 (4.3)
Device related infection	1 (4.3)	1 (4.3)
Pneumocystis jirovecii pneumonia	1 (4.3)	1 (4.3)
CMV infection	1 (4.3)	0
Hordeolum	1 (4.3)	0
Oral candidiasis	1 (4.3)	0
Skin infection	1 (4.3)	0
Tonsillitis	1 (4.3)	0
Upper respiratory tract infection	1 (4.3)	0
Bacterial infection	1 (4.3)	0

In Study 210, serious infection occurred in 2 patients (8.7%, urinary tract infection and *Pneumocystis jirovecii* pneumonia in 1 patient each), and a causal relationship to tucidinostat could not be ruled out for either of the events. Infection leading to discontinuation of tucidinostat was observed in 1 patient (4.3%) and infection leading to dose interruption in 1 patient (4.3%). There was no infection leading to death or infection leading to dose reduction of tucidinostat.

In Study 201, there was no Grade ≥3 infection, fatal infection, or serious infection.

In Study 203, Grade ≥3 infection occurred in 3 patients (5.5%, pharyngitis, pneumonia, enterocolitis infectious, staphylococcal skin infection, and *Pneumocystis jirovecii* pneumonia in 1 patient each [some patients had more than one event]). Infection leading to death occurred in 1 patient (1.8%, pneumonia), and its causal relationship to tucidinostat could not be ruled out. Serious infection occurred in 2 patients (3.6%, pharyngitis, pneumonia, and *Pneumocystis jirovecii* pneumonia in 1 patient each [some patients had more than one event]). A causal relationship to tucidinostat could not be ruled out for pneumonia (1 patient) or *Pneumocystis jirovecii* pneumonia (1 patient).

PMDA asked the applicant to explain (a) the implementation status of screening and monitoring for opportunistic infection (including viral reactivation) and hepatitis B virus (HBV) infection and (b) the incidence of opportunistic infection and HBV infection and the implementation status of preventive treatment in Study 210.

The applicant's response:
Regarding (a) above, patients who were positive for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), or hepatitis B core antibody (anti-HBc) with HBV-DNA positive at screening were excluded.

Regarding (b) above, the protocol did not specify preventive treatment against opportunistic infection and HBV infection, but the preventive treatment was provided at the discretion of the investigator as described below.

- No preventive treatments for cytomegalovirus (CMV) infection[45)] were provided. CMV infection occurred in 1 of 23 patients (4.3%).

[45)] Tabulated by PTs coded to the MedDRA high level term (HLT) "Cytomegaloviral infections."

- Preventive treatment for *Mycobacterium tuberculosis* infection[46)] was provided to 3 of 23 patients (13.0%). *Mycobacterium tuberculosis* infection did not occur irrespective of preventive treatment status.
- Preventive treatment for *Pneumocystis jirovecii* infection[47)] was provided to 16 of 23 patients (69.6%). *Pneumocystis jirovecii* infection did not occur in patients who had received preventive treatment but occurred in 1 of 7 patients (1.4%) who had not received preventive treatment.
- Preventive treatment for varicella zoster virus (VZV) infection[48)] was provided to 5 of 23 patients (21.7%). VZV infection did not occur irrespective of preventive treatment status.
- Preventive treatment for HBV infection[49)] was provided to 1 of 23 patients (4.3%). HBV infection did not occur irrespective of preventive treatment status.

PMDA's view:
Serious and fatal infections (including opportunistic infections) for which a causal relationship to tucidinostat could not be ruled out occurred in multiple patients, although the number of patients included in the foreign and Japanese clinical studies is limited. Given the above findings, patients should be carefully monitored for the risk of infection during treatment with tucidinostat. The applicant should appropriately warn healthcare professionals of the risk of infection by providing information on the incidence of infection including opportunistic infection in the clinical studies through the package insert. In addition, the safety measures against infection such as preventive treatment taken in Study 210 should also be communicated to healthcare professionals via the information materials.

7.R.3.3 ILD

The applicant's explanation about ILD associated with the use of tucidinostat:
Adverse events related to ILD were tabulated by PTs coded to the MedDRA SMQ "Interstitial lung disease (narrow)."

In Study 210, all-Grade ILD occurred in 1 patient (4.3%, ILD), and Grade ≥3 ILD occurred in 1 patient (4.3%, ILD). Serious ILD occurred in 1 patient (4.3%, ILD), and its causal relationship to tucidinostat could not be ruled out. ILD leading to discontinuation of tucidinostat occurred in 1 patient (4.3%, ILD). There was no ILD resulting in death or ILD leading to dose interruption or dose reduction of tucidinostat.

In Study 201, there was no Grade ≥3 ILD, fatal ILD, or serious ILD.

In Study 203, Grade ≥3 ILD occurred in 3 patients (5.5%, pneumonitis in 2 patients, ILD in 1 patient). There was no fatal ILD. Serious ILD occurred in 2 patients[50)] (3.6%, ILD and pneumonitis in 1 patient each), and a causal relationship to tucidinostat could not be ruled out for either of the events.

46) Tabulated by PTs coded to the MedDRA HLT "Tuberculous infections."
47) Tabulated by PTs coded to the MedDRA HLT "*Pneumocystis* infections."
48) Tabulated by PTs coded to the MedDRA HLT "*Herpes virus* infections."
49) Tabulated by PTs coded to the MedDRA HLT "Hepatitis viral infections."
50) Both were Japanese patients.

PMDA's view:
Serious ILDs for which a causal relationship to tucidinostat could not be ruled out occurred in multiple patients, although the number of patients included in the Japanese and foreign clinical studies was limited. Given the above and other findings, patients should be carefully monitored for the risk of ILD during treatment with tucidinostat. Thus, the applicant should inform healthcare professionals of the incidence of ILD in the clinical studies. In addition, the package insert should include a precautionary statement that appropriately advises healthcare professionals to take adequate measures such as dose interruption, dose reduction, and discontinuation of tucidinostat, if any abnormality is found.

7.R.3.4 Cardiac disorder

The applicant's explanation about cardiac disorder associated with the use of tucidinostat:
Adverse events related to cardiac disorder were tabulated by PTs coded to the MedDRA SOC "Cardiac disorders" and MedDRA SMQ "Torsade de pointes/QT prolongation (narrow)."

In Study 210, all-grade cardiac disorder occurred in 2 patients (8.7%, atrioventricular block first degree and palpitations in 1 patient each). Serious cardiac disorder occurred in 1 patient (4.3%, palpitations), and its causal relationship to tucidinostat could not be ruled out. There was no Grade ≥3 cardiac disorder, fatal cardiac disorder, or cardiac disorder leading to discontinuation, interruption, or dose reduction of tucidinostat.

In Study 201, there was no all-grade or Grade ≥3 cardiac disorder, fatal cardiac disorder, or serious cardiac disorder.

