Report on the Deliberation Results

June 7, 2017

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

Brand Name	Istodax Injection 10 mg
Non-proprietary Name	Romidepsin (JAN*)
Applicant	Celgene K.K.
Date of Application	September 2, 2016

Results of Deliberation

In the meeting held on May 30, 2017, 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 classified as powerful drugs and poisonous drugs, respectively.

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

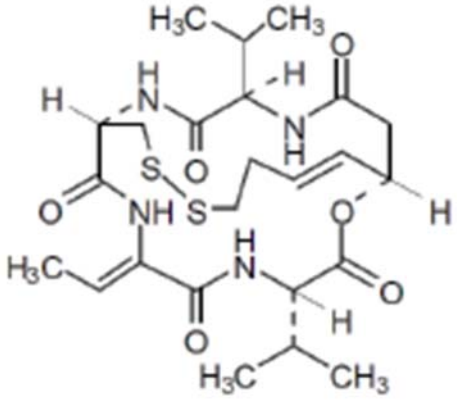
** Japanese Accepted Name (modified INN)*

Review Report

May 10, 2017
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.

Brand Name	Istodax Injection 10 mg
Non-proprietary Name	Romidepsin
Applicant	Celgene K.K.
Date of Application	September 2, 2016
Dosage Form/Strength	Lyophilized powder for reconstitution for injection: Each vial contains 11 mg of Romidepsin.
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Chemical Structure	



Molecular formula: $C_{24}H_{36}N_4O_6S_2$
Molecular weight: 540.70
Chemical name:
(1*S*,4*S*,10*S*,16*E*,21*R*)-7-[(2*Z*)-Ethylidene]-4,21-bis(1-methylethyl)-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone

Items Warranting Special Mention
Orphan drug (Orphan Drug Designation No. 387 of 2016 [*28 yaku*]; PSEHB/PED Notification No. 0824-7 dated August 24, 2016, 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
The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in the treatment of patients with relapsed or refractory peripheral T-cell lymphoma and acceptable safety in view of the benefits indicated by the data submitted, as shown in Attachment.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The occurrences of bone marrow depression, infection, cardiac disorders (abnormal electrocardiogram such as QT interval prolongation, among others), tumour lysis syndrome, hypersensitivity, haemorrhage, and venous thromboembolism need to be further investigated via post-marketing surveillance.

Indication
Relapsed or refractory peripheral T-cell lymphoma

Dosage and Administration
The usual adult dosage is 14 mg/m^2 (body surface area) of romidepsin administered as an intravenous infusion over 4 hours on Days 1, 8, and 15, followed by a rest period (Days 16-28). This 28-day cycle is repeated. The dose may be reduced according to the patient's condition.

Conditions of Approval
The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

March 27, 2017

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.

Product Submitted for Approval

Brand Name	Istodax Injection 10 mg
Non-proprietary Name	Romidepsin
Applicant	Celgene K.K.
Date of Application	September 2, 2016
Dosage Form/Strength	Lyophilized powder for reconstitution for injection: Each vial contains 11 mg of Romidepsin.
Proposed Indication	Relapsed or refractory peripheral T-cell lymphoma
Proposed Dosage and Administration	The usual adult dosage is 14 mg/m^2 (body surface area) of romidepsin administered as an intravenous infusion over 4 hours on Days 1, 8, and 15, followed by a rest period (Days 16-28). This 28-day cycle is repeated. The dose may be reduced according to the patient's condition.

Table of Contents

List of Abbreviations

^{14}C- romidepsin	^{14}C-labeled romidepsin
5-FU	5-fluorouracil
A/G ratio	albumin/globulin ratio
AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APA	action potential amplitude
APD_{90}	action potential duration at 90% repolarization
Application	marketing application
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
Brentuximab	brentuximab vedotin (genetical recombination)

BSEP	bile salt export pump
BUN	blood urea nitrogen
CBDCA	carboplatin
CI	confidence interval
CK	creatine kinase
CMV	cytomegalovirus
CPT-11	irinotecan hydrochloride hydrate
CR	complete response
CRu	complete response unconfirmed
CTCL	cutaneous T cell lymphoma
CYP	cytochrome P450
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dV/dt max	maximum rate of rise
DXR	doxorubicin hydrochloride
EBV	Epstein-Barr virus
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GC	gas chromatography
Hb	hemoglobin
HBV	hepatitis B virus
HCT	hematocrit value
HDAC	histone deacetylase
hERG	human *ether-a-go-go* related gene
HPLC	high performance liquid chromatography
IR	infrared absorption spectrum
IRB	institutional review board
Istodax	Istodax Injection
ITT	intent-to-treat
IWC	International Workshop Response Criteria for non-Hodgkin's lymphomas
Japanese Clinical Practice Guideline	Clinical Practice Guideline for the Management of Hematologic Malignancy 2013, edited by the Japanese Society of Hematology (Kanehara & Co., Ltd., 2013)
JCOG	Japan Clinical Oncology Group
JCOG criteria	Criteria established by JCOG (JCOG-LSG Manual Committee for Clinical Research of Lymphoma and Myeloma, 2003)
K_{ATP} channel	ATP-sensitive potassium channels
Ki	inhibition constant
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LDH	lactate dehydrogenase
LSG	Lymphoma Study Group
MCB	master cell bank
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
mIWC	modified International Workshop Response Criteria for non-Hodgkin's lymphomas
MMC	mitomycin C
Mogamulizumab	Mogamulizumab (genetical recombination)
mRNA	messenger ribonucleic acid
MRP	multidrug resistance-associated protein

MST	median survival time
MTD	maximum tolerated dose
MWCB	manufacturing working cell bank
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas
NCI	National Cancer Institute
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NCI-PDQ	National Cancer Institute Physician Data Query, Adult Non-Hodgkin Lymphoma Treatment
NE	not evaluated
NK2	neurokinin2
NMR	nuclear magnetic resonance spectrum
NZW	New Zealand White
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
$P_{app\ B \rightarrow A}$	apparent permeability in basolateral to apical direction
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PT	preferred term
PTCL	peripheral T-cell lymphoma
PTCL-NOS	peripheral T-cell lymphoma, not otherwise specified
PTX	paclitaxel
QOL	quality of life
QTcF	QT interval corrected by Fridericia method
QTcI	QT interval corrected for heart rate of individual subjects
Romidepsin	romidepsin
RT-PCR	reverse transcription polymerase chain reaction
SCID mouse	severe combined immunodeficiency mouse
SD	stable disease
SK_{CA} channel	small-conductance calcium-activated potassium channels
SMQ	standard MedDRA queries
SOC	system organ class
ST combination product	fixed combination of sulfamethoxazole and trimethoprim
Study 0002	Study GPI-06-0002
Study 001	Study ROMI-TCL-001
T/NK cell neoplasms	mature T cell and NK cell neoplasms
TG	triglyceride
TLS	tumor lysis syndrome
UV/VIS	ultraviolet/visible spectrum
VEGF	vascular endothelial growth factor
WHO	World Health Organization
γ-GTP	gamma-glutamyl transferase
ΔQTcF	change in QTcF from baseline (before administration of romidepsin and after administration of antiemetic)

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

1.1 Overview of the product submitted for registration

Histone deacetylase (HDAC) is an enzyme family that catalyzes the removal of the acetyl group (deacetylation) from acetylated lysine residues in proteins such as histones and transcription factors. The deacetylation catalyzed by this enzyme group is considered to lead to chromatin condensation, thereby inhibiting gene transcription.

Romidepsin is a low molecule HDAC inhibitor. The compound was isolated from *Chromobacterium violaceum* No. 968 by Fujisawa Pharmaceutical Co., Ltd. (currently known as Astellas Pharma Inc.). The applicant claims that romidepsin inhibits deacetylation of histones and other proteins, thereby inducing cell cycle arrest and apoptosis, leading to tumor growth suppression.

1.2 Development history, etc.

A foreign phase I study (Study T-95-0022) was initiated in February 1997 by Fujisawa Pharmaceutical Co., Ltd. and the US National Cancer Institute (NCI), involving patients with advanced solid tumor. Also, a phase II study (Study NCI 1312) was initiated in March 2001, involving patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) or cutaneous T cell lymphoma (CTCL). Subsequently, a phase II study (Study GPI-06-0002 [Study 0002]) was initiated by Gloucester Pharmaceuticals, Inc. in the US in June 2007, involving patients with relapsed or refractory PTCL.

In the US and EU, marketing application for romidepsin was submitted in December 2010 and March 2011, respectively, based on the pivotal study data from Study 0002. Romidepsin received accelerated approval in the US in June 2011 with the following indication: "ISTODAX is a histone deacetylase (HDAC) inhibitor indicated for treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy." In the EU, on the other hand, the marketing authorization was refused in 2013, on the ground that there were no data from randomized controlled study, resulting in the absence of established clinical benefits of romidepsin.

As of February 2017, romidepsin is approved in 5 countries for treatment of PTCL.

In Japan, a phase I/II study (Study ROMI-TCL-001 [Study 001]) in patients with relapsed or refractory PTCL or CTCL was initiated by the applicant in December 2011.

Marketing application for romidepsin has been submitted based on the results of Studies 001 and 0002 as the pivotal study data.

Romidepsin was designated as an orphan drug with the intended indication of "peripheral T-cell lymphoma" in August 2016 (Orphan Drug Designation No. 387 of 2016 [*28 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 is a white to pale yellowish white crystals or crystalline powder. The general properties of the drug substance, including description, solubility, optical rotation, thermal analysis, and hygroscopicity, have been determined. The drug substance is shown to have 6 crystalline forms (Forms 1, 2, 3, 4, 5, and 6). However, it has been confirmed that only Form 1 is formed in the manufacturing process selected for the commercial-scale production and the drug substance is stable at room temperature.

The chemical structure of the drug substance has been elucidated by nuclear magnetic resonance spectrum (NMR) (^{1}H-NMR, ^{13}C-NMR), mass spectrometry, infrared absorption spectrum (IR), ultraviolet/visible spectrum (UV/VIS), elemental analysis, and single crystal X-ray diffractometry. The drug substance has 4 stereogenic centers but is manufactured as a compound with a single steric conformation.

2.1.2 Manufacturing process

The drug substance is manufactured through a process comprised of generation of master cell bank (MCB) and manufacturing working cell bank (MWCB) from *Chromobacterium violaceum* strain 1986, a mutant strain of *Chromobacterium violaceum* strain 968, cell culture and harvest, isolation by [redacted] chromatography, purification by [redacted] chromatography, purification by [redacted] chromatography and [redacted], purification by [redacted] chromatography, crystallization, and [redacted] recrystallization.

[redacted], purification by [redacted] chromatography, and [redacted] are identified as the critical steps, and process control parameters and limits are defined for all manufacturing steps.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR), optical rotation, purity (heavy metals, related substances [high performance liquid chromatography (HPLC)], and residual solvents [gas chromatography (GC)]), water content, residue on ignition, bacterial endotoxin, microbial limit test, and assay (HPLC).

2.1.4 Stability of drug substance

Table 1 shows stability studies conducted on the drug substance. A photostability testing showed that the drug substance is photolabile.

Table 1. Stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 commercial-scale batches	25°C	60% RH	High-density polyethylene container + polypropylene closure	60 months
Accelerated testing	3 commercial-scale batches	40°C	75% RH		6 months

Based on the above, a retest period of 60 months has been proposed for the drug substance when stored at room temperature in a high-density polyethylene container sealed with a polypropylene cap, under light-protected conditions.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for solution for injection containing 11 mg of romidepsin in each vial. The drug product contains povidone and hydrochloric acid as excipients. Each vial is filled with the drug substance in overage of the labeled amount to ensure an extractable volume of 2 mL of a solution containing 5 mg/mL of romidepsin after the lyophilized product is reconstituted with 2.2 mL of the accompanying reconstitution diluent.

The drug product is supplied with a reconstitution diluent comprising of a mixture of propylene glycol and anhydrous ethanol (4:1) (2.2 mL) filled in a glass vial.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of drug solution preparation, sterile filtration/filling, lyophilization, clamping, visual inspection, labeling, and packaging. [redacted], [redacted], and [redacted] are identified as the critical steps, and the process control parameters and limits have been established for [redacted] and [redacted].

The accompanying reconstitution diluent is manufactured through a process comprised of drug solution preparation, sterile filtration/filling, clamping, visual inspection, and labeling. [redacted] is identified as the critical step, and the process control parameters and limits have been established for [redacted] and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product include content, description, identification (HPLC and UV/VIS), purity (clarity and color of solution, related substances [HPLC], residual solvents [GC]), water

content, bacterial endotoxin, uniformity of dosage unit (test for content uniformity [HPLC]), foreign insoluble matter, insoluble particulate matter, sterility, and assay (HPLC).

The proposed specifications for the accompanying reconstitution diluent include strength, description, identification (GC), bacterial endotoxin, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, and assay (GC).

2.2.4 Stability of drug product

Table 2 shows the stability studies performed on the drug product. A photostability testing showed that the drug product is photolabile.

Table 2. Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 commercial-scale batches	25°C	60% RH	Glass vial + rubber cap + paper box	36 months
Accelerated testing	3 commercial-scale batches	40°C	75% RH		6 months

Based on the above, the shelf life of 36 months has been proposed for the drug product when placed in a glass vial stoppered with a rubber cap (bromobutyl rubber) and placed together with the accompanying reconstitution diluent in a paper box to protect from light, and stored at room temperature.

The accompanying reconstitution diluent was subjected to a long-term testing (25°C/60% RH) for 48 months and to an accelerated testing (40°C/75% RH) for 6 months, and results showed that the diluent is stable for 48 months when stored at room temperature.

2.R Outline of the review conducted by PMDA

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

2.R.1 Novel excipients

Since povidone contained in the drug product has never been used in intravenous administration, it is classified as a novel excipient.

2.R.1.1 Specifications and stability

PMDA confirmed that the quality of povidone meets the Japanese Pharmacopoeia and that there is no problem in the specifications or stability.

2.R.1.2 Safety

As data on the toxicity of povidone, the applicant submitted results of single-dose toxicity studies, repeated-dose toxicity studies, a local tolerance study, a carcinogenicity study, and pharmacokinetic studies.

The applicant's explanation about the safety of povidone:
In a single intravenous administration study in dogs, hypersensitivity reaction was observed at dose of ≥6.5 mg/kg of povidone (*J Exp Clin Cancer Res.* 2013;32:74, etc.), raising concerns of hypersensitivity reaction induced by intravenous administration of povidone used in the drug product. Also, in the re-evaluation of the safety of povidone used in cosmetics, it is reported that, high-molecular-weight povidone, following parenteral administration, is retained over a long period in various tissues in animals (CIR Expert Panel Meeting June 10-11, 2013). In contrast, the povidone used in the drug product has a K value of 17, and it is reported from the results of pharmacokinetic studies, etc., that povidone with a K value of <18 is rapidly excreted from the body (*N Engl J Med.* 1952;247:921-9, *Am J Clin Pathol*. 1953;23:311-21). These results suggest that, in contrast to high-molecular-weight povidone, povidone used in the drug product is unlikely to pose safety concerns due to accumulation in tissues.