In Study 203, all-grade cardiac disorder occurred in 12 patients (21.8%, electrocardiogram QT prolonged in 5 patients, palpitations in 3 patients, atrial fibrillation in 2 patients, and angina unstable, arrhythmia, and pericardial effusion in 1 patient each [some patients had more than one event]). Grade ≥3 cardiac disorder occurred in 1 patient (1.8%, angina unstable). Serious cardiac disorder occurred in 1 patient (1.8%, angina unstable), and its causal relationship to tucidinostat was ruled out. There was no fatal cardiac disorder.

Cardiac disorder reported in the submitted clinical studies other than the above studies (Studies 101, TG0702CDM, and TG0902CDM) and that reported as the post-marketing information are shown below.

- In Study 101, Grade ≥3 cardiac disorder occurred in 2 patients (8.0%, cardio-respiratory arrest in 2 patients). Fatal cardiac disorder occurred in 2 patients (8.0%, cardio-respiratory arrest in 2 patients), and a causal relationship to tucidinostat could not be ruled out for 1 event of these.[51)] Serious cardiac disorder occurred in 2 patients (8.0%, cardio-respiratory arrest in 2 patients), and a causal relationship to tucidinostat could not be ruled out for 1 event of these.[51)]
- In Study TG0702CDM, Grade ≥3 cardiac disorder occurred in 1 patient[52)] (3.2%, left ventricular failure). There was no fatal cardiac disorder or serious cardiac disorder.

[51)] A 6[redacted]-year-old male patient with bile duct cancer. The patient died of cardio-respiratory arrest on Day 5 of tucidinostat treatment (25 mg). The investigator determined that he might have died of pulmonary embolism or the other events causally unrelated to tucidinostat. This patient had multiple complications (hepatic failure, diabetes mellitus, and hypertension) that might cause cardio-respiratory arrest.
[52)] 50 mg cohort (administered 3 times a week)

- In Study TG0902CDM, Grade ≥3 cardiac disorder occurred in 1 patient (1.2%, sudden cardiac death). Fatal cardiac disorder occurred in 1 patient (1.2%, sudden cardiac death), and its causal relationship to tucidinostat could not be ruled out. Serious cardiac disorder occurred in 1 patient (1.2%, sudden cardiac death), and its causal relationship to tucidinostat could not be ruled out.[53)]
- In Focused Monitoring[54)] conducted in the overseas post-marketing setting, electrocardiogram QT prolonged classified as Grade ≥3 cardiac disorder occurred in 6 of 1,787 patients (0.34%). There was no fatal cardiac disorder or serious cardiac disorder.

The applicant's additional explanation about QT interval prolonged reported in patients during treatment with tucidinostat:
In Studies 210, 201, and 203, 12-lead electrocardiography was regularly performed. Table 25 shows changes in QTcF.

Table 25. Changes in QTcF in patients for whom QTcF data were available (Studies 210, 201, and 203)

	n (%)		
	Study 210 N = 23	Study 201 N = 14	Study 203 N = 55
Maximum			
≤450 ms	20 (87.0)	9 (64.3)	50 (90.9)
>450 ms and ≤480 ms	2 (8.7)	4 (28.6)	4 (7.3)
>480 ms and ≤500 ms	1 (4.3)	1 (7.1)	1 (1.8)
>500 ms	0	0	0
Increase from baseline (max)			
<0 ms	8 (34.8)	0	5 (9.1)
≥0 ms and ≤30 ms	13 (56.5)	10 (71.4)	42 (76.4)
>30 ms and ≤60 ms	2 (8.7)	4 (28.6)	8 (14.5)
>60 ms	0	0	0

As shown above, events related to arrhythmia (including QT interval prolonged) including Grade ≥3 events occurred during treatment with tucidinostat at a certain frequency, although serious cardiac disorder for which a causal relationship to tucidinostat could not be ruled out is extremely limited. The applicant, thus, plans to include a precautionary statement about the risk of arrhythmia (including QT interval prolonged) in the package insert.

PMDA's view:
At present, it is difficult to conclude a relationship between tucidinostat and cardiac disorder (arrhythmia [including QT interval prolonged]), given the limited number of patients who experienced cardiac disorder (arrhythmia [including QT interval prolonged]) in the clinical studies in and outside Japan or in the overseas post-marketing setting. Attention, however, should be paid to the risk of arrhythmia (including QT interval prolonged) during treatment with tucidinostat, given that (a) a death for which a causal relationship to tucidinostat could not be ruled out occurred; (b) QTcF increased in some of the patients (Table 25); and (c) label information for romidepsin and panobinostat that have the same mechanism of action as that of tucidinostat includes a precautionary statement that advises healthcare professionals to pay attention to the risk of QT interval prolonged. Thus, the applicant

53) A 54-year-old male patient with NK/T lymphoma. The patient had pyrexia at 40°C and swollen arms on both sides at baseline. After 3 doses of tucidinostat, the pyrexia at 40°C and swollen arms on both sides were aggravated, precluding him from eating, and 2 days later tachypnoea and cardiac arrest occurred.
54) Active post-marketing surveillance conducted between 2015 and 2018 with 1,787 enrollments (as patients treated with tucidinostat alone). Only events for which a causal relationship to tucidinostat could not be ruled out were tabulated.

should provide healthcare professionals with information on the incidence of arrhythmia (including QT interval prolonged) in the clinical studies. In addition, the package insert should include a precautionary statement that appropriately advises healthcare professionals to perform an electrocardiography in patients where necessary and then take appropriate measures such as interruption and dose reduction of tucidinostat, if any abnormality is found.

7.R.4 Clinical positioning and indication

The proposed indication of tucidinostat is the treatment of "relapsed or refractory adult T-cell leukemia/lymphoma." The proposed Precautions Concerning Indication section includes the following statement:

- Physicians should be well-versed in information presented in the Clinical Studies section, including the disease types of the patients included in clinical studies and the presence or absence of poor prognostic factors in such patients, to have a full understanding of the efficacy and safety of tucidinostat before selecting eligible patients.

Based on the review in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the discussion in following subsection, PMDA concluded that the proposed Indication and the Precautions Concerning Indication are appropriate.

7.R.4.1 Clinical positioning and indication of tucidinostat

None of Japanese and foreign clinical practice guidelines[55)] and representative textbooks[56)] on hematology include descriptions on tucidinostat for the treatment of relapsed or refractory ATLL.

The applicant's explanation about the clinical positioning and indication of tucidinostat for the treatment of relapsed or refractory ATLL:

(a) Disease type:

ATLL is classified into 4 different clinical subtypes: acute, lymphoma, chronic, and smoldering types. Of these subtypes, the acute and lymphoma types and chronic type with poor prognostic factors[44)] are referred to as aggressive ATLL. Drug combination chemotherapy is administered to patients with aggressive ATLL, but there is no established standard therapy that prolongs OS, and such patients have a poor prognosis (Practical Guidelines for Hematological Malignancies, 2018, Revised Version [Japanese Society of Hematology ed.]). Under the circumstances, Study 210 demonstrated the clinical benefit of tucidinostat in patients with relapsed or refractory aggressive ATLL [see Sections 7.R.2 and 7.R.3], and thus tucidinostat can be positioned as one of the treatment options for this patient population.