PMDA's view:
The explanation of the applicant is acceptable. Given the seriousness of the indicated disease, use of povidone in the drug product is acceptable. However, since povidone-induced hypersensitivity may occur in clinical use of the drug product, povidone used in the drug product for intravenous administration should be handled as an excipient without prior use experience.

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

3.1 Primary pharmacodynamics

3.1.1 HDAC inhibition (CTD 4.3.3, *Nat Chem Biol.* 2010;6:238-43)

Using a fluorescence-labeled substrate released by the enzyme reaction, the inhibitory effect of romidepsin against 11 HDAC isoforms (recombinant proteins) was investigated. Table 3 shows inhibition constant (Ki) of romidepsin against each HDAC isoform.

Table 3. Inhibitory effect of romidepsin against HDAC isoforms

Isoform	Ki (nmol/L)
HDAC1	0.0015 ± 0.0001
HDAC2	0.038 ± 0.003
HDAC3	0.15 ± 0.03
HDAC4	20.5 ± 3.5
HDAC5	550 ± 60
HDAC6	9.5 ± 4.0
HDAC7	1250 ± 200
HDAC8	0.15 ± 0.03
HDAC9	1100 ± 220
HDAC10	-
HDAC11	-

Mean ± standard deviation (SD); n = 3; -, Undetectable

3.1.2 Inhibition of deacetylation (CTD 4.2.1.1.2, 4.2.1.1.7)

Using human malignant lymphoma-derived U-937 cell line, the inhibitory effect of romidepsin against deacetylation of histone in the promoter region of the gene encoding a cell cycle inhibitor *p21* was investigated by the chromatin immunoprecipitation method. As a result, romidepsin inhibited deacetylation of histone H3 and H4.

Using human prostate cancer-derived PC-3 cell line, the inhibitory effect of romidepsin against deacetylation of histone in the promoter region of vascular endothelial growth factor *(VEGF)* gene was investigated by the chromatin immunoprecipitation method. Results showed that romidepsin inhibited deacetylation of histone H3 and H4.

3.1.3 Cell cycle-arresting effect (CTD 4.2.1.1.2)

Using U-937 cell line, the effect of romidepsin on *p21* gene expression was investigated by reverse transcription polymerase chain reaction (RT-PCR). As a result, romidepsin increased the expression level of *p21* messenger ribonucleic acid (mRNA).

Using U-937 cell line, the cell cycle-arresting effect of romidepsin was investigated by flow cytometry. Romidepsin arrested the cell cycle at G1 and G2/M stages.

3.1.4 Apoptosis induction (CTD 4.2.1.1.2, 4.2.1.1.5)

Using U-937 and PC-3 cell lines, the apoptosis-inducing effect of romidepsin was investigated with annexin V and propidium iodide staining as the indices. As a result, romidepsin induced apoptosis in both cell lines.

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

3.1.5.1 Effect against leukemia- and malignant lymphoma-derived cell lines

3.1.5.1.1 *In vitro* (CTD 4.2.1.1.3)

The growth-inhibitory effect of romidepsin against various human leukemia-derived cell lines and U-937 cell line was investigated using the reductase activity in viable cells as the index. Table 4 shows IC_{50} of romidepsin against the growth of each cell line.

Table 4. Growth-inhibitory effect of romidepsin against malignant tumor-derived cell lines

Cell line	IC_{50} (ng/mL)
CCRF-CEM	3.76
THP-1	4.09
ML-3	3.31
HL-60	0.60
JOSK-1	3.75
K562	4.52
JOK-1	2.97
U-937	3.20

n = 3 (mean)

3.1.5.1.2 *In vivo* (CTD 4.2.1.1.2, 4.2.1.1.4)

U-937 cell line was transplanted intraperitoneally into severe combined immunodeficiency (SCID) mice and, romidepsin was administered intraperitoneally to the mice once or twice weekly starting from Day 1 after the transplantation. The effect of romidepsin on the survival of animals was investigated using median survival time (MST) as the index. A statistically significant prolongation of the survival was observed in all romidepsin groups regardless of dose or dosage regimen compared with the control group (physiological saline containing 10% polyoxyethylene hydrogenated castor oil 60) ($P < 0.01$, Peto's test) (Table 5).

Table 5. Effect of romidepsin on the survival of SCID mice intraperitoneally transplanted with U-937 cell line

Administration method	Romidepsin dose (mg/kg)	n	MST (days)	T/C value* (%)
Control	0	12	20.0	100
Romidepsin Once weekly administration	0.10	6	22.5	113
	0.18	6	27.0	135
	0.32	6	28.0	140
	0.56	6	30.5	153
	1.00	6	28.0	140
Romidepsin Twice weekly administration	0.10	6	25.0	125
	0.18	6	26.0	130
	0.32	6	33.0	165
	0.56	6	27.0	135
	1.00	6	25.5	128

* T/C value = {(MST of the romidepsin group) / (MST of the control group)} × 100

3.1.5.2 Growth inhibitory effect against cell lines derived from malignant tumors other than leukemia and malignant lymphoma (CTD 4.2.1.1.4, 4.2.1.1.8, 4.2.1.1.9)

Romidepsin inhibited tumor growth in the following mice:

- Mice subcutaneously transplanted with Colon 38 cell line derived from mouse colorectal cancer, M5076 cell line derived from mouse reticulosarcoma, or B16 cell line derived from mouse malignant melanoma

- Nude mice subcutaneously transplanted with LU-65, LC-6, and NCI-H522 cell lines derived from human lung cancer, SC-6 cell line derived from human gastric cancer, MX-1 cell line derived from human breast cancer, LOX (IMVI) cell line derived from human malignant melanoma, RXF-631L cell line derived from human renal cell carcinoma, and PC-3 cell line derived from human prostate cancer

3.2 Safety pharmacology

3.2.1 Effect on the central nervous system (CTD 4.2.1.3.1, 4.2.1.3.2)

Romidepsin (0.1, 0.3, 1.0 mg/kg) was continuously infused intravenously to rats (n = 6/group) over 4 hours, and the effect of romidepsin on the clinical signs and the behavior was investigated by Irwin method. A transient decrease in locomotor activity, limb tonus, and decreased grip strength were observed in the 0.3 mg/kg group and death, ataxia, abnormal gait, etc., in the 1.0 mg/kg group.

Romidepsin (0.1, 0.3, 1.0 mg/kg) was continuously infused intravenously over 4 hours to dogs (n = 4/group), and the effect of romidepsin on clinical signs and behavior was investigated. Increased locomotor activity was observed in the 0.1 and 0.3 mg/kg groups, increased body temperature in the 0.3 mg/kg group, and decreased food consumption and increased body temperature in the 1.0 mg/kg group.

Taking account of the observation that romidepsin is scarcely distributed in the central nervous system [see Section 4.2.1], the applicant explained that the findings observed in rats and dogs are unlikely due to the direct effect of romidepsin on the central nervous system.

3.2.2 Effect on cardiovascular system

3.2.2.1 Effect on human hERG potassium current (CTD 4.2.1.3.3)

Using human fetal kidney-derived HEK293 cell line introduced with *ether-a-go-go* related gene (hERG), the effect of romidepsin (0.3, 1.0, 10.0 μg/mL) on hERG potassium current was investigated. Romidepsin at 1.0 and 10.0 μg/mL inhibited hERG potassium current by 18.0% ± 1.4% and 37.3% ± 2.0% (mean ± standard error), respectively, showing a statistically significant inhibition ($P < 0.001$, Dunnett's multiple test) compared with the control (extracellular perfusate[1)]) group (8.3% ± 0.6%).

3.2.2.2 Effect on blood pressure, heart rate, and electrocardiogram (CTD 4.2.1.3.2, 4.2.1.3.4)

Using papillary muscles isolated from guinea pig hearts, the effect of romidepsin (0.3, 1.0, 10.0 μg/mL) on the action potential of cardiac muscle (action potential duration at 90% repolarization [APD_{90}], action potential amplitude [APA], resting potential, maximum rate of rise [dV/dt max]) was investigated. APD_{90} and APA in the 10.0 μg/mL group showed a statistically significant decrease ($P < 0.01$, Student's t-test) compared with the control (Tyrode's solution[2)]) group.

Romidepsin (0.1, 0.3, 1.0 mg/kg) was continuously infused intravenously to dogs (n = 4) over 4 hours, and the effect of romidepsin on systolic blood pressure, diastolic blood pressure, mean blood pressure, heart rate, and electrocardiogram (PR, QRS, RR, QT, and QTc intervals) was investigated. Animals in the 1.0 mg/kg group showed increases in systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rate, decreased RR interval, and prolonged QTc interval.

Taking account of the fact that romidepsin-induced prolongation of QT/QTc was observed not only in the above study but also in clinical studies [see Section 7.R.3], the applicant explained that appropriate advice will be provided to healthcare professionals using the package insert, etc.

3.2.3 Effect on respiratory system (CTD 4.2.1.3.2)

Romidepsin (0.1, 0.3, 1.0 mg/kg) was continuously infused intravenously to dogs (n = 4) over 4 hours, and the effect of romidepsin on respiratory rate and hemoglobin oxygen saturation was investigated. Animals in the 0.1 and 1.0 mg/kg groups showed a statistically significant increase in respiratory rate ($P < 0.05$ and $P < 0.01$, respectively, in Dunnett's multiple test).

Since no dose-response correlation was observed in the above results, the applicant explained that the increased respiratory rate is unlikely related to romidepsin.

3.2.4 Effect on hematopoietic system (CTD 4.2.1.3.2)

Romidepsin (0.1, 0.3, 1.0 mg/kg) was continuously infused intravenously to dogs (n = 4) over 4 hours, and the effect of romidepsin on white blood cell count, lymphocyte count, red blood cell count, hemoglobin (Hb), hematocrit value (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration (MCHC), and platelet count was investigated. The findings observed were increased platelet count in the 0.1 mg/kg group, increased MCHC and decreases in lymphocyte count and MCV in the ≥0.3 mg/kg groups, and increases in red blood cell count and Hb in the 1 mg/kg group.

Taking account of the observation that lymphocyte count decreased not only in the above study but also in clinical studies [see Section 7.R.3], the applicant explained that appropriate advice will be provided to healthcare professionals using the package insert, etc.

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1) 137.0 mmol/L sodium chloride, 4.0 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.

2) 137.0 mmol/L sodium chloride, 4.7 mmol/L potassium chloride, 0.4 mmol/L sodium dihydrogenphosphate dihydrate, 23.8 mmol/L sodium hydrogen carbonate, 11.0 mmol/L glucose, 2.2 mmol/L calcium chloride hexahydrate, and 1.3 mmol/L magnesium chloride hexahydrate.

3.2.5 Effect on receptors and ion channels (CTD 4.2.1.3.5, 4.2.1.3.6 [non-GLP])

The effect of romidepsin (10 μmol/L) on potassium channels (hERG, adenosine triphosphate (ATP)-sensitive potassium channels [K_{ATP}], small-conductance calcium-activated potassium channels [SK_{CA}]) was investigated using ^{3}H-astemizole, ^{3}H-glibenclamide, and ^{125}I-propericiazine, respectively. Romidepsin inhibited hERG and K_{ATP} channels by 7% and 15%, respectively.

The effect of romidepsin (0.3, 1.0, 10.0 μg/mL) on 62 types of receptors and ion channels was investigated using ^{3}H- or ^{125}I-labeled ligands. Romidepsin inhibited estrogen receptor by 9.3%, 26.6%, and 97.8%, respectively, and neurokinin 2 (NK2) receptor by 7.3%, 16.3%, and 71.4%, respectively.

Taking account of the clinical exposure in humans (C_{max}, 593.5 ng/mL)[3)] and the concentration used in the above nonclinical study (10,000 ng/mL), the applicant explained that romidepsin in clinical use is unlikely to cause adverse events induced by the inhibition of the above receptors or channels.

3.3 Pharmacodynamic drug interactions (CTD 4.2.1.4.2)

Using mice intraperitoneally transplanted with mouse lymphocytic leukaemia-derived L1210 cell line, the tumor growth inhibitory effect of the concomitant use of romidepsin with irinotecan hydrochloride hydrate (CPT-11), carboplatin (CBDCA), paclitaxel (PTX), mitomycin C (MMC), or doxorubicin hydrochloride (DXR) was investigated using combination index. Concomitant use of romidepsin (0.14 mg/kg) with DXR (1 mg/kg) brought about an enhanced tumor growth suppression compared with the administration of romidepsin or DXR alone. Also, concomitant use of romidepsin (0.14 mg/kg) with PTX (12.5 mg/kg) and concomitant use of romidepsin (0.14 mg/kg) with CBDCA (0.5 mg/kg) brought about an enhanced tumor growth suppression compared with the administration of romidepsin, PTX, or CBDCA alone.

3.R Outline of the review conducted by PMDA

Based on the results of the reviews on the submitted data and on the results of the following reviews, PMDA has concluded that romidepsin may possibly be effective against PTCL.

3.R.1 Mechanism of action of romidepsin and its efficacy in treatment of PTCL

The applicant's explanation about the mechanism of action of romidepsin and its efficacy against PTCL: Romidepsin is considered to inhibit tumor growth by the following mechanism: It inhibits HDAC activity, resulting in the inhibition of deacetylation of histone and other proteins, which in turn leads to activation of gene transcription through relaxation of the chromatin structure. Romidepsin thus regulates the expression of *p21* gene, etc., thereby inducing cell cycle arrest and apoptosis (*Biochem Pharmacol.* 2005;69:603-16, etc.) [see Sections 3.1.1 to 3.1.4].

Although there are no nonclinical studies that investigated the growth-suppressive effect of romidepsin against human PTCL-derived cell lines, romidepsin inhibited the growth of multiple tumor cell lines including human malignant lymphoma-derived U-937 cell line [see Section 3.1.5]. In addition, expression levels of HDAC1, 2, and 6 are increased in PTCL (*Histopathology*. 2009;54:688-98). These results suggest that romidepsin may possibly be effective against PTCL.

PMDA's view:

The explanation of the applicant is generally acceptable. However, there are many unknown factors that may be affected by the inhibitory effect of romidepsin against deacetylation in PTCL, and the direct relationship between the HDAC-inhibitory effect of romidepsin and its tumor growth-suppressive effect remains unclear. Information on factors affecting the efficacy of romidepsin in the treatment of PTCL may be important for predicting the efficacy of romidepsin in clinical use and for determining the eligibility of patients for the use of romidepsin. Therefore, such information should be continuously collected and any new findings should be communicated to healthcare professionals in a timely manner.