In addition, patients with the smoldering type and chronic type without poor prognostic factors, which were not included in Study 210, are also considered to be eligible for the use of tucidinostat because the therapy can be expected to be effective in these patient populations, given that (i) the smoldering

55) National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology in Non-Hodgkin's Lymphomas (NCCN guideline) (v.3.2019) and Practical Guidelines for Hematological Malignancies, 2018, Revised Version (Japanese Society of Hematology ed.)

56) *Wintrobe's Clinical Hematology*. 14th Edition (USA: Lippincott Williams & Wilkins; 2018), *Williams Hematology*. 9th Edition (USA: The McGraw-Hill Company Inc,; 2016)

type with skin lesions has a poor prognosis (*Journal of Dermatology.* 2014;41:26-8); and (ii) in Study 210, response was observed in 5 of 8 patients (62.5%) with aggressive ATLL involving the skin lesion.

(b) Prior treatment:
Study 210 included patients who had been previously treated with mogamulizumab, and these patients responded to tucidinostat to a certain extent. For this reason, tucidinostat can be recommended to this patient population. Patients which have no prior use of mogamulizumab, on the other hand, are also considered to be eligible for the use of tucidinostat, given that (i) in Study 201, the efficacy was observed in 1 of 3 patients (33.3%) although the clinical experience is limited; and (ii) the patient population is extremely small in size and has very limited treatment options.

Only 6 patients with refractory ATLL were included in Studies 201 and 210 and did not achieve response. However, of these, 3 patients who showed the best overall response of stable disease (SD) had reduced tumor volume. The patient population with refractory ATLL is also considered to be eligible for the use of tucidinostat, given that a clinical study was conducted in patients with refractory ATLL, but no drugs indicated for this condition have been approved; and such patients have a particularly poor prognosis.

Based on the discussion in (a) and (b) above, the proposed indication of tucidinostat was "relapsed or refractory adult T-cell leukemia/lymphoma" with the following precautionary statement included in the Precautions Concerning Indication section. Furthermore, differentiation of tucidinostat from other antineoplastic agents indicated for ATLL is as follows: Mogamulizumab can be indicated for not only patients with relapsed or refractory but also those with treatment-naive CC chemokine receptor 4 (CCR4)-positive ATLL.[57)] Mogamulizumab and lenalidomide hydrate (lenalidomide) are approved for the treatment of relapsed or refractory ATLL in Japan, but there are no results from a clinical study evaluating the clinical benefit of tucidinostat versus the above approved drugs, which precludes drawing a clear conclusion. However, healthcare professionals can choose an appropriate drug by comparing the efficacy and safety of these drugs and taking account of each individual patient's condition.

- Physicians should be well-versed in information presented in the Clinical Studies section, including the disease types of the patients enrolled in clinical studies and the presence or absence of poor prognostic factors in such patients, to have a full understanding of the efficacy and safety of tucidinostat before selecting eligible patients.

PMDA's view:
The efficacy and safety of tucidinostat in patients with relapsed or refractory ATLL who was not included in Study 210 remain unclear, and thus tucidinostat is not recommended for these patients. Taking account of the points presented below in addition to the above applicant's explanation, however, the proposed indication of tucidinostat and the Precautions Concerning Indication section are appropriate.

- Patients with refractory ATLL did not achieve response. However, the use of tucidinostat for the treatment of refractory ATLL is acceptable in light of the above applicant's explanation and the

[57)] For treatment-naïve patients, combination with the other antineoplastic agent is required.

current situation that the second-line and subsequent treatments of ATLL based on response to the previous treatment have not been established.

- The Japanese practical guideline recommends that treatment-naïve patients with ATLL classified as the smoldering type or chronic type without poor prognostic factors should be just monitored without treatment, but it recommends that once the disease has progressed to the acute type, the patient should be treated as done for the acute or lymphoma type or chronic type with poor prognostic factors. If disease progression occurs even after such treatment, the disease should be also treated as done for the acute or lymphoma type or chronic type with poor prognostic factors.
- Neither mogamulizumab nor lenalidomide, drugs approved for the treatment of relapsed or refractory ATLL, is shown to prolong OS in the patient population. There is no established standard treatment.
- Tucidinostat will be used by a physician with adequate knowledge and experience in the treatment of hematopoietic malignancies.

7.R.5 Dosage and administration

The proposed dosage and administration of tucidinostat was "the usual adult dosage is 40 mg of tucidinostat administered orally after a meal twice weekly." After the submission of the application, the proposed dosage and administration statement was changed according to the dosing interval of tucidinostat employed in the clinical studies (every 3-4 days) to "the usual adult dosage is 40 mg of tucidinostat administered orally after a meal twice weekly (every 3 to 4 days)." In addition, the Precautions Concerning Dosage and Administration section includes a guide for dose adjustment in case of adverse drug reactions.

Based on the review in Sections "6.R.1 Timing of administration of tucidinostat," "7.R.2 Efficacy," "7.R.3 Safety," and the discussion in following subsection, PMDA has concluded that the Dosage and Administration and the Precautions Concerning Dosage and Administration sections should be specified as shown below.

Dosage and Administration

The usual adult dosage is 40 mg of tucidinostat administered orally once daily after a meal twice weekly (every 3 or 4 days). The dose may be reduced according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of tucidinostat in combination with other antineoplastic agents have not been established.
- If adverse drug reactions occur after the administration of tucidinostat, tucidinostat should be interrupted, reduced in dose, or discontinued in accordance with the following criteria.

Steps of dose reduction for tucidinostat

Initial dose	40 mg
Step 1 (1-level lower dose)	30 mg
Step 2 (2-level lower dose)	20 mg
Step 3	Discontinuation

Guide for interruption, dose reduction, and discontinuation in case of adverse drug reactions

Adverse drug reaction*		Measure to be taken
Neutrophil count decreased	Neutrophil count decreased to <1,000/mm^3 except for the cases below	Interrupt tucidinostat until the neutrophil count recovers to ≥1,500/mm^3. After recovery, tucidinostat may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tucidinostat until recovery. After recovery, tucidinostat may be resumed at a 1-level lower dose.
	Neutrophil count decreased to <500/mm^3 persistent for more than 7 days Neutrophil count decreased to <1,000/mm^3 accompanied by pyrexia or infection	Interrupt tucidinostat until the neutrophil count recovers to ≥1,500/mm^3. After recovery, tucidinostat may be resumed at a 1-level lower dose.
Platelets decreased	Platelet count decreased to <50,000/mm^3 except for the cases below	Interrupt tucidinostat until the platelet count recovers to ≥75,000/mm^3. After recovery, tucidinostat may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tucidinostat until recovery. After recovery, tucidinostat may be resumed at a 1-level lower dose.
	Platelet count decreased to <50,000/mm^3 accompanied by clinically relevant bleeding or requiring platelet transfusion	Interrupt tucidinostat until the platelet count recovers to ≥75,000/mm^3. After recovery, tucidinostat may be resumed at a 1-level lower dose.
Non-hematological events (excluding clinically non-relevant and asymptomatic abnormal laboratory values)	Grade 3	Interrupt tucidinostat until the event returns to Grade ≤1. After resolution of the event, tucidinostat may be resumed at a 1-level lower dose.
	Grade 4	Discontinue tucidinostat.

* Graded is based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

7.R.5.1 Dosage and administration of tucidinostat

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

In the Japanese phase I study (Study 201), the 30 mg and 40 mg cohorts had almost the same safety profile, and the dosage regimen of tucidinostat 40 mg QD twice weekly was demonstrated to be tolerable. Based on the results, tucidinostat 40 mg QD twice weekly was selected in the Japanese phase IIb study (Study 210). Because Study 210 demonstrated the clinical benefit of tucidinostat in patients with relapsed or refractory ATLL, the dosage and administration of tucidinostat was proposed based on the dosage regimen used in this study.

PMDA accepted the applicant's explanation.

7.R.5.2 Dose adjustment of tucidinostat

The applicant's explanation about the criteria for dose adjustment of tucidinostat in patients with relapsed or refractory ATLL:

In Study 210, criteria for resumption, interruption, dose reduction, and discontinuation of tucidinostat following an adverse event were specified, and tucidinostat administered in accordance with the criteria was tolerable. The Precautions Concerning Dosage and Administration section, therefore, includes the criteria for dose adjustment of tucidinostat based on those used in Study 210.

PMDA accepted the applicant's explanation.

7.R.5.3 Concomitant use of tucidinostat with other antineoplastic agents

The applicant's explanation about the concomitant use of tucidinostat with other antineoplastic agents in patients with relapsed or refractory ATLL:
Because there are currently no data from a clinical study investigating the clinical benefit of the concomitant use of tucidinostat with other antineoplastic agents in patients with relapsed or refractory ATLL, such combination therapy is not recommended.

PMDA accepted the applicant's explanation and concluded that the Precautions Concerning Dosage and Administration section in the package insert should include a precautionary statement that the efficacy and safety of tucidinostat in combination with other antineoplastic agents have not been established.

7.R.6 Post-marketing investigations

The applicant's explanation about planed post-marketing surveillance:
In order to investigate the safety and other aspects of tucidinostat in the post-marketing clinical setting, the applicant plans to conduct post-marketing surveillance covering all patients who are treated with tucidinostat.

The safety specification of the surveillance includes myelosuppression, infection, ILD, and arrhythmia (including QT interval prolonged), which are events requiring special attention during treatment with tucidinostat, as well as the use of tucidinostat in patients with hepatic impairment in light of limited safety information in this population.

A planned sample size of 70 patients and a follow-up period of 52 weeks were selected for the surveillance, in light of the incidence of adverse events and the median OS (12.1 months) in Study 210.

PMDA's view:
Because of extremely limited information about the safety of tucidinostat, the applicant should conduct a post-marketing surveillance covering all patients treated with tucidinostat for a certain period in order to collect safety data promptly in an unbiased manner and to provide obtained safety information to healthcare professionals immediately.

Based on the review in Section "7.R.3 Safety," the safety specification of the surveillance should include myelosuppression, infection, ILD, and arrhythmia (including QT interval prolonged). safety information obtained from patients with hepatic impairment during treatment with tucidinostat is limited, but no clear difference was observed in the incidence of adverse events between patients with normal hepatic function and patients with mild hepatic impairment in a foreign phase Ib/II study (Study 302) [see Section 6.R.2]. In view these and other findings, it is less necessary to include the use of tucidinostat in patients with hepatic impairment in the safety specification of the surveillance. Instead, a current history of hepatic impairment should be included in the surveillance to collect relevant safety information.

The planned sample size and follow-up period for the surveillance should be re-considered in view of the incidences of adverse events in clinical studies included in the safety specification of this surveillance.

7.3 Adverse events observed in clinical studies

Deaths included in the clinical data submitted for safety evaluation were reported 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 201)

Adverse events occurred in 6 of 7 patients (85.7%) in the 30 mg cohort and 7 of 7 patients (100%) in the 40 mg cohort. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 6 of 7 patients (85.7%) in the 30 mg cohort and 7 of 7 patients (100%) in the 40 mg cohort. Table 26 shows adverse events occurring in ≥20% of patients in either cohort.

Table 26. Adverse events occurring in ≥20% of patients in either cohort

SOC PT (MedDRA/J ver.19.1)	n (%)			
	30 mg cohort N = 7		40 mg cohort N = 7	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	6 (85.7)	5 (71.4)	7 (100)	6 (85.7)
Blood and lymphatic system disorders				
Anaemia	5 (71.4)	1 (14.3)	0	0
Neutropenia	1 (14.3)	1 (14.3)	2 (28.6)	2 (28.6)
Thrombocytopenia	2 (28.6)	0	4 (57.1)	2 (28.6)
Gastrointestinal disorders				
Diarrhoea	3 (42.9)	0	1 (14.3)	0
Nausea	1 (14.3)	0	2 (28.6)	0
General disorders and administration site conditions				
Fatigue	3 (42.9)	0	1 (14.3)	0
Pyrexia	1 (14.3)	0	2 (28.6)	1 (14.3)
Infections and infestations				
Nasopharyngitis	0	0	2 (28.6)	0
Investigations				
Neutrophil count decreased	2 (28.6)	2 (28.6)	0	0
Platelet count decreased	3 (42.9)	0	3 (42.9)	0
Weight decreased	1 (14.3)	0	2 (28.6)	0
White blood cell count decreased	3 (42.9)	1 (14.3)	1 (14.3)	1 (14.3)
Metabolism and nutrition disorders				
Hyperuricaemia	2 (28.6)	0	0	0
Hypocalcaemia	0	0	3 (42.9)	0
Hypokalaemia	2 (28.6)	0	1 (14.3)	0
Decreased appetite	1 (14.3)	0	2 (28.6)	0
Musculoskeletal and connective tissue disorders				
Back pain	0	0	2 (28.6)	0
Nervous system disorders				
Dysgeusia	2 (28.6)	0	1 (14.3)	0

Serious adverse events occurred in 1 of 7 patients (14.3%) in the 30 mg cohort and 1 of 7 patients (14.3%) in the 40 mg cohort. The serious adverse events were Parkinsonism in 1 patient (14.3%) in the 30 mg cohort and abdominal pain and enterocolitis in 1 patient (14.3%) each in the 40 mg cohort. A causal relationship to the study drug could not be ruled out for abdominal pain in 1 patient in the 40 mg cohort.

Adverse events leading to study drug discontinuation occurred in 2 of 7 patients (28.6%) in the 30 mg cohort and 4 of 7 patients (57.1%) in the 40 mg cohort. The adverse events were perivascular dermatitis and blood creatine phosphokinase increased in 1 patient (14.3%) each in the 30 mg cohort and computerised tomogram thorax abnormal, abdominal pain, erythema multiforme, and neutropenia in 1 patient (14.3%) each in the 40 mg cohort. A causal relationship to the study drug could not be ruled out for any of these events.

7.3.2 Japanese phase IIb study (Study 210)

Adverse events occurred in 23 of 23 patients (100%), and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 23 of 23 patients (100%). Table 27 shows adverse events occurring in ≥10% of patients.