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3) Geometric mean of C_{max} following the continuous intravenous infusion of romidepsin (14 mg/m^2) over 4 hours in patients with relapsed or refractory PTCL in the Japanese phase I/II study (Study 001).

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

Pharmacokinetics (PK) of romidepsin in animals was investigated using rats and dogs. Investigations on plasma protein binding of romidepsin, drug metabolizing enzymes, and transporters were performed using biomaterials derived from humans and animals.

4.1 Absorption

4.1.1 Single-dose administration

A single dose of ^{14}C-labeled romidepsin (^{14}C-romidepsin) (0.3 mg/kg) was bolus administered intravenously to male rats, and radioactivity concentrations in blood and plasma were investigated. Following the intravenous administration, radioactivity in blood and plasma disappeared rapidly. AUC_{inf} of radioactivity in blood and plasma was 2546.4 and 483.5 ng Eq.·h/mL, respectively.

A single dose of romidepsin (0.3, 1.0 mg/kg) was administered intravenously to male and female dogs over 4 hours, and plasma romidepsin concentration was investigated (Table 6). No clear sex difference was observed in C_{max} and AUC_{last} of romidepsin.

Table 6. PK parameters of romidepsin (male and female dogs, single intravenous administration)

Dose (mg/kg)	Sex	C_{max} (ng/mL)	t_{max} (h)	AUC_{last} (ng·h/mL)
0.3	M	48.8 ± 23.4	1.0 ± 0	163 ± 90.1
	F	43.3 ± 8.4	1.7 ± 0.6	143 ± 31.6
1.0	M	218 ± 77	1.0 ± 0	671 ± 201
	F	146 ± 49	1.3 ± 0.6	454 ± 159

Mean ± SD, n = 3

4.1.2 Repeated-dose administration

Romidepsin (0.1, 0.33, 0.67 mg/kg) was bolus administered intravenously to male and female rats once a day on Days 1, 8, and 15 in each of 28-day cycles, and plasma romidepsin concentration was investigated (Table 7). In the 0.67 mg/kg group, the dose was increased to 1.0 mg/kg from Day 15.

On all days of measurement, C_{max} and AUC_{last} of romidepsin increased roughly in proportion to dose within the dose range investigated. No clear sex difference was observed in C_{max} and AUC_{last} of romidepsin. C_{max} and AUC_{last} of romidepsin on Day 176 were higher than those on Day 1.

Table 7. PK parameters of romidepsin (male and female rats, 26-week repeated intravenous administration)

Day of measurement	Dose (mg/kg)	Sex	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)
1	0.1	M	9.50	1.76	-
		F	17.9	2.49	-
	0.33	M	53.0	11.7	0.722
		F	37.1	7.96	0.208
	0.67	M	60.7	17.0	0.867
		F	93.0	18.7	0.479
176	0.1	M	19.0	5.16	0.206
		F	19.2	4.22	0.229
	0.33	M	129	28.7	1.11
		F	92.3	20.4	0.681
	1.0	M	377	86.9	1.95
		F	362	73.2	1.18

Mean; n = 3/measuring timepoint (PK parameters were calculated based on the mean plasma romidepsin concentration at each measuring timepoint); -, Not calculated

4.2 Distribution

4.2.1 Tissue distribution

A single dose of ^{14}C-romidepsin (0.3 mg/kg) was bolus administered intravenously to male albino rats, and tissue distribution of the radioactivity was investigated. The radioactivity concentration reached the maximum level at 5 minutes after dosing in all tissues except ileum, showing a particularly high level in kidney, urinary bladder, jejunum, liver, and adrenals (2187.3, 791.0, 684.3, 663.7, and 586.7 ng Eq./mL, respectively). At 4 hours after dosing, radioactivity concentrations in tissues other than brain, testis, and eyeballs were higher than the concentration in plasma. The tissue/plasma ratio of the

radioactivity concentration was higher at 24 hours after dosing than at 4 hours after dosing, from which the applicant explained that the radioactivity disappeared from tissues more gradually than from the plasma. Radioactivity concentration in each tissue at 168 hours after dosing was ≤21.5% of the level at 5 minutes after dosing, and undetectable in brain, white adipose tissue, and prostate.

4.2.2 Plasma protein binding

Human plasma or rat, dog, and human serum samples were incubated with ^{14}C-romidepsin (50-5000 ng/mL) for 3 minutes at 37°C, and plasma or serum protein binding of romidepsin was investigated by ultrafiltration. The binding rate of romidepsin to human plasma protein was 82.3% to 93.8%, and the binding rate of romidepsin to rat, dog, and human serum protein was 37.8% to 40.8%, 73.1% to 87.7%, and 82.2% to 94.5%, respectively.

Human serum albumin (40 mg/mL) or human α1-acid glycoprotein (1 mg/mL) was incubated with ^{14}C-romidepsin (50-5000 ng/mL) for 3 minutes at 37°C, and the binding of the radioactivity to human serum albumin and human α1-acid glycoprotein was investigated by ultrafiltration. The binding rate of romidepsin to human serum albumin and human α1-acid glycoprotein was 19.9% and 93.5%, respectively.

The applicant explained that these results suggest that, in human plasma and serum, romidepsin is bound mainly to α1-acid glycoprotein.

4.2.3 Distribution in blood cells

^{14}C-romidepsin (50-5000 ng/mL) was added to rat, dog, and human blood samples, and distribution of romidepsin in blood cells was investigated. The blood/plasma ratio of the radioactivity concentration in rats, dogs, and humans was 0.68 to 0.75, 0.58 to 0.65, and 0.56 to 0.61, respectively, with the distribution rate in blood cells being 15.6% to 25.2%, 1.5% to 12.3%, and 1.4% to 8.7%, respectively. The applicant explained that the above results suggest a higher distribution rate of romidepsin in plasma than in blood cells in all animal species tested.

4.2.4 Placental and fetal transfer

The applicant explained that although placental transfer of romidepsin was not investigated, taking account of the fact that romidepsin is a lipophilic low molecular weight compound, romidepsin may possibly cross the placenta and be transferred to fetuses.

4.3 Metabolism

4.3.1 *In vitro*

Rat, dog, and human liver microsomes were incubated with ^{14}C-romidepsin (10 μmol/L) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 40 minutes, and metabolites of romidepsin were investigated. In all animal species tested, the unchanged romidepsin was mainly detected, together with ≥20 types of metabolites. The recovery rate of the radioactivity was 76.4%, 89.8%, and 75.9% in rats, dogs, and humans, respectively, and the elimination rate of romidepsin was 117, 49.7, and 192 pmol/min/mg, respectively.

S9 fractions of rat, dog, and human liver were incubated with ^{14}C-romidepsin (10 μmol/L) in the presence of glutathione at 37°C for 10 minutes, and metabolites of romidepsin were investigated. M1 (reduced form) was the main metabolite detected, and the applicant explained that the results suggested that, after uptake into cells, romidepsin is rapidly metabolized to form M1.

The following investigations were conducted on cytochrome P450 (CYP) isoforms involved in the metabolism of romidepsin in humans. The applicant explained that the results obtained showed that romidepsin is metabolized mainly by CYP3A.

- Microsomes prepared from insect cells expressing human CYP isoforms (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5, and CYP4A11) were incubated with ^{14}C-romidepsin (10 μmol/L) in the presence of NADPH at 37°C for 10 minutes, and CYP isoforms involved in romidepsin metabolism were

investigated. Romidepsin was metabolized mainly by CYP3A4 and by CYP3A5, slightly by CYP1A1, CYP2B6, and CYP2C19, but scarcely by other CYP isoforms.

- Human liver microsomal fraction was incubated with ^{14}C-romidepsin (10 μmol/L) in the presence of NADPH and a CYP3A inhibitor (ketoconazole, 0.1-10 μmol/L) or anti-CYP3A4 monoclonal antibody at 37°C for 7.5 minutes, and the contribution of CYP3A to romidepsin metabolism was investigated. The CYP3A inhibitor inhibited romidepsin metabolism in a concentration-dependent manner, and the anti-CYP3A4 monoclonal antibody inhibited romidepsin metabolism by ≥90%.

4.3.2 *In vivo*

A single dose of ^{14}C-romidepsin (0.3 mg/kg) was bolus administered intravenously to bile duct-cannulated and -noncannulated male rats, and metabolites in plasma, urine, feces, and bile were investigated. In bile duct-noncannulated male rats, 12 different metabolites (radioactivity concentration of each metabolite ≤9.1% of the total radioactivity in each sample) were detected in plasma in addition to the unchanged romidepsin (5.2% to 14.8%) up to 4 hours after dosing. In bile duct-cannulated male rats, 21, 30, and 24 different metabolites (radioactivity concentration of each metabolite ≤4.9% of the total radioactivity in each sample), respectively, were detected in urine, feces, and bile in addition to the unchanged romidepsin (4.2%, 1.6%, 3.0%) up to 48 hours after dosing.

4.4 Excretion

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

A single dose of ^{14}C-romidepsin (0.3 mg/kg) was bolus administered intravenously to bile duct-cannulated and -noncannulated male rats, and the excretion rate of radioactivity in urine, feces, expired air, and bile (percentage of administered radioactivity) was investigated. In bile duct-noncannulated male rats, the urinary and fecal excretion rates of radioactivity up to 168 hours after dosing were 16.5% and 79.4%, respectively, and the excretion rate of radioactivity in expired air up to 72 hours after dosing was 0.1%. In bile duct-cannulated male rats, the urinary, fecal, and biliary excretion rates of radioactivity up to 48 hours after dosing were 20.0%, 5.2%, and 66.1%, respectively.

Based on the above results, the applicant explained that romidepsin is excreted mainly in feces via bile.

4.4.2 Excretion in milk

The applicant explained that although excretion of romidepsin in milk was not investigated, taking account of the fact that romidepsin is a lipophilic compound, romidepsin may possibly be excreted in milk.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The inhibitory effect of romidepsin against CYP isoforms was investigated, and the following results were obtained. The applicant explained that taking account of these results together with the finding that C_{max} of romidepsin following the administration by the proposed dosage and administration is approximately 1 μmol/L [see Section 6.2.1.1], romidepsin in clinical use is unlikely to cause pharmacokinetic interactions mediated by inhibition of CYP isoforms.

- When human liver microsomal fraction was incubated with substrates[4)] of CYP isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A) in the presence of romidepsin (1-100 μmol/L) and NADPH, romidepsin inhibited the metabolism of the substrates of CYP2C19, CYP2D6, and CYP3A with IC_{50} of ≥10 μmol/L. Romidepsin did not clearly inhibit the metabolism of the substrates of CYP1A2, CYP2C9, or CYP2E1.

- When human liver microsomal fraction was incubated with substrates[5)] of CYP isoforms (CYP2B6 and CYP2C8) in the presence of romidepsin (0.1-100 μmol/L) and NADPH, romidepsin inhibited the metabolism of the substrates of CYP2B6 and CYP2C8 with IC_{50} of ≥100 μmol/L. Also,

4) As the substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1, ethoxyresorufin, tolbutamide, *S*-mephenytoin, debrisoquine sulfate, and chlorzoxazone were used respectively. As the substrates of CYP3A, nifedipine and testosterone were used.

5) As the substrates of CYP2B6 and CYP2C8, bupropion and PTX were used respectively.

romidepsin inhibited CYP2B6 and CYP2C8 in a time-dependent manner, both with IC_{50} of ≥30 μmol/L.

4.5.2 Enzyme induction

Human liver cells were treated with romidepsin (0.5-10 μmol/L) for 2 days, and the effect of romidepsin to induce CYP isoforms (CYP1A2, CYP2B6, and CYP3A) was investigated. Romidepsin induced both the enzyme activity and mRNA of CYP1A2. In groups treated with romidepsin, the enzyme activity and mRNA expression level increased 1.0 to 3.8 fold and 2.2 to 8.5 fold, respectively, compared with the vehicle (0.1% dimethyl sulfoxide [DMSO] solution) group. The inducing activity was 0.2% to 9.6% and 0.8% to 5.2%, respectively, compared with CYP1A2-inducing activity of omeprazole (50 μmol/L), the active control. In contrast, romidepsin had no clear inducing effect on the enzyme activity or mRNA expression of CYP2B6 or CYP3A.

Taking account of (a) the above results, together with (b) the observation that C_{max} of romidepsin following the administration by the proposed dosage and administration is approximately 1 μmol/L [see Section 6.2.1.1], the applicant explained that romidepsin in clinical use is unlikely to cause pharmacokinetic interactions mediated by CYP isoform induction.

4.5.3 Transporters

Results of the following studies have shown that romidepsin is a substrate for P-glycoprotein (P-gp) and multidrug resistance-associated protein (MRP) 1. However, taking account of the observations (a) that the urinary excretion rate of the unchanged romidepsin following a single intravenous administration of ^{14}C-romidepsin in rats was 4.2% [see Section 4.3.2] and (b) that no clear difference was observed in the incidence of adverse events between the group co-administered with MRP1 inhibitor and the group co-administered without the inhibitor in clinical studies (Studies 001 and 0002), the applicant explained that co-administration of romidepsin with P-gp or MRP1 inhibitor is unlikely to cause pharmacokinetic interactions in clinical use.

- Using human colon cancer-derived Caco-2 cell line, P-gp-mediated transport of romidepsin (0.5-20 μmol/L) was investigated. The ratio of apparent permeability in basolateral to apical direction ($P_{app\ B\rightarrow A}$) to apparent permeability in apical to basolateral direction ($P_{app\ A\rightarrow B}$) of romidepsin was 1.65 and 2.47, respectively, in the presence of a P-gp inhibitor cyclosporine (5 mol/L) or verapamil (100 mol/L), and 32 in the absence of P-gp inhibitor (*J Pharmacol Expt Ther*. 2005;313:268-76).

- Using human red blood cells and HL60Adr cell line expressing MRP1, MRP1-mediated transport of romidepsin (1.8-18 μmol/L) was investigated. In the presence of an MRP1 inhibitor (MK571 50 μmol/L), romidepsin uptake into human red blood cells and the cytotoxic effect of romidepsin against HL60Adr cell line increased (*J Pharmacol Expt Ther.* 2005;313:268-76).

- Using membrane vesicles expressing human breast cancer resistance protein (BCRP), bile salt export pump (BSEP), or MRP2, each transporter-mediated transport of romidepsin (1, 10 μmol/L) was investigated. The uptake of romidepsin into BCRP, BSEP, or MRP2-expressing membrane vesicles was similar to that into non-expressing membrane vesicles.