Table 27. Adverse events occurring in ≥10% of patients

SOC PT (MedDRA/J ver.21.1)	n (%) N = 23 All Grades	 Grade ≥3
Any adverse event	23 (100)	18 (78.3)
Blood and lymphatic system disorders		
Anaemia	8 (34.8)	4 (17.4)
Thrombocytopenia	3 (13.0)	3 (13.0)
Gastrointestinal disorders		
Diarrhoea	6 (26.1)	0
Abdominal pain	3 (13.0)	0
Nausea	3 (13.0)	0
General disorders and administration site conditions		
Malaise	7 (30.4)	0
Fatigue	3 (13.0)	2 (8.7)
Pyrexia	3 (13.0)	0
Investigations		
Platelet count decreased	15 (65.2)	9 (39.1)
Neutrophil count decreased	11 (47.8)	9 (39.1)
White blood cell count decreased	9 (39.1)	7 (30.4)
Weight decreased	4 (17.4)	1 (4.3)
Metabolism and nutrition disorders		
Decreased appetite	8 (34.8)	0
Hypoalbuminaemia	3 (13.0)	0
Musculoskeletal and connective tissue disorders		
Back pain	4 (17.4)	0
Nervous system disorders		
Dysgeusia	4 (17.4)	0

Serious adverse events occurred in 7 of 23 patients (30.4%). The serious adverse events were platelet count decreased in 2 patients (8.7%), neutrophil count decreased, palpitations, *Pneumocystis jirovecii* pneumonia, urinary tract infection, acute respiratory failure, and ILD in 1 patient (4.3%) each. A causal relationship to the study drug could not be ruled out for any of these events except for acute respiratory failure (1 patient).

Adverse events leading to study drug discontinuation occurred in 9 of 23 patients (39.1%). The adverse events were platelet count decreased and neutrophil count decreased in 3 patients (13.0%) each, thrombocytopenia, fatigue, *Pneumocystis jirovecii* pneumonia, ILD, blood ALP increased, and gamma-glutamyl transferase (GGT) increased in 1 patient (4.3%) each. A causal relationship to the study drug could not be ruled out for any of these events.

7.3.3 Foreign phase I study (Study TG0702CDM)

Adverse events occurred in 2 of 3 patients (66.7%) in the 5 mg cohort (twice weekly), 2 of 3 patients (66.7%) in the 10 mg cohort (twice weekly), 2 of 4 patients (50.0%) in the 17.5 mg cohort (twice weekly), 4 of 4 patients (100%) in the 25 mg cohort (twice weekly), 4 of 4 patients (100%) in the 32.5 mg cohort (twice weekly), 4 of 4 patients (100%) in the 50 mg cohort (twice weekly), 4 of 7 patients (57.1%) in the 32.5 mg cohort (3 times weekly), and 2 of 2 patients (100%) in the 50 mg cohort (3 times weekly). Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 2 of 3 patients (66.7%) in the 5 mg cohort (twice a week), 2 of 3 patients (66.7%) in the 10 mg cohort (twice weekly), 2 of 4 patients (66.7%) in the 17.5 mg cohort (twice a weekly), 4 of 4 patients (100%) in the 25 mg cohort (twice weekly), 4 of 4 patients (100%) in the 32.5 mg cohort (twice weekly), 4 of 4 patients (100%) in the 50 mg cohort (twice weekly), 4 of 7 patients (57.1%) in the 32.5 mg cohort (3 times weekly), and 2 of 2 patients (100%) in the 50 mg cohort (3 times weekly). Adverse events occurring in ≥40% of patients in a cohort were fatigue in 2 patients (50.0%) in the 17.5 mg cohort (twice weekly), myocardial necrosis marker increased in 2 patients (50.0%) in the 25 mg cohort (twice weekly), fatigue in 3 patients (75.0%) and decreased appetite, nausea, myocardial necrosis marker increased, and urine analysis abnormal in 2 patients (50.0%) each in the 32.5 mg cohort (twice weekly), fatigue in 4 patients (100%) and pyrexia, anaemia, thrombocytopenia, and neutropenia in 2 patients (50.0%) each in the 50 mg cohort (twice weekly), thrombocytopenia in 5 patients (71.4%) and decreased appetite and neutropenia in 3 patients (42.9%) each in the 32.5 mg cohort (3 times a weekly), fatigue, decreased appetite, nausea, and diarrhoea in 1 patient (50.0%) each in the 50 mg cohort (3 times weekly) (no applicable event in the 5 mg cohort [twice weekly] or the 10 mg cohort [twice weekly]).

There was no serious adverse event in any cohort.

Adverse events leading to study drug discontinuation occurred in 1 of 7 patients (14.3%) in the 32.5 mg cohort (3 times weekly) and 2 of 2 patients (100%) in the 50 mg cohort (3 times weekly) (no applicable event in any of the 5 mg cohort [twice weekly] to the 50 mg cohort [twice weekly]). The adverse events leading to study drug discontinuation were neutropenia in 1 patient (14.3%) in the 32.5 mg cohort (3 times weekly) and diarrhoea and vomiting in 1 patient (50.0%) each in the 50 mg cohort (3 times weekly). A causal relationship to the study drug could not be ruled out for any of these events.

7.3.4 Foreign phase I study (Study 101)

Adverse events occurred in 1 of 1 patient (100%) in the 5 mg fasted cohort, 2 of 2 patients (100%) in the 10 mg fasted cohort, 3 of 3 patients (100%) in the 20 mg fasted cohort, 6 of 6 patients (100%) in the 25 mg fasted cohort, 3 of 3 patients (100%) in the 20 mg fed cohort, 5 of 5 patients (100%) in the 25 mg fed cohort, and 5 of 5 patients (100%) in the 30 mg fed cohort. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 1 of 1 patient (100%) in the 5 mg fasted cohort, 2 of 2 patients (100%) in the 10 mg fasted cohort, 2 of 3 patients (66.7%) in the 20 mg fasted cohort, 6 of 6 patients (100%) in the 25 mg fasted cohort, 3 of 3 patients (100%) in the 20 mg fed cohort, 5 of 5 patients (100%) in the 25 mg fed cohort, and 5 of 5 patients (100%) in the 30 mg fed cohort. Adverse events reported by ≥2 patients in a cohort and occurring at an incidence of

≥40% were headache in 2 patients (100%) in the 10 mg fasted cohort, neutrophil count decreased and platelet count decreased in 2 patients (66.7%) each in the 20 mg fasted cohort, fatigue in 4 patients (66.7%) and nausea and decreased appetite in 3 patients (50.0%) each in the 25 mg fasted cohort, fatigue in 2 patients (66.7%) in the 20 mg fed cohort, fatigue in 4 patients (80.0%), anaemia in 3 patients (60.0%), and nausea, diarrhoea, vomiting, electrocardiogram QT prolonged, and decreased appetite in 2 patients (40.0%) each in the 25 mg fed cohort, fatigue in 4 patients (80.0%) and nausea, diarrhoea, and dysphonia in 2 patients (40.0%) each in the 30 mg fed cohort (no applicable event in the 5 mg fasted cohort).