- Using mouse kidney-derived S2 cell line expressing human organic anion transporter (OAT) 1 or OAT3, OAT1- or OAT3-mediated transport of romidepsin (1, 10 μmol/L) was investigated. The uptake of romidepsin into OAT1- or OAT3-expressing cells was similar to that into the non-expressing cells.

- Using HEK293 cell line expressing human organic anion transporting polypeptide (OATP) 1B1, OATP1B3, or organic cation transporter (OCT) 2, each transporter-mediated transport of romidepsin (1, 10 μmol/L) was investigated. The uptake of romidepsin into OATP1B1-, OATP1B3-, or OCT2-expressing cells was similar to that into non-expressing cells.

The following results showed that romidepsin inhibited BSEP, OAT1, OATP1B1, OATP1B3, and OCT2. However, taking account of the observation that C_{max} of romidepsin following the administration of romidepsin by the proposed dosage and administration is approximately 1 μmol/L [see Section 6.2.1.1],

the applicant explained that romidepsin in clinical use is unlikely to cause pharmacokinetic interactions mediated by the inhibition of BSEP, OAT1, OATP1B1, OATP 1B3, or OCT2.

- Using pig kidney-derived LLC-PK1 cell line expressing human P-gp, the inhibitory effect of romidepsin (1, 10 μmol/L) against P-gp-mediated transport of ^{3}H-digoxin (1 μmol/L) was investigated. Romidepsin did not clearly inhibit the transport of ^{3}H-digoxin.

- Using membrane vesicles expressing human BCRP, BSEP, or MRP2, the inhibitory effect of romidepsin (1, 10 μmol/L) against BCRP-, BSEP-, or MRP2-mediated transport of each substrate[6)] was investigated. Romidepsin inhibited the transport of the substrate of BSEP by 39.7% and 57.3%, but did not clearly inhibit the transport of the substrate of BCRP or MRP2.

- Using S2 cell line expressing human OAT1 or OAT3, the inhibitory effect of romidepsin (1, 10 μmol/L) against the transport of OAT1- or OAT3-mediated transport of each substrate[6)] was investigated. Romidepsin at the maximum concentration tested inhibited the transport of the substrate of OAT1 by 41.3%, but did not clearly inhibit the transport of the substrate of OAT3.

- Using HEK293 cell line expressing human OATP1B1, OATP1B3, or OCT2, the inhibitory effect of romidepsin (1, 10 μmol/L) against OATP1B1-, OATP1B3-, or OCT2-mediated transport of each substrate[6)] was investigated. Romidepsin inhibited the transport of the substrates of OATP1B1 by 35.9% and 80.4%, respectively, and, at the maximum concentration tested, inhibited the transport of the substrates of OATP1B3 or OCT2 by 56.5% and 32.1%, respectively.

4.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's discussions on the absorption, distribution, metabolism, excretion, and pharmacokinetic interactions of romidepsin are acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

5.1.1 Single intravenous dose toxicity study in rats

A single dose of romidepsin (0 [negative control, physiological saline], 0 [vehicle, 80% aqueous propylene glycol solution], 0.7, 1.0, 1.4, 1.9, 2.6, 3.6, 5.1 mg/kg) was administered intravenously to rats (SD, n = 5/sex/group).

Death occurred in 1 male in the 0.7 mg/kg group, in all males and 1 female in the 3.6 mg/kg group, and in all males and 4 females in the 5.1 mg/kg group. White turbidity and dark reddish macule of the thymus and darkening of the lung were observed in dead animals. The applicant explained that romidepsin is unlikely related to the death of animals, for the following reasons: (1) Although 1 male in the 0.7 mg/kg group died, no death occurred in the 1.0 to 2.6 mg/kg groups, and (2) the animal in the 0.7 mg/kg group and 1 male in the 3.6 mg/kg group died within 10 minutes after administration, whereas in other animals, death occurred 1 day after administration or later, which suggests that the death in these animals was due to the toxicity of vehicle (propylene glycol) (*Pharm Res.* 2004;21:201-30).

Surviving animals showed white foci in the thymus, white turbidity in the thymic parenchyma, petechia in the glandular stomach, loss of tail tip, and tail discoloration in the ≥1.4 mg/kg groups, and spleen discoloration in the 5.1 mg/kg group.

Based on the above, the approximate lethal dose in this study was determined to be 2.6 to 3.6 mg/kg in males and 3.6 mg/kg in females.

5.1.2 Single intravenous dose toxicity study in dogs

A single dose of romidepsin (0 [vehicle, propylene glycol and ethanol diluted with physiological saline], 0.01, 0.1, 1.0 mg/kg) was administered intravenously to dogs (beagle, n = 1/sex/group), and the animals were observed for 14 days post-dose.

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6) The substrate used for each transporter was ^{3}H-methotrexate (100 μmol/L) for BCRP, ^{3}H-taurocholic acid (2 μmol/L) for BSEP, ^{3}H-estradiol-17β-glucuronide (10, 0.05, and 0.05 μmol/L, respectively) for MRP2, OATP1B1, and OATP1B3, ^{3}H- *p*-aminohippuric acid (1 μmol/L) for OAT1, ^{3}H-estrone sulfate (0.05 μmol/L) for OAT3, and ^{14}C-metformin (10 μmol/L) for OCT2.

No death occurred. Animals in the ≥0.1 mg/kg groups showed decreased locomotor activity, lacrimation, dry nose, vomiting, body temperature increase (on the next day of administration), decreased body weight, decreased food consumption, decreased relative lymphocyte count, thymic atrophy, and decreased lymphocyte count in the thymic cortex. Animals in the 1.0 mg/kg group showed tremor, irregular heart rate, tachypnea, cough, salivation, body temperature decrease during administration, decreased white blood cell count, increases in aspartate aminotransferase (AST), glucose, and total cholesterol, and decreases in calcium, potassium, and blood urea nitrogen (BUN).

Based on the above, the approximate lethal dose in this study was determined to be >1.0 mg/kg.

5.1.3 Single dose toxicity study in rats (Reference data)

A single dose of romidepsin (17.5, 55, 175, 550 mg/kg) was administered orally to female rats (SD, n = 1-2/group). One of 2 animals in the 55 mg/kg group, 2 of 2 in the 175 mg/kg group, and 1 of 1 in the 550 mg/kg group died or were moribund sacrificed because of severe changes in clinical signs or decreased body weight.

Based on the above, 50% lethal dose of romidepsin in a single oral administration in this study was estimated to be 55 mg/kg.

5.2 Repeated-dose toxicity

5.2.1 Four-week intermittent intravenous dose study in mice (Reference data)

Romidepsin was bolus administered intravenously to male mice (CD2F1, n = 10/group) for 4 weeks once weekly at a dose of 3.6, 5.3, or 8.0 mg/kg, or twice weekly at a dose of 0 (vehicle, propylene glycol and ethanol diluted with physiological saline), 3.6, 5.3, or 8.0 mg/kg. Some of the animals were allowed to undergo a 22-day (twice weekly group) or 27-day (once weekly group) recovery period after the end of the 4-week administration period.

In the 8.0 mg/kg once weekly group, 2 animals died on Day 4, and 2 animals were moribund-sacrificed on Day 15 because of the aggravation of the clinical signs. In the 8.0 mg/kg twice weekly group, 2 animals were moribund-sacrificed on Day 20 because of the aggravation of the clinical signs. Dead or moribund-sacrificed animals showed inflammation of tail skin, growth of myeloid cells and growth and necrosis of erythroid cells in spleen, growth or depletion of hematopoietic cells in bone marrow, liver fatty metamorphosis, extramedullary hematopoiesis in the liver, thymic atrophy, and testicular degeneration.

Surviving animals showed reduced body weight gain, swelling of tail and inflammatory changes of skin at the injection site, discoloration of femoral bone marrow, spleen enlargement, and smaller testis in the ≥3.6 mg/kg groups; hunchback position, emaciation, decreases in red blood cell count, Hb, and HCT, and increased white blood cell count in the ≥5.3 mg/kg groups; and increases in MCV, mean corpuscular hemoglobin (MCH), platelet count, and reticulocyte count, decreased MCHC, spleen discoloration, depletion of hematopoietic cells in bone marrow, testicular degeneration, and splenic red pulp atrophy in the 8.0 mg/kg group.

Among the findings observed after the end of administration, testicular findings were irreversible, whereas all other changes were reversible or tended to be reversible.

Based on the above, the maximum tolerated dose (MTD) in this study was determined to be 5.3 mg/kg once or twice weekly.

5.2.2 Three-week intermittent intravenous dose toxicity study in rats

Romidepsin (0 [vehicle, propylene glycol and ethanol diluted with physiological saline], 0.1, 0.3, 1.0 mg/kg) was continuously infused intravenously to rats (SD, n = 10-12/sex/group) once weekly for 3 weeks. Some of the animals were allowed to undergo a 2-week recovery period after the end of the 3-week administration period.

Four of 11 males and 5 of 12 females in the 1.0 mg/kg group died 2 to 3 days after the first dose. They showed decreased locomotor activity, tremor, tonic convulsion, clonic convulsion, bradypnea, salivation, prone position, loose stool, smudge of perinasal and perioral area, thrombus and thickening of vascular intima at the injection site (femoral vein), necrosis of adrenal cortex, depletion of bone marrow hematopoietic cells, lymphocyte necrosis in ileum and cecum, degeneration and necrosis of colonic epithelium, necrosis and depletion of lymphocytes in lymph nodes, pulmonary granuloma, acinar cell necrosis in mammary gland, salivary gland, and submandibular gland, necrosis and depletion of splenic lymphocytes, degeneration and necrosis of gastric epithelium, and necrosis of thymic lymphocytes.

Surviving animals showed transient decrease in food consumption, necrosis of thymic lymphocytes, and increased tingible body macrophage count in the bone marrow in the ≥0.1 mg/kg groups; decreased alkaline phosphatase (ALP) in the 0.3 mg/kg group; localized lenticular opacities, decreases in white blood cell count and lymphocyte count in differential white blood cell count, increased segmented and band neutrophil counts in differential white blood cell count, prolonged prothrombin time and activated partial thromboplastin time (APTT), increased AST and lactate dehydrogenase (LDH), decreased thymic and adrenal weights, necrosis of lymphocytes in splenic pulp, necrosis of lymphocytes in lymph nodes, necrosis of acinar cells in the submandibular gland, ossification of femoral bone marrow, extramedullary hematopoiesis in the liver, necrosis of lymphocytes in ileum and cecum, decreased ovarian follicles, and smaller corpus luteum in the ≥0.3 mg/kg groups; and transient decrease in body weight, increased water consumption, increased urine volume, decreased urinary osmotic pressure, decreases in red blood cell count, HCT, Hb, MCV, and reticulocyte count, increased MCHC, increased monocyte count in differential white blood cell count, increases in fibrinogen, amylase, and creatine kinase (CK), decreases in potassium and calcium, increases in cholesterol, phospholipids, and α2-globulin ratio, decreases in γ-globulin, sodium, chlorine, and albumin/globulin ratio (A/G ratio), increases in alanine aminotransferase (ALT) and ALP, changes in triglyceride (TG) (increase in males, decrease in females), decreased weights of salivary gland, spleen, and ovary, dark red foci in heart, depletion of lymphocytes and hematopoietic cells in spleen, mineralization of gastric mucosa, degeneration and necrosis of duodenal, jejunal, and ileal epithelia, duodenal erosion, atrophy of mammary acinar cells, necrosis of adrenocortical cells, eosinophilic droplets in adrenal medullas, and cardiac congestion in the 1.0 mg/kg group.

Of the findings observed after the end of administration, those of the ovary were more frequent and severe after the recovery period than after the end of administration, whereas other changes were reversible or tended to be reversible. Increased hematopoietic cells in spleen were observed after the recovery period.

Based on the above, the no observed adverse effect level (NOAEL) in this study was determined to be <0.1 mg/kg/dose.

5.2.3 Twenty six-week intermittent intravenous dose toxicity study in rats

Romidepsin (0 [vehicle, ethanol diluted with physiological saline], 0.1, 0.33, 0.67/1.0 mg/kg) was bolus administered intravenously to rats (SD, n = 20/sex/group) once weekly for 3 weeks, followed by a 1-week rest period. This treatment cycle was repeated for 26 weeks. Animals in the 0.67/1.0 mg/kg group received 0.67 mg/kg at the first 2 doses and 1.0 mg/kg at the third and subsequent doses.

One animal in the 0.1 mg/kg group died. The animal showed onychoclasis, browning of fur, and skin exfoliation, but the cause of death was not identified.

Surviving animals showed increases in reticulocyte count and red cell distribution width, decreases in white blood cell count and eosinophil count, decreased thymic weight, smaller thymus and ovary, decreased hematopoietic cells and pigmentation in bone marrow, pigmentation of spleen, atrophy and necrosis of lymphocytes in thymus, lymphocyte hyperplasia in thymus, pigmentation of hepatocytes and Kupffer cells, atrophy of ovary, decreases in corpora lutea and follicle counts in ovary, increased cysts in ovary, atrophy of uterus and vagina, decreased thickness of endometrial epithelium and decreased activity of endometrial gland, mucus secretion from vaginal epithelium and mammary gland atrophy in the ≥0.1 mg/kg groups; increased mean platelet volume, decreased lymphocyte count, increased ALT, decreased total protein, decreased weights of adrenal, renal, hepatic, ovarian, and prostatic, increased

pituitary weight, pituitary enlargement, hyperplasia of anterior pituitary gland, lymphatic tissue atrophy and necrosis of lymphocytes in spleen, increased extramedullary hematopoiesis, degeneration and necrosis of vaginal endothelium, and degeneration and atrophy of seminiferous tubule in the ≥0.33 mg/kg groups; and decreases in albumin and calcium, prolonged prothrombin time, decreased uterine weight, increased megakaryocyte count in bone marrow, and vacuolization of anterior pituitary gland in the 0.67/1.0 mg/kg group.

Based on the above, the NOAEL in this study was determined to be <0.1 mg/kg/dose. AUC in the 0.1 mg/kg group (4.22-5.16 ng·h/mL) was less than the clinical exposure.[7)]

5.2.4 Nine-day intermittent intravenous dose toxicity study in dogs (once every 4 days, 3 times in total)

Romidepsin (0 [vehicle, propylene glycol and ethanol diluted with physiological saline], 1.0, 2.0 mg/kg) was continuously infused intravenously to dogs (beagle, n = 2/sex/group) over 4 hours (the 1.0 and 2.0 mg/kg groups) or 24 hours (the 0 and 2.0 mg/kg groups) once every 4 days, 3 times in total. Some of the animals were allowed to undergo a 42-day recovery period after the end of the 9-day administration period.

Four animals in the group receiving 2.0 mg/kg of romidepsin over 24 hours died on Day 2. One animal in the group receiving 2.0 mg/kg of romidepsin over 4 hours was moribund-sacrificed on Day 4 because of aggravation of clinical signs supposedly caused by infection. Dead or moribund-sacrificed animals showed haemorrhagic diarrhoea, vomiting, salivation, tachypnoea, scleral hyperaemia, redness of ear and gum, depletion of hematopoietic cells in bone marrow, haemorrhage from heart, lung, and brain, haemorrhage and necrosis of large intestinal mucosa, necrosis of small intestinal mucosa, haemorrhage and atrophy of lymph nodes, atrophy of splenic lymphoid follicles, atrophy of thymus and tonsil, urinary bladder haemorrhage, and skin oedema at the injection site.

Surviving animals showed aggressive behavior, protrusion of nictitating membrane, and haemorrhage of mammary gland and mesenterium in the 1.0 mg/kg group; vomiting, diarrhoea, salivation, eye discharge, scleral hyperaemia, redness of ear and gum, claudication, swelling, inflammation, and oedema of injection site, increased neutrophil count, decreased lymphocyte count, increases in AST and CK, degeneration of small intestinal mucosa, atrophy of lymph nodes, thymus, and tonsil, atrophy of splenic lymphoid follicles, decreased sperm count in testis and epididymis, and degeneration of seminiferous tubules in the ≥1.0 mg/kg groups; and whitish discoloration of gum, skin redness, increased ALT, prolonged prothrombin time, infiltration of plasma cells into large intestinal mucosa, enlarged mucosal glands of large intestine, pulmonary haemorrhage, and inflammation of lymph nodes in the 2.0 mg/kg group.

Of the findings observed after the end of administration, atrophy of lymph nodes, thymus, and tonsil, atrophy of splenic lymphoid follicles, skin inflammation at the injection site, and decreased sperm count in testis were irreversible.

Based on the above, the MTD in this study was determined to be 1.0 mg/kg/dose (once every 4 days).

5.2.5 Three-week intermittent intravenous dose toxicity study in dogs

Romidepsin (0 [vehicle control, propylene glycol and ethanol diluted with physiological saline], 0.3, 1.0 mg/kg) was continuously infused intravenously to dogs (beagle, n = 2/sex/group) over 4 hours once weekly for 3 weeks. Some of the animals were allowed to undergo a 2-week recovery period after the end of the 3-week administration period.

No death occurred. Findings observed were vomiting, loose stool, transient decrease in body weight and food consumption, increased heart rate, prolonged QT interval, decreases in red blood cell count, Hb, HCT, fractional reticulocyte count, white blood cell count, and fractional lymphocyte count, increased fractional neutrophil count, increased fibrinogen, prolonged APTT, increases in AST and LDH,

7) In patients with PTCL receiving romidepsin (14 mg/m^2) on Days 1, 8, and 15, AUC_t on Day 15 was 1825.74 ng·h/mL (Study 001).

decreased BUN, decreases in inorganic phosphorus, calcium, sodium, potassium, and chlorine, necrosis of hematopoietic cells in bone marrow, haemosiderin deposition in spleen and extramedullary haemopoiesis, atrophy of lymphoid follicles and necrosis of lymphocytes in spleen and lymph nodes, thymic atrophy and lymphocyte necrosis, infiltration of inflammatory cells in lymph nodes and stomach, infiltration of mononuclear cells in basophilic renal tubules and stroma of kidney, atrophy of seminiferous tubules in testis, and atrophy of prostate gland in the ≥0.3 mg/kg groups; and dark red watery stool, tachypnoea, hypertonia, swelling of injection site, prolonged QTc, increases in ALT and CK, increased relative kidney weight, decreased relative testicular weight, perivascular necrosis at injection site, decreased hematopoietic cells in bone marrow, infiltration of inflammatory cells in spleen, degeneration of mucosal epithelium of small and large intestines, and decreased sperm count in epididymis in the 1.0 mg/kg group. Changes in clinical chemistry parameters were observed mainly after the first dose, but mostly recovered at the test performed after the third dose.

Of the findings observed after the end of administration, haemosiderin deposition in spleen, atrophy of lymphoid follicles and extramedullary haemopoiesis, thymic atrophy and lymphocyte necrosis, atrophy of lymphoid follicles and infiltration of inflammatory cells in lymph nodes, atrophy of seminiferous tubules in testis, decreased sperm count in epididymis, and prostatic atrophy were irreversible.

Based on the above, the NOAEL in this study was determined to be <0.3 mg/kg/week. The estimated AUC in the 0.3 mg/kg group (143.2-163.4 ng·h/mL) was below the clinical exposure.[7)]

5.3 Genotoxicity

In vitro genotoxicity studies consisted of a bacterial reverse mutation assay and a chromosomal aberration assay in mouse lymphocytes. The *in vivo* genotoxicity study consisted of a rat bone marrow micronucleus assay.

The reverse mutation assay and the micronucleus assay were both negative. The chromosomal aberration assay showed an increase in mutation frequency.

Based on the observations that, in the chromosomal aberration assay, biologically significant increase in mutation rate was induced only at cytotoxic doses, and that, in the rat micronucleus assay, no micronucleus was induced by romidepsin of up to the MTD (1 mg/kg in males, 3 mg/kg in females), the applicant explained that romidepsin in clinical use is unlikely to be genotoxic.

5.4 Carcinogenicity

Since romidepsin is intended to be used for the treatment of patients with advanced cancer, no carcinogenicity study was conducted.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

No study on the effect of romidepsin on fertility was conducted. Instead, the effect of romidepsin on male and female fertility was evaluated based on the findings of male and female reproductive organs in repeated-dose toxicity studies.

The repeated-dose toxicity studies in rats [see Sections 5.2.2 and 5.2.3] showed, as the findings of female reproductive organs, ovarian atrophy, decreased follicles in the ovary, smaller corpora lutea, and findings of uterus and vagina. The findings of ovary were irreversible.

The repeated-dose toxicity studies in mice, rats, and dogs [see Sections 5.2.1, 5.2.3, 5.2.4, and 5.2.5] showed, as the findings of male reproductive organs, prostatic atrophy, smaller testis, degeneration and necrosis of seminiferous tubular epithelium, decreased sperm count in testis and epididymis, and the findings of the testis were irreversible.

Based on the above toxicity study results, the applicant explained the effect of romidepsin on male and female fertility as follows:
The findings on the male and female reproductive organs observed in the repeated-dose toxicity studies of romidepsin may also occur in clinical use of romidepsin, thus suggesting the possibility of the effects

on the fertility of men and women. Therefore, the data of the above toxicity studies will be provided together with appropriate advice in the package insert.

5.5.2 Embryo-fetal development in rats

Romidepsin (0 [vehicle, ethanol diluted with physiological saline], 0.1, 0.2, 0.5 mg/kg) was bolus administered intravenously to pregnant rats (SD, n = 21-25/group) once daily from Gestation Day 6 to Gestation Day 17. One maternal animal in the 0.5 mg/kg group died on Gestation Day 18.

Surviving maternal animals showed decreased body weight, reduced body weight gain, and decreased food consumption in the ≥0.1 mg/kg groups; decreased gravid uterus weight in the ≥0.2 mg/kg groups; increased early resorption in the 0.2 mg/kg group; and brown or reddish substances around the vagina, hunchback position, dehydration, swollen tail, whitening of ear and limbs, decreased locomotor activity, and total resorption of litter in the 0.5 mg/kg group.

Findings observed in fetuses were increased frequency of fetuses with hindlimb torsion or folded retina in the 0.2 mg/kg group; decreased fetal body weight and delayed ossification in the ≥0.2 mg/kg groups; and increased frequency of extra ribs in the 0.5 mg/kg group.

Based on the above, the NOAEL in this study was determined to be <0.1 mg/kg in maternal animals and 0.1 mg/kg in embryo-fetal development. AUC_t of romidepsin in the 0.1 mg/kg group (2.44 ng·h/mL) was below the clinical exposure.[7)]

5.6 Local tolerance

5.6.1 Skin irritation study in rabbits

A gauze patch (2.5 cm × 2.5 cm) containing romidepsin (0 or 0.5 g) was applied to male rabbits (New Zealand White [NZW], n = 1/group) at the ventral part for 4 hours and, at 1, 24, 48, and 72 hours after the removal of the patch, animals were monitored for skin reaction at the application site and for clinical signs. No romidepsin-associated findings were observed, from which it was determined that romidepsin is not irritating to the skin.

5.6.2 Local lymph node assay

Romidepsin (0 [vehicle, a mixture of acetone and olive oil (4:1) (v/v)], 0.025%, 0.05%, 0.1%, and 0.25% solution [25 μL]) was applied to the backside of the ear of female mice (CBA/Ca, n = 5/group) for 3 days. Growth of lymphocytes in the lymph node was observed 3 days after the final applying, from which it was determined that romidepsin has a sensitizing effect in mice.

5.7 Other studies

5.7.1 Repeated-dose toxicity study of *t*-butyl alcohol

In order to evaluate the safety of *t*-butyl alcohol, an impurity contained in romidepsin, a repeated-dose toxicity study was conducted in rats.

t-Butyl alcohol (vehicle, [physiological saline], 5, 50, 500 mg/kg) was bolus administered intravenously to rats (SD, n = 10/sex/group) once weekly, 3 times in total, and the animals were necropsied on Day 16 after the first dose.

Animals in the ≥5 mg/kg groups showed increased urine volume and decreased urine specific gravity, suggesting a diuretic effect. However, since the findings in the 5 and 50 mg/kg groups were not accompanied by related laboratory changes or histopathological findings, they were not considered to be toxic findings. Animals in the 500 mg/kg group showed changes in clinical signs (abnormal gait, ataxia, general debility, lateral position, shallow respiration, laboured respiration, hypotonia, partially closed eyes, red urine, etc.), changes at injection site (tail) (skin discolouration, dry skin, scab and swelling, inflammation, thrombosis, ulceration, etc.), and increased frequency and severity of hyaline droplets in proximal renal tubules of kidney in males.

Based on the above, the NOAEL of *t*-butyl alcohol in this study was determined to be 50 mg/kg/week.

The applicant's explanation about the safety of *t*-butyl alcohol contained in romidepsin:

According to the "Impurities: Guidelines on Residual Solvents" (PMSB/ELD Notification No. 307 dated March 30, 1998), and based on the NOAEL (50 mg/kg/week) in this study, the acceptable weekly exposure to *t*-butyl alcohol is considered to be 10 mg. Since the amount of t-butyl alcohol contained in the maximum dose of romidepsin per dose in clinical use (1.6 mg/week at the upper limit of acceptance criteria) is below the acceptable weekly exposure, t-butyl alcohol is unlikely to pose any safety problem.

5.7.2 Cardiovascular toxicity study in nude mice (Reference data)

In order to evaluate the cardiac toxicity of romidepsin in mice, romidepsin was administered to female nude mice (NCr, n = 5/group) by the following methods: (1) Intraperitoneally or intravenously at 0 to 5.3 mg/kg or at 0 to 8.0 mg/kg (vehicle, aqueous polyethylene glycol solution or water) once every 4 days, 3 times in total, (2) intravenously at 0 to 2.16 mg/kg once daily for 5 days, or (3) intraperitoneally at 0 to 0.66 mg/kg 8 times daily at intervals of 3 hours, every 4 days, 3 times in total. Histopathological examination of the heart was performed 3 to 5 days after the last dose.

The histopathological examination of the heart showed chronic localized inflammation in the group intravenously administered with 2.16 mg/kg/day for 5 days or 5.3 mg/kg/dose 3 times. The applicant explained that the result suggests a possible effect of romidepsin on the heart.

5.7.3 *In vitro* cardiac toxicity study (Reference data)

Using cardiac myocytes isolated from newborn F344 and SD rats and beagle dogs, and human fetal cardiac myocyte-derived immortalized cell line W1, cytotoxicity of romidepsin (0.1-100 μmol/L) and the effect of romidepsin to induce LDH release from cardiac myocytes were evaluated. In all cardiac myocytes investigated, romidepsin showed cytotoxicity and induced the release of LDH; in human fetus-derived cardiac myocyte cell line, romidepsin showed cytotoxicity at ≥0.1 μmol/L. The cytotoxicity and LDH release-inducing effect of romidepsin was more potent compared with positive controls minoxidil (0.1-100 μmol/L) and DXR (0.001-10 μmol/L). The applicant explained that the results suggest that romidepsin may affect the heart.

5.7.4 *In vitro* bone marrow toxicity (Reference data)

The growth-suppressive effect of romidepsin (0.001-10.0 nmol/L) against bone marrow cells of male CD2F1 mice, beagle dogs, and humans was investigated. Romidepsin concentration required for suppressing cell growth by 50% was 1.0 and 0.35 nmol/L, respectively, with mouse and dog bone marrow cells, whereas the 50% inhibitory concentration in human bone marrow cells was 0.03 nmol/L.

5.7.5 Effect on the uterus of immature female rats

Romidepsin (0 [vehicle, ethanol diluted with physiological saline], 0.1, 0.4 mg/kg) was bolus administered intravenously to immature female rats (SD, n = 10/group) for 3 days from Postnatal Day 19 to 21, and body weight and weights of uterus, ovary, and fallopian tube were evaluated.

Animals in the ≥0.1 mg/kg groups showed reduced body weight gain and decreased body weight, and those in the 0.4 mg/kg group showed decreased ovary weight and decreased fallopian tube weight. However, no change was observed in uterine weight in romidepsin groups.

The applicant explained that the above results suggest that romidepsin does not induce uterine enlargement in immature female rats.

5.7.6 Photosafety evaluation

No photosafety study was conducted on romidepsin. However, since romidepsin does not absorb light in the wavelength range of 290 to 700 nm, the applicant explained that romidepsin is unlikely to be phototoxic.

5.R Outline of the review conducted by PMDA

Based on the submitted data and on the results of the following review, PMDA concluded that non-clinical toxicity data do not pose any problems about clinical use of romidepsin.

5.R.1 Lenticular opacities

PMDA asked the applicant to explain the extrapolability to humans of localized lenticular opacities observed in the rat 3-week intermittent intravenous dose toxicity study [see Section 5.2.2].