Serious adverse events occurred in 1 of 1 patient (100%) in the 5 mg fasted cohort, 1 of 2 patients (50.0%) in the 10 mg fasted cohort, 1 of 6 patients (16.7%) in the 25 mg fasted cohort, 1 of 5 patients (20.0%) in the 25 mg fed cohort, and 1 of 5 patients (20.0%) in the 30 mg fed cohort (no applicable event in the 20 mg fasted cohort or the 20 mg fed cohort). The serious adverse events were hyponatraemia in 1 patient (100%) in the 5 mg fasted cohort, pulmonary embolism in 1 patient (50.0%) in the 10 mg fasted cohort, cardio-respiratory arrest in 1 patient (16.7%) in the 25 mg fasted cohort, arthritis infective in 1 patient (20.0%) in the 25 mg fed cohort, and cardio-respiratory arrest in 1 patient (20.0%) in the 30 mg fed cohort. A causal relationship to the study drug could not be ruled out for cardio-respiratory arrest in 1 patient in the 25 mg fasted cohort (no applicable event in any of the 5 mg fasted cohort, the 10 mg fasted cohort, the 25 mg fed cohort, or the 30 mg fed cohort).

Adverse events leading to study drug discontinuation occurred in 2 of 3 patients (66.7%) in the 20 mg fasted cohort, 1 of 6 patients (16.7%) in the 25 mg fasted cohort, 1 of 3 patients (33.3%) in the 20 mg fed cohort, and 1 of 5 patients (20.0%) in the 25 mg fed cohort (no applicable event in any of the 5 mg fasted cohort, the 10 mg fasted cohort, and the 30 mg fed cohort). The adverse events leading to study drug discontinuation were embolism arterial and neutrophil count decreased in 1 patient (33.3%) each in the 20 mg fasted cohort, cardio-respiratory arrest in 1 patient (16.7%) in the 25 mg fasted cohort, fatigue in 1 patient (33.3%) in the 20 mg fed cohort, and arthritis infective in 1 patient (20.0%) in the 25 mg fed cohort. A causal relationship to the study drug could not be ruled out for neutrophil count decreased in 1 patient in the 20 mg fasted cohort, cardio-respiratory arrest in 1 patient in the 25 mg fasted cohort, and fatigue in 1 patient in the 20 mg fed cohort, (no applicable event in the 25 mg fed cohort).

7.3.5 Foreign phase I study (Study 304)

Adverse events occurred in 1 of 16 subjects (6.3%) in the fed-state administration phase, 1 of 16 subjects (6.3%) in the fasted-state administration phase, and 3 of 15 subjects (20.0%) in the tucidinostat + itraconazole co-administration phase. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 3 of 15 subjects (20.0%) in the tucidinostat + itraconazole co-administration phase (no applicable event in the fed-state administration phase or the fasted-state administration phase). There was no adverse event occurring in ≥10% of patients in an administration phase.

There was no serious adverse event or adverse event leading to study drug discontinuation.

7.3.6 Foreign phase Ib/II study (Study 302)

Adverse events occurred in 3 of 3 patients (100%) in the 20 mg cohort, 79 of 79 patients (100%) in the 30 mg cohort, and 7 of 7 patients (100%) in the 40 mg cohort. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 3 of 3 patients (100%) in the 20 mg cohort, 72 of 79 patients (91.1%) in the 30 mg cohort, and 6 of 7 patients (85.7%) in the 40 mg cohort. Adverse events occurring in ≥40% of patients in a cohort were nausea, diarrhoea, fatigue, myalgia, and dyspnoea in 2 patients (66.7%) each in the 20 mg cohort, fatigue in 48 patients (60.8%), platelet count decreased in 41 patients (51.9%), nausea and diarrhoea in 38 patients (48.1%) each, and anaemia in 34 patients (43.0%) in the 30 mg cohort, and anaemia and decreased appetite in 4 patients (57.1%) each, atrial fibrillation, nausea, fatigue, contusion, platelet count decreased, white blood cell count decreased, dyspnoea, and hypotension in 3 patients (42.9%) each in the 40 mg cohort.

Serious adverse events occurred in 1 of 3 patients (33.3%) in the 20 mg cohort, 41 of 79 patients (51.9%) in the 30 mg cohort, and 4 of 7 patients (57.1%) in the 40 mg cohort. Serious adverse events reported by ≥2 patients in a cohort were pneumonia and lipase increased in 4 patients (5.1%) each, anaemia, pulmonary embolism, pleural effusion, pneumonitis, and respiratory failure in 3 patients (3.8%) each, vomiting, cholelithiasis, and chronic obstructive pulmonary disease in 2 patients (2.5%) each in the 30 mg cohort. A causal relationship to the study drug could not be ruled out for any of the following events: pneumonitis in 2 patients, anaemia, vomiting, pneumonia, and respiratory failure in 1 patient each in the 30 mg cohort.

Adverse events leading to study drug discontinuation occurred in 2 of 3 patients (66.7%) in the 20 mg cohort, 35 of 79 patients (44.3%) in the 30 mg cohort, and 5 of 7 patients (71.4%) in the 40 mg cohort. Adverse events that led to study drug discontinuation and were reported by ≥2 patients in a cohort were fatigue and lipase increased in 4 patients (5.1%) each, anaemia and pneumonitis in 3 patients (3.8%) each, diarrhoea, vomiting, amylase increased, and dyspnoea in 2 patients (2.5%) each in the 30 mg cohort, and fatigue in 2 patients (28.6%) in the 40 mg cohort. A causal relationship to the study drug could not be ruled out for any of the following events: fatigue in 4 patients, diarrhoea and vomiting in 2 patients each, anaemia, lipase increased, and dyspnoea in 1 patient each in the 30 mg cohort and fatigue in 2 patients in the 40 mg cohort.

7.3.7 Foreign phase II study (Study TG0902CDM)

7.3.7.1 Exploratory part

Adverse events occurred in 6 of 9 patients (66.7%) in the 30 mg cohort and 8 of 10 patients (80.0%) in the 50 mg cohort. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 4 of 9 patients (44.4%) in the 30 mg cohort and 7 of 10 patients (70.0%) in the 50 mg cohort. Adverse events occurring in ≥20% of patients in a cohort were platelet count decreased in 3 patients (33.3%) in the 30 mg cohort and platelet count decreased in 6 patients (60.0%), white blood cell count decreased in 4 patients (40.0%), and pyrexia and asthenia in 3 patients (30.0%) each, and nausea in 2 patients (20.0%) in the 50 mg cohort.

Serious adverse events occurred in 1 of 10 patients (10.0%) in the 50 mg cohort. The serious adverse events were platelet count decreased and pyrexia in 1 patient (10.0%) each. A causal relationship to the study drug could not be ruled out for any of these events.