The applicant's response:
The lenticular opacities observed in rats are unlikely to be extrapolable to humans for the following reasons:

- No lenticular opacities or other ocular findings were observed either in the 26-week intermittent intravenous dose toxicity study in rats [see Section 5.2.3] or in the repeated-dose toxicity studies in dogs [see Sections 5.2.4 and 5.2.5].
- In clinical studies (Studies 001, 0002, and NCI 1312), the incidence of eye-related adverse events was <20% (6.9%-10%) [see Sections 7.3.1, 7.3.2, and 7.3.8]. After the marketing approval in foreign countries, 16 eye-related adverse events were reported (data cut-off date of October 31, 2016). However, (a) periorbital oedema and other major adverse events among the observed eye-related adverse events are highly likely due to hypersensitivity or infection, and (b) a causal relationship of cataract (reported in 2 patients in Study NCI 1312 and 1 patient after the marketing approval in a foreign country), which is considered to be related to lenticular opacities, to romidepsin was ruled out.

PMDA accepted the explanation of the applicant.

5.R.2 Administration in pregnant women or women who may possibly be pregnant

PMDA asked the applicant to explain the administration of romidepsin in pregnant women or women who may possibly be pregnant.

The applicant's response:
In the study of embryo-fetal development in rats [see Section 5.5.2], adverse effects on fetuses were observed at the dose below the clinical exposure, suggesting that romidepsin may have adverse effects on fetuses if romidepsin is administered to pregnant women or if patients receiving romidepsin become pregnant. Therefore, romidepsin should be contraindicated in pregnant women or women who may possibly be pregnant. Also, precautions should be provided in the package insert, etc., advising women of childbearing potential to avoid pregnancy during the treatment with romidepsin.

PMDA's view:
PMDA generally accepted the explanation of the applicant. However, taking account of the ovulation cycle of women and the elimination half-life of romidepsin, it is necessary to advise women of childbearing potential to take contraceptive measures not only during treatment with romidepsin but also for a certain period after the last dose of romidepsin.

5.R.3 Necessity of contraceptive measures in male patients

Since testicular toxicity was observed in the repeated-dose toxicity studies in mice, rats, and dogs [see Section 5.2], PMDA asked the applicant to explain the necessity of contraceptive measures in male patients and the necessity of providing precautions in the package insert, etc., that the findings of the testis were irreversible.

The applicant's response:
Repeated-dose toxicity studies showed changes in male reproductive organs, suggesting that romidepsin in clinical use may affect the male reproductive organs. Therefore, it is necessary to provide precautions in the package insert, etc., requesting physicians to instruct male patients, if they have partners of childbearing potential, to take appropriate contraceptive measures during the romidepsin treatment period.

PMDA's view:
PMDA generally accepted the explanation of the applicant. However, male patients should be instructed to take contraceptive measures not only during the romidepsin treatment period but also for a certain period after the last dose of romidepsin, by taking account of the elimination half-life of romidepsin and the time required for spermatogenesis.

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

The amount of romidepsin in human plasma and urine was determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation was 0.1 ng/mL in both samples.

6.2 Clinical pharmacology

PK of romidepsin in patients with cancer was investigated following the administration of romidepsin alone or in combination with ketoconazole or rifampicin.

6.2.1 Japanese clinical study

6.2.1.1 Japanese phase I/II study (CTD 5.3.5.2.1, Study 001 [ongoing since December 2011 (data cut-off date of July 28, 2015)])

An open-label, uncontrolled study was conducted to investigate PK, etc., of romidepsin in 51 patients with relapsed or refractory PTCL (including 2 patients with CTCL in phase I part; 10 patients included in PK analysis). Each treatment cycle consisted of 28 days. In phase I part for PK evaluation, romidepsin (9, 14 mg/m^2) was to be administered intravenously over 4 hours once a day on Days 1, 8, and 15, and plasma romidepsin concentration was measured.

Table 8 shows PK parameters of romidepsin. Multiple-dose did not cause romidepsin accumulation at any dose tested.

Table 8. PK parameters of romidepsin

Day of measurement	Dose (mg/m^2)	n	C_{max} (ng/mL)	t_{max} *1 (h)	AUC_t (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_z (L)
1	9	3	269.8 (48.9)	4.0 (1.9, 4.0)	1023.8 (66.7)	9.5 (19.8)	14.3 (60.8)	196.2 (86.8)
	14	7	593.5 (37.2)	2.0 (1.0, 4.1)	2325.6 (35.3)	9.1 (11.6)	9.3 (35.4)	122.5 (40.4)
15	9	3	250.1 (63.3)	2.0 (1.9, 3.9)	1024.7 (78.1)	8.8 (18.6)	-	-
	14	6	489.5 (31.2)	2.9 (1.0, 4.3)	1825.7 (25.8)	9.0 (15.8)	-	-

Geometric mean (coefficient of variation [CV]%); *1 Median (range); -, Not calculated

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.3.2.1, Study T-95-0077 [August 1997 to November 1999])

An open-label, uncontrolled study was conducted to investigate PK, etc., of romidepsin in 38 patients with advanced solid cancer (35 patients included in PK analysis). In each of 21-day treatment cycle, romidepsin (1.0-24.9 mg/m^2) was to be administered intravenously over 4 hours once a day on Days 1 and 5, and plasma romidepsin concentration was investigated.

Table 9 shows PK parameters of romidepsin. On all days of measurement, C_{max} and AUC_t of romidepsin increased roughly in proportion to dose within the range investigated.

Table 9. PK parameters of romidepsin

Day of measurement	Dose (mg/m^2)	n	C_{max} (ng/mL)	AUC_t (ng·h/mL)	$t_{1/2}$ (h)	CL ($mL/min/m^2$)	V_{ss} (L/m^2)
1	1.0	3	29.1 (100.2)	114 (74.2)	1.7, 2.7[*1]	138 (74.4)	9.9, 3.6[*1]
	1.7	3	32.9 (35.0)	145 (53.1)	13.3 (74.9)	188 (56.7)	31.3 (64.1)
	2.5	3	31.1 (102.8)	87 (92.3)	1.2, 5.6[*1]	478 (91.6)	30.6 (68.6)
	3.5	1	81	234	11.8	248	38.3
	6.5	3	179.3 (32.3)	533 (9.3)	6.9 (45.2)	202 (9.2)	17.6 (22.7)
	9.1	4	174.6 (21.2)	527 (33.8)	9.1 (79.8)[*2]	277 (33.5)	28.5 (108.4)
	12.7	2	187.6[*3]	349[*3]	9.0, 17.6	593[*3]	119.5[*3]
	17.8	7	545.6 (62.6)	1619 (68.1)	11.4 (15.4)[*4]	181 (68.2)	20.4 (117.7)
	24.9	8	411.4 (66.9)	1510 (77.2)	6.7 (80.1)[*5]	274 (77.2)	17.8 (44.7)
22	1.0	2	24.2, 40.2	81, 138	2.1[*3]	204, 118	6.6, 8.1
	1.7	2	26.6, 74.7	88, 290	1.3, 11.7	320, 97	12.1, 19.6
	2.5	3	52.3 (71.9)	140 (35.9)	1.8 (75.7)	296 (36.4)	33.5 (46.1)
	3.5	1	200.1	570	7.2	101	14.6
	6.5	2	324.5, 177.4	661, 725	11.2, 6.3	163, 149	32.0, 24.3
	9.1	3	140.1 (59.5)	363 (70.1)	4.3 (154.2)	416 (69.4)	41.9 (52.4)
	12.7	3	155.9 (270.4)	454 (255.3)	8.8, 8.8[*1]	458 (251.5)	45.8 (316.4)
	17.8	7	395.9 (39.8)	1446 (39.9)	8.9 (62.0)	203 (40.2)	26.3 (69.4)
	24.9	4	385.2 (75.2)	1493 (74.9)	8.3 (61.6)[*2]	277 (75)	15 (44.0)

Geometric mean (CV%) (individual value(s) for n = 1 or 2); [*1] n = 2, [*2] n = 3, [*3] n = 1, [*4] n = 5, [*5] n = 7

6.2.2.2 Foreign phase I study (CTD 5.3.4.2.2, Study GPI-06-0005 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate PK, etc., of romidepsin in 29 patients with advanced solid cancer or hematopoietic malignancy (29 patients included in PK analysis). Each treatment cycle consisted of 28 days. In Cycle 1 of the first and second periods, romidepsin (14 mg/m^2) was to be administered intravenously over 4 hours once a day on Days 1, 8, and 15. In Cycle 2 of the first period, romidepsin (14, 20, 28, 42 mg/m^2) was to be administered orally once a day on Day 1. In Cycle 2 of the second period, romidepsin (8, 10, 12 mg/m^2) was to be administered intravenously over 1 hour once a day on Day 1. Plasma and urine romidepsin concentrations[8)] in the patients were investigated. Detailed results of PK parameters of oral romidepsin in the first period are omitted from description.

Table 10 shows PK parameters of romidepsin. CL, $t_{1/2}$, and V_z of romidepsin were similar regardless of the dose. The urinary excretion rate of romidepsin up to 24 hours after intravenous administration was <0.5% at all doses tested.

Table 10. PK parameters of romidepsin

Day of measurement	Dose (mg/m^2)	n	C_{max} (ng/mL)	t_{max}[*1] (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_z (L)
1	14[*2]	29	761.3 (31.2)	3.0 (1.1, 4.0)	3151.6 (33.9)	3.7 (8.3)	8.4 (36.8)	44.5 (40.3)
29	8[*3]	3	1096.9 (8.3)	1.0 (0.5, 1.4)	1483.4 (17.0)	4.9 (5.4)	9.6 (19.1)	68.1 (13.6)
	10[*3]	6	1341.1 (43.0)	1.0 (0.5, 1.3)	1672.2 (49.0)	4.9 (11.4)	11.1 (38.2)	78.3 (41.5)
	12[*3]	6	1862.7 (37.6)	1.0 (0.5, 1.0)	2800.2 (54.6)	4.3 (7.5)	8.7 (60.9)	54.4 (63.2)

Geometric mean (CV%); [*1] Median (range), [*2] Intravenous administration over 4 hours, [*3] Intravenous administration over 1 hour

6.2.3 Drug interactions

6.2.3.1 Interaction with ketoconazole (CTD 5.3.3.4.1, Study ROMI-ADVM-001 [[redacted] 20[redacted] to [redacted] 20[redacted]]

An open-label, uncontrolled study was conducted to investigate the effect of ketoconazole (CYP3A inhibitor) on PK of romidepsin in 15 patients with advanced cancer (15 patients included in PK analysis). Romidepsin (8 mg/m^2) was to be administered intravenously over 4 hours once a day on Days 1 and 8 in combination with once daily oral administration of ketoconazole (400 mg) from Day 4 to Day 8. Plasma romidepsin concentration in these patients was investigated.

Table 11 shows PK parameters of romidepsin. The geometric mean ratio [90% confidence interval (CI)] of C_{max} and AUC_{inf} of romidepsin in combination with ketoconazole to those in romidepsin monotherapy was 1.095 [0.949, 1.264] and 1.246 [1.090, 1.424], respectively. The above results showed that the

8) Romidepsin concentration in urine was measured for samples taken from patients receiving romidepsin (8, 12, 14 mg/m^2) intravenously.

exposure to romidepsin increases when romidepsin is concomitantly administered with a CYP3A inhibitor, based on which the applicant explained that it is necessary to take precautions against concomitant use with a CYP3A inhibitor.

Table 11. PK parameters of romidepsin following administration of romidepsin alone or in combination with ketoconazole

	n	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
Romidepsin alone	15	229.1 (76.1)	911.0 (76.0)	915.3 (75.9)	9.7 (26.4)
Romidepsin + ketoconazole	13	224.8 (45.2)	1020.7 (56.4)	1027.6 (59.3)	10.2 (15.5)

Geometric mean (CV%)

6.2.3.2 Interaction with rifampicin (CTD 5.3.3.4.2, Study ROMI-ADVM-002 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the effect of rifampicin (CYP3A inducer) on PK of romidepsin in 14 patients with advanced cancer (14 patients included in PK analysis). Romidepsin (14 mg/m^2) was to be administered intravenously over 4 hours once a day on Days 1 and 8, in combination with once daily oral administration of rifampicin (600 mg) from Day 4 to Day 8. Plasma romidepsin concentration in these patients was investigated.

Table 12 shows PK parameters of romidepsin. The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of romidepsin in combination with rifampicin to those in romidepsin monotherapy were 1.591 [1.358, 1.865] and 1.796 [1.605, 2.010], respectively.

Based on the above results, the applicant explained as follows:
Since the results showed that exposure to romidepsin was increased by concomitant use with rifampicin, it is necessary to take precautions against concomitant use with rifampicin. Although the mechanism of the increased exposure to romidepsin is unknown, concomitant use with CYP3A inducers other than rifampicin is unlikely to cause any increase in the exposure to romidepsin in clinical use, when the following observations are taken into account.

- In Studies 001, 0002, and NCI 1312, concomitant use with CYP3A inducers other than rifampicin did not cause any safety concerns.
- It is reported that no clear difference was observed in the exposure to romidepsin between patients receiving CYP3A inducers (phenytoin and oxcarbazepine) in combination with romidepsin and those not receiving the inducers (*Neuro Oncol*. 2011;13:509-16).

Table 12. PK parameters of romidepsin following administration of romidepsin alone or in combination with rifampicin

	n	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
Romidepsin alone	14	571.2 (81.0)	2225.1 (71.4)	2229.8 (71.3)	9.7 (27.9)
Romidepsin + rifampicin	13	900.1 (104.9)	3966.3 (76.5)	3980.7 (76.1)	8.3 (24.0)

Geometric mean (CV%)

6.2.4 Relationship between exposure and changes in QT/QTc interval

In the foreign phase I study (Study GPI-06-0005), the relationship between plasma romidepsin concentration and QT interval corrected by Fridericia method (QTcF), QT interval corrected for heart rate of individual subjects (QTcI), and change in QTcF from baseline (before romidepsin administration and after antiemetic administration) (ΔQTcF) was investigated by a nonlinear mixed-effects model. Results did not show any clear relationship between plasma romidepsin concentration and QTcF, QTcI, or ΔQTcF. Also, the upper limit of 90% CI of ΔQTcF following an intravenous administration of romidepsin (14 mg/m^2) over 4 hours was <10 ms at all timepoints of measurement.

Based on the above, the applicant explained that romidepsin is unlikely to affect QT/QTc interval.

6.2.5 PPK analysis

Population pharmacokinetics (PPK) analysis was performed using the non-linear mixed-effects model (software used, NONMEM version VI), based on PK data of romidepsin (930 measuring timepoints in

137 patients) obtained from foreign clinical studies (Studies NCI 1312, FJ-228-0001,[9] and GPI-06-0005). PK of romidepsin was described by a 3-compartment model.

The following parameters were evaluated as possible covariates for CL: Age, race, gender, renal impairment,[10] hepatic impairment,[11] test effect, and body weight. As a result, the body weight and test effect were selected as significant covariates. Approximately 2% and 4%, respectively, of the inter-individual variability of CL were considered to be due to body weight and the test effect. The applicant explained that since the inter-individual variability of CL is approximately 34%, the effect of body weight and of test effect on CL is limited.