Adverse events leading to study drug discontinuation occurred in 2 of 9 patients (22.2%) in the 30 mg cohort and 1 of 10 patients (10.0%) in the 50 mg cohort. The adverse events leading to study drug discontinuation were platelet count decreased, white blood cell count decreased, and oedema peripheral in 1 patient (11.1%) each in the 30 mg cohort and platelet count decreased and protein urine present in 1 patient (10.0%) each in the 50 mg cohort. A causal relationship to the study drug could not be ruled out for any of these events.

7.3.7.2 Pivotal part

Adverse events occurred in 68 of 83 patients (81.9%), and adverse events with a possible causal relationship to the study drug occurred in 60 of 83 patients (72.3%). Adverse events occurring in ≥10% of patients were platelet count decreased in 42 patients (50.6%), white blood cell count decreased in 33 patients (39.8%), and neutrophil count decreased in 18 patients (21.7%).

Serious adverse events occurred in 7 of 83 patients (8.4%). There was no serious adverse event reported by ≥2 patients.

Adverse events leading to study drug discontinuation occurred in 14 of 83 patients (16.9%). Adverse events that led to discontinuation of the study drug and were reported by ≥2 patients were platelet count decreased in 4 patients (4.8%), white blood cell count decreased in 3 patients (3.6%), and hepatic function abnormal in 2 patients (2.4%). A causal relationship to the study drug could not be ruled out for any of these events.

7.3.8 Global phase IIb study (Study 203)

Adverse events occurred in 55 of 55 patients (100%), and adverse events with a possible causal relationship to the study drug were observed in 51 of 55 patients (92.7%). Adverse events occurring in ≥20% of patients were platelet count decreased in 31 patients (56.4%), neutrophil count decreased in 20 patients (36.4%), anaemia and white blood cell count decreased in 18 patients (32.7%) each, diarrhoea in 17 patients (30.9%), thrombocytopenia in 15 patients (27.3%), decreased appetite in 13 patients (23.6%), nausea in 12 patients (21.8%), neutropenia, pyrexia, and lymphocyte count decreased in 11 patients (20.0%) each.

Serious adverse events occurred in 14 of 55 patients (25.5%). The serious adverse event reported by ≥2 patients was febrile neutropenia in 2 patients (3.6%). A causal relationship to the study drug could not be ruled out for either case.

Adverse events leading to study drug discontinuation occurred in 18 of 55 patients (32.7%). Adverse events that led to study drug discontinuation and were reported by ≥2 patients were neutrophil count decreased in 4 patients (7.3%), platelet count decreased in 3 patients (5.5%), and GGT increased and

pneumonitis in 2 patients (3.6%) each. A causal relationship to the study drug could not be ruled out for any of these events except for pneumonitis (1 patient).

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 5.3.5.2-1) 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 tucidinostat has certain efficacy in the treatment of relapsed or refractory ATLL, and that tucidinostat has acceptable safety in view of its benefits. Tucidinostat is a drug with a new active ingredient that suppress tumor growth by inhibiting histone deacetylation and thereby inducing cell cycle arrest and apoptosis. Tucidinostat is therefore expected to be of clinical significance as a treatment option for relapsed or refractory ATLL. The efficacy and safety of tucidinostat and post-marketing investigations should be further evaluated.

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

Review Report (2)

May 11, 2021

Product Submitted for Approval

Brand Name	Hiyasta Tablets 10 mg
Non-proprietary Name	Tucidinostat
Applicant	Huya Japan G.K.
Date of Application	September 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 the review in Section "7.R.2 Efficacy" of the Review Report (1), PMDA concluded that the efficacy of tucidinostat in patients with relapsed or refractory ATLL was demonstrated to a certain extent, based on the results of a Japanese phase IIb study (Study 210) in patients with relapsed or refractory ATLL. In the study, the response rate [95% CI] centrally accessed according to the modified version of the criteria developed by the International Conference on Human Retrovirology, the primary endpoint, was 30.4% [13.2%, 52.9%] (7 of 23 patients), which exceeded the predetermined threshold response rate (5%).

The above conclusion of PMDA was 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 has concluded that adverse events requiring special attention during treatment with tucidinostat are myelosuppression, infection, ILD, and arrhythmia (including QT interval prolonged).

PMDA has also concluded that although use of tucidinostat requires attention to these adverse events, tucidinostat is tolerable as long as physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies take appropriate measures such as monitoring and controlling of these adverse events and interruption, dose reduction, and discontinuation of tucidinostat.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication

As a result of the review in Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that tucidinostat should be indicated for the treatment of "relapsed or refractory adult T-cell leukemia/lymphoma" as proposed, provided that the package insert should include information about the disease types of the patients enrolled in Study 210 and the presence or absence of poor prognosis factors in such patients in the Clinical Studies section, along with the following precautionary statement in the Precautions Concerning Indication section.

Precautions Concerning Indication

- Physicians should be well-versed in information presented in the Clinical Studies section, including the disease types of the patients enrolled in clinical studies and the presence or absence of poor prognostic factors in such patients, to have a full understanding of the efficacy and safety of tucidinostat before selecting eligible patients.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.4 Dosage and administration

As a result of the review in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA has concluded that the Dosage and Administration and Precautions Concerning Dosage and Administration sections for the package insert of tucidinostat should be specified as shown below.

Dosage and Administration

The usual adult dosage is 40 mg of tucidinostat administered orally once daily after a meal twice weekly (every 3 or 4 days). The dose may be reduced according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of tucidinostat in combination with other antineoplastic agents have not been established.
- Guide for interruption of tucidinostat or other actions in case of adverse drug reactions

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to use the above descriptions in the Dosage and Administration section and the Precautions Concerning Dosage and Administration section. The applicant agreed to do so.

1.5 Risk management plan (draft)

In order to investigate the safety and other aspects of tucidinostat in the post-marketing clinical setting, the applicant plans to conduct post-marketing surveillance covering all patients treated with tucidinostat. The planned sample size is 70 patients and the follow-up period is 52 weeks.

As a result of the review in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA has concluded that the applicant should conduct post-marketing surveillance covering all patients treated with tucidinostat for a certain period in order to collect safety data promptly in an unbiased manner and to provide the obtained safety information to healthcare professionals immediately.

PMDA has further concluded on the surveillance plan as follows:
- The safety specification of the surveillance should include myelosuppression, infection, ILD, and arrhythmia (including QT interval prolonged).
- The planned sample size and follow-up period for the surveillance should be re-considered in view of the incidences of adverse events in clinical studies included in the safety specification of the surveillance.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above review, PMDA instructed the applicant to re-consider the surveillance plan.

The applicant's response:
- The safety specification of the surveillance will represent myelosuppression, infection, ILD, and arrhythmia (including QT interval prolonged).
- The planned sample size and follow-up period for the surveillance will be 150 patients and 36 weeks, respectively, in view of the incidences of adverse events in clinical studies included in the safety specification of the surveillance.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for tucidinostat should include the safety specification presented in Table 28 and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 29 and 30.