6.2.6 Impact of renal impairment on PK of romidepsin

The applicant explained that renal impairment is unlikely to affect PK of romidepsin, taking account of the following:

- Data have suggested that hepatic metabolism is the major contributor to romidepsin elimination, while renal excretion plays only a minor role [see Section 4.3].
- In the PPK analysis, renal impairment was not selected as a significant covariate for PK parameters of romidepsin [see Section 6.2.5].

6.2.7 Difference in PK of romidepsin between Japanese and non-Japanese patients

Results of the Japanese phase I/II study (Study 001) and the foreign phase I study (Study ROMI-ADVM-002) did not show any clear difference between the 2 studies in PK parameters of romidepsin following the intravenous administration of romidepsin (14 mg/m^2) over 4 hours [see Sections 6.2.1.1 and 6.2.3.2]. The applicant explained that these results suggest that there is no clear difference in PK of romidepsin between Japanese and non-Japanese patients.

6.R Outline of the review conducted by PMDA

6.R.1 Romidepsin administration in patients with hepatic impairment

The applicant's explanation about the romidepsin administration in patients with hepatic impairment:
The effect of hepatic impairment on PK of romidepsin was investigated in the foreign phase I study in patients with hepatic impairment (Study NCI 9008). In each of 28-day cycles, romidepsin (14, 14, 7, 5 mg/m^2) was to be administered intravenously over 4 hours once a day on Days 1, 8, and 15 to patients with normal hepatic function and patients with mild, moderate, or severe hepatic impairment.

Table 13 shows the results of preliminary analysis of PK parameters of romidepsin in Study NCI 9008 (ongoing since [redacted] 20[redacted] [data cut-off date of July 12, 2016]). CL of romidepsin decreased with the increase in the severity of hepatic impairment. The exposure to romidepsin following the administration of romidepsin (14 mg/m^2) to patients with normal hepatic function and patients with mild hepatic impairment was similar to that observed following the administration of romidepsin (7 and 5 mg/m^2, respectively) to patients with moderate and severe hepatic impairment.

The above results suggest that it is unnecessary to reduce the starting dose of romidepsin in patients with mild hepatic impairment while, in patients with moderate or severe hepatic impairment, the starting dose should be reduced to 7 and 5 mg/m^2, respectively. The information justifying such adjustment should be provided to healthcare professionals. The timing of obtaining the final analytical results of Study NCI 9008 is yet to be finalized.

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9) Foreign phase II study in patients with metastatic renal cell carcinoma
10) Classified according to Food and Drug Administration (FDA) guidance (Guidance for Industry. Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling. May 1998).
11) Classified according to NCI-ODWG criteria.

Table 13. PK parameters of patients with normal hepatic function and patients with hepatic impairment (data cut-off date of July 12, 2016)

Severity of hepatic impairment[*1]	Dose (mg/m^2)	n	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	CL (L/h)
Normal	14	12	428 (35.3)	1692 (38.6)[*2]	16.2 (54.0)[*2]
Mild	14	8	494 (40.1)	2444 (30.2)[*3]	9.6 (27.9)[*3]
Moderate	7	3	551 (38.8)	2451 (43.8)	5.8 (79.5)
Severe	5	4	425 (30.6)	2136 (46.3)	4.2 (80.7)

Geometric mean (CV%); *[1] Classified according to National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, *[2] n = 10, *[3] n = 7

PMDA's view:
Since the results of Study NCI 9008 suggest that the exposure to romidepsin may increase in patients with hepatic impairment, attention should be paid to the occurrences of adverse drug reactions associated with the increase in the exposure. However, no clinical study data are available on the efficacy of romidepsin at reduced doses in patients with hepatic impairment, nor are data available on the relationship between exposure and efficacy. Therefore, it is unknown currently whether the adjustment of the starting dose according to hepatic function, as suggested by the applicant, is appropriate. The information on the results of Study NCI 9008 should be provided to healthcare professionals in an appropriate manner using package inserts, etc. At the same time, it is necessary to provide an advice in the Precautions for Dosage and Administration section of the package insert that, in patients with hepatic impairment, romidepsin dose reduction should be considered by referring to these results and that patients should be closely monitored for adverse events during treatment with romidepsin [see Section 7.R.5]. The final analytical results of ongoing Study NCI 9008, when available, should be provided to healthcare professionals in an appropriate manner.

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 data from a total of 2 studies, 1 Japanese phase I/II study and 1 foreign phase II study, as shown in Table 14. The applicant also submitted the results from a total of 6 studies, 5 foreign phase I studies and 1 foreign phase II study, as reference data, as shown in Table 14.

Table 14. List of clinical studies on efficacy and safety

Data category	Region	Study identifier	Phase	Subjects	Sample size	Dosage regimen	Main endpoints
Evaluation	Japan	001	I/II	Patients with relapsed or refractory PTCL (patients with CTCL included in phase I part)	51 (a) 11 (b) 40	(a) Phase I part: Romidepsin (9 or 14 mg/m^2) was administered intravenously on Days 1, 8, and 15 of a 28-day cycle. (b) Phase II part: Romidepsin (14 mg/m^2) was administered intravenously on Days 1, 8, and 15 of a 28-day cycle.	Efficacy Safety PK
	Foreign	0002	II	Patients with relapsed or refractory PTCL	131	Romidepsin (14 mg/m^2) was administered intravenously on Days 1, 8, and 15 of a 28-day cycle.	Efficacy Safety
Reference	Foreign	T-95-0077	I	Patients with advanced solid cancer	38	Romidepsin (1.0, 1.7, 2.5, 3.5, 6.5, 9.1, 12.7, 17.8, or 24.9 mg/m^2) was administered intravenously on Days 1 and 5 of a 21-day cycle.	Safety PK
		T-95-0022	I	Patients with advanced solid cancer	33	Romidepsin (1.0, 2.0, 3.25, 5.0, 7.5, 10.0, 13.3, 17.7, or 23.54 mg/m^2) was administered intravenously on Days 1, 8, and 15 of a 28-day cycle.	Safety PK
		ROMI-ADVM-001	I	Patients with advanced cancer	15	Romidepsin (8 mg/m^2) was administered intravenously on Days 1 and 8.	Safety PK
		ROMI-ADVM-002	I	Patients with advanced cancer	14	Romidepsin (14 mg/m^2) was administered intravenously on Days 1 and 8.	Safety PK
		GPI-06-0005	I	Patients with advanced solid cancer or hematopoietic malignancy	29 (a) 13 (b) 16	(a) The first period: Romidepsin (14 mg/m^2) was administered intravenously on Days 1, 8, and 15 of a 28-day cycle.* (b) The second period: Each treatment cycle consisted of 28 days. In Cycle 1, romidepsin (14 mg/m^2) was administered intravenously on Days 1, 8, and 15. In Cycle 2 and subsequent cycles, romidepsin (8, 10, 12 mg/m^2) was administered intravenously on Days 1, 8, and 15.	Safety PK
		NCI 1312	II	Patients with relapsed or refractory PTCL or CTCL	131 (a) 126 (b) 5	(a) Romidepsin (14 mg/m^2) was administered intravenously on Days 1, 8, and 15 of a 28-day cycle. (b) Romidepsin (18 mg/m^2) was administered intravenously on Days 1 and 5 of a 21-day cycle.	Efficacy Safety

* Only on Day 1 of Cycle 2, romidepsin (14, 20, 28, or 42 mg/m^2) was administered orally in a single dose.

The outline of each clinical study was described below.

Main adverse events observed in each clinical study, except death, are described in Section "7.3 Adverse events, etc. observed in clinical studies," and PK-related data are described in Section "6.1 Summary of biopharmaceutic studies and associated analytical methods" and Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase I/II study (CTD 5.3.5.2.1, Study 001 [ongoing since December 2011 (data cut-off date of July 28, 2015)])

An open-label, uncontrolled study in patients with relapsed or refractory PTCL (target sample size, 12 subjects at the maximum in phase I part,[12)] 40 subjects in phase II part) was conducted to investigate the efficacy, safety, etc., of romidepsin in 18 study centers in Japan.

[12)] In phase I part, patients with CTCL were eligible for enrollment. One each of patients with CTCL was included in the 9 mg/m^2 and 14 mg/m^2 groups.

Each treatment cycle consisted of 28 days. Romidepsin was to be administered intravenously at 9 or 14 mg/m^2 in phase I part, and at 14 mg/m^2 in phase II part, once a day on Days 1, 8, and 15 of each cycle. The treatment was to be continued until disease progression or the patient met a criterion for treatment discontinuation.

Of 11 patients enrolled in phase I part of the study, 10 patients (3 in the 9 mg/m^2 group, 7 in the 14 mg/m^2 group), excluding 1 patient with GCP violation,[13)] and all 40 patients enrolled in phase II part were included in the safety analysis population. Also, 40 patients enrolled in phase II part were included in the intent-to-treat (ITT) population and subjected to efficacy analysis.

As for efficacy, Table 15 shows the best overall response by central assessment based on the modified International Workshop Response Criteria for non-Hodgkin's lymphomas (mIWC) 1999,[14)] the primary endpoint, and the response rate.[15)] The response rate in patients with relapsed[16)] PTCL and in patients with refractory[16)] PTCL was 52.4% (11 of 21 subjects) and 33.3% (5 of 15 subjects), respectively.

Table 15. Best overall response and response rate (central assessment, efficacy analysis population [phase II part], data cut-off date of July 28, 2015)

Best overall response	Number of patients (%) N = 40
Complete response (CR)	10 (25.0)
Complete response unconfirmed (CRu)	0
Partial response (PR)	7 (17.5)
Stable disease (SD)	9 (22.5)
Progressive disease (PD)	7 (17.5)
Not evaluated (NE)	7 (17.5)
Response (CR, CRu, or PR) (response rate [95% CI] (%)[*1])	17 (42.5 [27.2, 57.8])
P value (one-sided)[*2]	<0.0001

[*1] Normal approximation (Wald type), [*2] Significance level of 0.05 (one-sided) on binomial test

As for safety, death occurred in 2 of 50 patients (4.0%) during the treatment period or within 30 days after the end of administration. The causes of death were multi-organ failure and pneumonia bacterial (1 patient each). A causal relationship of multi-organ failure to romidepsin could not be ruled out.

7.1.2 Foreign clinical study

7.1.2.1 Foreign phase II study (CTD 5.3.5.2.2, Study 0002 [ongoing since June 2007 (data cut-off date of [redacted])])

An open-label, uncontrolled study in patients with relapsed or refractory PTCL (target sample size, ≥100 subjects) was conducted to investigate the efficacy and safety of romidepsin in 48 study centers overseas.

13) Informed consent was obtained using the patient information and consent form before the approval of the form by the institutional review board (IRB), resulting in GCP violation.

14) Response assessment criteria modified from the IWC 1999 (*J Clin Oncol* 1999;17:1244-53) and the JCOG criteria

Overall response	Sum of the products of the greatest diameters of target lesion	Non-target lesion		Hepatomegaly, splenomegaly, kidney enlargement	Tumor-related symptoms Tumor-related laboratory tests	Bone marrow infiltration	New lesion
		Nodal	Extranodal				
CR	Reduced by ≥75%	Normal	Disappeared	Disappeared	Normal	Negative	No
CRu	Reduced by ≥75%	Normal	Disappeared	Disappeared	Normal	Indeterminate	No
PR	Reduced by ≥75%	Normal	Disappeared	Disappeared	Normal	Positive	No
	Reduced by ≥50%	Normal or no increase in size	Disappeared or no increase in size	Disappeared or no aggravation	Normal or no aggravation	Irrelevant (or untested)	No
SD	Reduced by <50% or increased by <50%	Normal or no increase in size	Disappeared or no increase in size	Disappeared or no aggravation	Normal or no aggravation	Irrelevant (or untested)	No
Relapsed /PD	Increased by ≥50%	Increased in size	Increased in size	Aggravated	Aggravated	Positive after negative test results	Yes

15) In Study 0002 (data cut-off date of [redacted]), the lower limit of 95% CI of the response rate was 19.9%, and there was no established treatment method at the time when Study 001 was planned. Therefore, the threshold response rate was 10%.

16) PTCL recurring in patients who had achieved CR, CRu, or PR during the immediately previous treatment was defined as "relapsed." PTCL in patients had failed to achieve PR or better response was defined as "refractory." Patients with PTCL who had not evaluated (NE) or had had no data during the immediately previous treatment were not classified into patients with "refractory" disease.

In each of 28-day cycles, romidepsin (14 mg/m^2) was to be administered intravenously once a day on Days 1, 8, and 15 of each cycle. The treatment was to be continued until disease progression or the patient met a criterion for treatment discontinuation.

Of 131 patients enrolled in the study, 130 patients histopathologically diagnosed with PTCL by central assessment were included in the efficacy analysis population, and all of 131 patients receiving romidepsin were included in the safety analysis population.

As for efficacy, Table 16 shows the best overall response by central assessment based on the mIWC,[17] the primary endpoint, and the complete response rate.[18] In patients with relapsed PTCL[16] and patients with refractory PTCL,[16] the response rate was 30.2% (16 of 53 patients) and 25.0% (17 of 68 patients), respectively, and the complete response rate was 15.1% (8 of 53 patients) and 16.2% (11 of 68 patients), respectively.

Table 16. Best overall response and complete response rate (central assessment, efficacy analysis population, data cut-off date of [redacted], 20[redacted])

Best overall response	Number of patients (%) N = 130
CR	15 (11.5)
CRu	5 (3.8)
PR	14 (10.8)
SD	32 (24.6)
PD	35 (26.9)
NE	29 (22.3)
Response (CR, CRu, or PR) (response rate [95% CI] (%))	34 (26.2 [18.8, 34.6])
Complete response (CR or CRu) (complete response rate [95% CI] (%))	20 (15.4 [9.7, 22.8])

As for safety, death occurred in 8 of 131 patients (6.1%) during the treatment period or within 30 days after the end of administration. Except for 3 patients who died of disease progression, the causes of death were sepsis/multi-organ failure, pneumonia/acute renal failure, septic shock, candida sepsis/pneumonia, and sepsis/cardiogenic shock/subendocardial ischaemia/gastrointestinal haemorrhage (1 patient each). A causal relationship of sepsis/multi-organ failure (1 patient) to romidepsin could not be ruled out.