Table 28. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infection • Myelosuppression • ILD	• Arrhythmia (including QT interval prolonged)	Not applicable
Efficacy specification		
Not applicable		

Table 29. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey (all-case surveillance)	Not applicable	• Dissemination of information obtained through the early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals

Table 30. Outline of use-results survey (draft)

Objective	To investigate the safety of tucidinostat in clinical use
Survey method	All-case surveillance
Study population	All patients treated with tucidinostat
Follow-up period	36 weeks
Planned sample size	150 patients
Main survey items	Safety specification: Myelosuppression, infection, ILD, and arrhythmia (including QT interval prolonged) Other main survey items: Patient characteristics (e.g., age, sex, disease type, medical history, comorbidities), previous treatments, status of tucidinostat administration, concomitant medications, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that tucidinostat may be approved after modifying the proposed indication and dosage and administration shown below, with the following approval conditions, provided that (i) precautions should be included in the package insert; (ii) healthcare professionals should be appropriately informed of the proper use of tucidinostat in the post-marketing setting, (iii) the proper use of tucidinostat should be strictly ensured under the supervision of aphysician with adequate knowledge and experience in the treatment of hematopoietic malignancies at a medical institution capable of emergency response. Since Hiyasta is designated as an orphan drug, the re-examination period is 10 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 adult T-cell leukemia/lymphoma

Dosage and Administration

The usual adult dosage is 40 mg of tucidinostat administered orally once daily after a meal twice weekly (every 3 or 4 days). 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. Since only a limited number of Japanese patients participated in clinical studies of the product, the applicant is required to conduct a post-marketing drug use-results survey involving all Japanese patients treated with the product until data from a certain number of patients have been gathered in order to understand the characteristics of patients using the product and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Warnings

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

Contraindications

1. Patients with a history of hypersensitivity to any ingredient of the product
2. Pregnant women or women who may possibly be pregnant

Precautions Concerning Indication

Physicians should be well-versed in information presented in the Clinical Studies section, including the disease types of the patients enrolled in clinical studies and the presence or absence of poor prognostic factors in such patients, to have a full understanding of the efficacy and safety of tucidinostat before selecting eligible patients.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of tucidinostat in combination with other antineoplastic agents have not been established.
2. If adverse drug reactions occur after the administration of tucidinostat, tucidinostat should be interrupted, reduced in dose, or discontinued in accordance with the following criteria.

Steps of tucidinostat dose reduction

Initial dose	40 mg
Step 1 (1-level lower dose)	30 mg
Step 2 (2-level lower dose)	20 mg
Step 3	Discontinuation

Guide for interruption, dose reduction, and discontinuation in case of adverse drug reactions

Adverse drug reaction*		Measures to be taken
Neutrophil count decreased	Neutrophil count decreased to $<1,000/mm^3$ except for the cases below	Interrupt tucidinostat until the neutrophil count recovers to $\geq 1,500/mm^3$. After recovery, tucidinostat may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tucidinostat until recovery. After recovery, tucidinostat may be resumed at a 1-level lower dose.
	Neutrophil count decreased to $<500/mm^3$ persistent for more than 7 days Neutrophil count decreased to $<1,000/mm^3$ accompanied by pyrexia or infection	Interrupt tucidinostat until the neutrophil count recovers to $\geq 1,500/mm^3$. After recovery, tucidinostat may be resumed at a 1-level lower dose.
Platelets decreased	Platelet count decreased to $<50,000/mm^3$ except for the cases below	Interrupt tucidinostat until the platelet count recovers to $\geq 75,000/mm^3$. After recovery, tucidinostat may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tucidinostat until recovery. After recovery, tucidinostat may be resumed at a 1-level lower dose.
	Platelet count decreased to $<50,000/mm^3$ accompanied by clinically relevant bleeding or requiring platelet transfusion	Interrupt tucidinostat until the platelet count recovers to $\geq 75,000/mm^3$. After recovery, tucidinostat may be resumed at a 1-level lower dose.
Non-hematological events (excluding clinically non-relevant and asymptomatic abnormal laboratory values)	Grade 3	Interrupt tucidinostat until the event returns to Grade ≤1. After resolution of the event, tucidinostat may be resumed at a 1-level lower dose.
	Grade 4	Discontinue tucidinostat.

*, Graded is based on NCI-CTCAE.

Appendix

List of Abbreviations

^{14}C-tucidinostat	^{14}C-labeled tucidinostat
3T3-NRU	3T3 neutral red uptake phototoxicity test
A/G	albumin/globulin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
Application	Marketing application
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATLL	adult T-cell leukemia/lymphoma
BCRP	breast cancer resistance protein
BUN	blood urea nitrogen
CCR4	CC chemokine receptor 4
CI	confidence interval
CL_r	renal clearance
CMV	cytomegalovirus
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CrCL	creatinine clearance
CRu	complete response unconfirmed
CTCL	cutaneous T-cell lymphoma
CYP	cytochrome P450
DLT	dose limiting toxicity
DMSO	dimethylsulfoxide
ECOG	Eastern Cooperative Oncology Group
efflux ratio	the ratio of permeability coefficient in the secretary direction to that in the absorptive direction
FC	film coating
GC	gas chromatography
G-CSF	granulocyte colony stimulating factor
GGT	gamma-glutamyl transferase
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HDAC	histone deacetylase
hERG	human *ether-a-go-go* related gene
HLT	high level term
Ht	hematocrit
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH M7 guideline	“Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk” (PSEHB/ELD Notification No. 1110-3 dated November 10, 2015)
ICH Q1E guideline	“Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ILD	interstitial lung disease
IR	infrared absorption spectroscopy
LC	liquid chromatography
LC-MS/MS	liquid chromatography/tandem mass spectrometry

LDH	lactate dehydrogenase
Lenalidomide	Lenalidomide hydrate
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
Mogamulizumab	Mogamulizumab (Genetical Recombination)
mRNA	messenger ribonucleic acid
MRP	multidrug resistance associated protein
mSWAT	modified Severity Weighted Assessment Tool
MTD	maximum tolerated dose
MTT	mean transit time
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN guideline	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology in Non-Hodgkin's Lymphomas
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NHL	non-Hodgkin lymphoma
Nivolumab	Nivolumab (Genetical Recombination)
NMR	nuclear magnetic resonance spectroscopy
NSCLC	non-small cell lung cancer
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
Panobinostat	Panobinostat lactate
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
PBMC	peripheral blood mononuclear cell
PD	progressive disease
P-gp	P-glycoprotein
PI	propidium iodide
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
PTCL	peripheral T-cell lymphoma
PTP	press through packaging
QbD	quality by design
QD	quaque die
QTcF	QT interval corrected with Fridericia approach
SD	stable disease
SMQ	standard MedDRA queries
SOC	system organ class
Study 101	Study HBI-8000-101
Study 201	Study HBI-8000-201
Study 203	Study HBI-8000-203
Study 210	Study HBI-8000-210
Study 302	Study HBI-8000-302
Study 304	Study HBI-8000-304
UVA	ultraviolet A

UVB	ultraviolet B
UV/VIS	ultraviolet/visible spectroscopy
Vc/F	apparent volume of distribution of central compartment
Vp/F	apparent volume of distribution of peripheral compartment
VZV	varicella zoster virus
ΔQTcF	Change in QTcF from baseline