7.2 Reference data

7.2.1 Clinical pharmacology

The following 5 clinical pharmacology studies in patients with advanced solid cancer or hematopoietic malignancy were submitted [see Section 6.2]. During the treatment period or within 30 days after the end of administration, death occurred in 4 of 33 patients (12.1%) in Study T-95-0022, in 2 of 15 patients (13.3%) in Study ROMI-ADVM-001, and in 1 of 29 patients (3.4%) in Study GPI-06-0005. Except in 5 patients who died of disease progression, the causes of death were pulmonary embolism and

[17] Response assessment criteria modified from the IWC 1999

Overall response	Physical findings	Lymph nodes	Lymph node mass	Extranodal and skin lesion	Bone marrow
CR	Normal	Normal	Normal	Disappeared	Negative
CRu	Normal	Normal	Normal	Disappeared	Indeterminate
	Normal	Normal	Reduced by ≥75%	Disappeared	Negative or indeterminate
PR	Normal	Normal	Normal	Reduced by ≥50%	Negative
	Normal	Reduced by ≥50%	Reduced by ≥50%	Reduced by ≥50%	Irrelevant
	Decreased size of liver or spleen	Reduced by ≥50%	Reduced by ≥50%	Reduced by ≥50%	Irrelevant
PD	Hypertrophy of liver or spleen, or appearance of new lesion	Appearance of new lesion or hypertrophy of existing lesion	Appearance of new lesion or hypertrophy of existing lesion	Appearance of new lesion or re-appearance after disappearance	Positive after negative test results

[18] No threshold complete response rate was set in this study.

pneumococcal sepsis (1 patient each) (Study T-95-0022), and their causal relationship to romidepsin was ruled out.

7.2.1.1 Foreign phase I study (CTD 5.3.3.2.1, Study T-95-0077 [August 1997 to November 1999])

7.2.1.2 Foreign phase I study (CTD 5.3.3.2.2, Study T-95-0022 [February 1997 to June 1999])

7.2.1.3 Foreign phase I study (CTD 5.3.3.4.1, Study ROMI-ADVM-001 [[redacted] to [redacted]])

7.2.1.4 Foreign phase I study (CTD 5.3.3.4.2, Study ROMI-ADVM-002 [[redacted] to [redacted]])

7.2.1.5 Foreign phase I study (CTD 5.3.4.2.2, Study GPI-06-0005 [[redacted] to [redacted]])

7.2.2 Foreign clinical study

7.2.2.1 Foreign phase II study (CTD 5.3.5.4.1, Study NCI 1312 [ongoing since March 2001 (data cut-off date of [redacted])])

An open-label, uncontrolled study in patients with relapsed or refractory PTCL or CTCL (target sample size, 161 subjects) was conducted to investigate the efficacy and safety of romidepsin in 7 study centers overseas.

All of 131 patients enrolled in the study (47 patients with PTCL, 84 patients with CTCL) received romidepsin and were included in the safety analysis population.

As for the safety in patients with PTCL, death occurred in 7 of 47 patients (14.9%) during the treatment period or within 30 days after the end of administration. Except in 3 patients who died of disease progression, the causes of death were disease progression/pericardial effusion, disease progression/oedema, AST increased, and death (1 patient each). A causal relationship to romidepsin could not be ruled out for disease progression/pericardial effusion, AST increased, and death in 1 patient each.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA decided that, among the evaluation data submitted, the Japanese phase I/II study in patients with relapsed or refractory PTCL (Study 001) was most important for evaluating the efficacy and safety of romidepsin. The agency therefore focused on Study 001 in the review of romidepsin.

7.R.2 Efficacy

Based on the following review, PMDA has concluded that a certain level of efficacy of romidepsin is demonstrated in patients with relapsed or refractory PTCL.

7.R.2.1 Primary endpoint and efficacy evaluation

The applicant's explanation about the primary endpoint and the efficacy of romidepsin in patients with relapsed or refractory PTCL:

Given that patients with relapsed or refractory PTCL have poor prognosis and there is no established standard treatment that demonstrates overall survival (OS) prolongation, responses achieved in these patients are of clinical significance. Therefore, it is appropriate that the response rate was used as the primary endpoint in Study 001.

At the time when Study 001 was planned, the internationally accepted criteria for efficacy assessment for non-Hodgkin's lymphoma were the International Workshop Response Criteria for non-Hodgkin's lymphomas (IWC) 1999 and the Japan Clinical Oncology Group (JCOG) criteria (JCOG-LSG [Lymphoma Study Group]'s Manual for Clinical Research of Lymphoma and Myeloma, version 1, edited by the JCOG-LSG Manual Committee for Clinical Research of Lymphoma and Myeloma [the Japan Foundation for Aging and Health, 2003]). Therefore, the mIWC 1999 was established which encompassed the 2 sets of the criteria to allow comprehensive evaluation and also included evaluation of skin lesion characteristic to PTCL.

In the phase II part of Study 001, *P* value (one-sided) of binominal test was <0.0001, with the observed response rate significantly greater than the pre-set threshold response rate [see Section 7.1.1.1]. Results thus demonstrated the efficacy of romidepsin in patients with relapsed or refractory PTCL.

The best overall response and the response rate in Study 001 according to the criteria other than the mIWC 1999 were as follows:

- For the analysis based on the IWC 1999, some of the measured data necessary for the analysis by the criteria were unavailable,[19] precluding the evaluation. The best overall response rate [95% CI], calculated according to the criteria[20] adjusted as closely as possible to the IWC 1999, was 38.9% [23.0, 54.8] (14 of 36 patients).
- The best overall response rate [95% CI] according to the JCOG criteria was 42.5% [27.2, 57.8] (17 of 40 patients).

PMDA's view:
As for the primary endpoint, the applicant's explanation that the response achieved in patients with relapsed or refractory PTCL is of clinical significance is understandable. Also, taking account of the results that the number of responders in the analysis according to the criteria adjusted as closely as possible to the IWC 1999 and in the analysis according to the JCOG criteria was similar to that observed in the analysis according to the mIWC 1999, romidepsin has demonstrated a certain level of efficacy in patients with relapsed or refractory PTCL.

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

As a result of the following review, PMDA has concluded that adverse events requiring particular attention in administering romidepsin to patients with relapsed or refractory PTCL are bone marrow depression, infection, cardiac disorders (abnormal electrocardiogram such as prolonged QT interval, in particular), tumour lysis syndrome (TLS), hypersensitivity, haemorrhage, and venous thromboembolism, and that a caution should be exercised against possible occurrence of these adverse events in using romidepsin.

PMDA also concluded that although attention should be paid to the above adverse events in using romidepsin, it is well tolerated provided that appropriate measures, such as monitoring and management of adverse events and interruption, dose reduction, or discontinuation of romidepsin, are taken by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancy.

7.R.3.1 Safety profile of romidepsin

The applicant explained the safety profile of romidepsin, based on the safety information obtained from Studies 001 and 0002, as follows:
Table 17 shows the outline of safety in Studies 001 and 0002.

Table 17. Outline of safety profile (Studies 001 and 0002)

	Number of patients (%)	
	Study 001 N = 50	Study 0002 N = 131
All adverse events	50 (100)	128 (97.7)
Grade ≥3 adverse events*	46 (92.0)	89 (67.9)
Adverse events leading to death	2 (4.0)	7 (5.3)
Serious adverse events	15 (30.0)	61 (46.6)
Adverse events leading to treatment discontinuation	13 (26.0)	25 (19.1)
Adverse events leading to treatment interruption	28 (56.0)	63 (48.1)
Adverse events leading to dose reduction	21 (42.0)	14 (10.7)

* Include adverse events of unknown Grade.

[19] In the IWC 1999, measurable lesion is defined as a lesion >1.0 cm in size. In Study 001, in contrast, measurable lesion was defined as a lesion >1.5 cm in the maximum diameter. As a result, data of lesions ≤1.5 cm the maximum diameter before romidepsin administration were not available for evaluation as measurable lesions. In the IWC 1999, lymph nodes were evaluated separately for "enlarged lymph nodes" and for "nodal masses," whereas in Study 001, all data were collected as "enlarged lymph nodes." Furthermore, in the IWC 1999, all measurable lymph node lesions were handled as evaluable lesions, whereas in Study 001, only up to 6 lesions selected as the target lesions were measured.

[20] Only up to 6 target lesions >1.5 cm in diameter were measured as the measurable lesions. Patients with only extranodal lesions (except those in spleen and liver) or with only skin lesion were excluded.

Table 18 shows all-Grade adverse events reported by ≥20% of subjects in either of Study 001 or Study 0002.

Table 18. Adverse events reported by ≥20% of subjects in either study (Studies 001 and 0002)

PT (MedDRA/J ver. 18.1)	Number of patients (%)			
	Study 001 N = 50		Study 0002 N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	50 (100)	46 (92.0)	128 (97.7)	89 (67.9)
Thrombocytopenia	49 (98.0)	19 (38.0)	53 (40.5)	32 (24.4)
Lymphopenia	44 (88.0)	37 (74.0)	5 (3.8)	4 (3.1)
Leukopenia	42 (84.0)	23 (46.0)	16 (12.2)	8 (6.1)
Neutropenia	40 (80.0)	27 (54.0)	39 (29.8)	26 (19.8)
Pyrexia	33 (66.0)	3 (6.0)	47 (35.9)	8 (6.1)
Dysgeusia	31 (62.0)	0	27 (20.6)	0
Decreased appetite	28 (56.0)	5 (10.0)	46 (35.1)	3 (2.3)
Nausea	27 (54.0)	0	77 (58.8)	3 (2.3)
Vomiting	21 (42.0)	0	51 (38.9)	6 (4.6)
Diarrhoea	18 (36.0)	0	47 (35.9)	3 (2.3)
Anaemia	17 (34.0)	6 (12.0)	33 (25.2)	14 (10.7)
Constipation	16 (32.0)	1 (2.0)	39 (29.8)	1 (0.8)
Fatigue	16 (32.0)	2 (4.0)	54 (41.2)	8 (6.1)
Malaise	13 (26.0)	2 (4.0)	2 (1.5)	0
Hb decreased	13 (26.0)	6 (12.0)	0	0
Hypokalaemia	10 (20.0)	0	14 (10.7)	3 (2.3)
Hypophosphataemia	10 (20.0)	5 (10.0)	3 (2.3)	1 (0.8)
ALT increased	10 (20.0)	2 (4.0)	5 (3.8)	1 (0.8)
Weight decreased	10 (20.0)	1 (2.0)	14 (10.7)	0

In Study 001, serious adverse events reported by ≥3% of subjects were cytomegalovirus (CMV) infection and pyrexia in 2 patients (4.0%) each, and their causal relationship to romidepsin could not be ruled out. Adverse events leading to treatment discontinuation reported by ≥3% of subjects were neutropenia, thrombocytopenia, and atrial fibrillation in 2 patients (4.0%) each, and their causal relationship to romidepsin could not be ruled out.

In Study 0002, serious adverse events reported by ≥3% of subjects were pyrexia in 11 patients (8.4%), pneumonia in 7 patients (5.3%), sepsis and vomiting in 6 patients (4.6%) each, cellulitis and deep vein thrombosis in 5 patients (3.8%) each, and abdominal pain and febrile neutropenia in 4 patients (3.1%) each. A causal relationship to romidepsin could not be ruled out for pyrexia in 8 patients, vomiting in 6 patients, cellulitis in 4 patients, pneumonia, deep vein thrombosis, and febrile neutropenia in 3 patients each, and sepsis and abdominal pain in 2 patients each. There were no adverse events leading to treatment discontinuation reported by ≥3% of subjects.

PMDA's view:
Not only adverse events observed with a high incidence in Study 001 or Study 0002, serious adverse events and adverse events leading to treatment discontinuation observed in Study 001 or Study 0002 require attention in romidepsin administration. Information on the incidence of these events should be provided to healthcare professionals in an appropriate manner. Because of the extremely limited safety information on romidepsin, relevant information should be continuously collected after the market launch, and any new findings should be communicated to healthcare professionals in a timely manner.

7.R.3.2 Difference in safety profile between Japanese and non-Japanese patient populations

The applicant provided the following explanation about the difference in the safety profile of romidepsin between Japanese patient and non-Japanese patient populations, based on the incidence of adverse events in Study 001 in Japanese patient population and in Study 0002 in non-Japanese patient population:
All-Grade adverse events with a ≥20% higher incidence in Study 001 than in Study 0002 were thrombocytopenia (49 of 50 patients [98.0%] in Study 001, 53 of 131 patients [40.5%] in Study 0002), lymphopenia (44 patients [88.0%], 5 patients [3.8%]), leukopenia (42 patients [84.0%], 16 patients [12.2%]), neutropenia (40 patients [80.0%], 39 patients [29.8%]), pyrexia (33 patients [66.0%], 47 patients [35.9%]), dysgeusia (31 patients [62.0%], 27 patients [20.6%]), decreased appetite (28 patients [56.0%], 46 patients [35.1%]), Hb decreased (13 patients [26.0%], 0 patients), and malaise (13 patients

[26.0%], 2 patients [1.5%]). Grade ≥3 adverse events with a ≥5% higher incidence in Study 001 than in Study 0002 were lymphopenia (37 patients [74.0%], 4 patients [3.1%]), neutropenia (27 patients [54.0%], 26 patients [19.8%]), leukopenia (23 patients [46.0%], 8 patients [6.1%]), thrombocytopenia (19 patients [38.0%], 32 patients [24.4%]), Hb decreased (6 patients [12.0%], 0 patients), hypermagnesaemia (5 patients [10.0%], 0 patients), hypophosphataemia (5 patients [10.0%], 1 patient [0.8%]), and decreased appetite (5 patients [10.0%], 3 patients [2.3%]). The serious adverse event reported by 2 or more patients and with a higher incidence in Study 001 than in Study 0002 was CMV infection (2 patients [4.0%], 0 patients). There were no adverse events that led to treatment discontinuation and occurred with a ≥5% higher incidence in Study 001 than in Study 0002. Adverse events leading to treatment interruption with a ≥5% higher incidence in Study 001 than in Study 0002 were thrombocytopenia (13 patients [26.0%], 23 patients [17.6%]), neutropenia (9 patients [18.0%], 15 patients [11.5%]) and hypokalaemia (3 patients [6.0%], 1 patient [0.8%]). Adverse events leading to dose reduction with a ≥5% higher incidence in Study 001 than in Study 0002 were neutropenia (8 patients [16.0%], 2 patients [1.5%]), thrombocytopenia (6 patients [12.0%], 4 patients [3.1%]), and atrial fibrillation (4 patients [8.0%], 0 patients).

PMDA's view:
Because of the limited number of patients investigated in Study 001, there are limitations to the comparison between Japanese and non-Japanese patient populations. However, attention should be paid to adverse events reported frequently in Study 001 than in Study 0002. Information on data related to the difference in the safety of romidepsin between Japanese and foreign clinical studies should be appropriately provided to healthcare professionals using materials, etc. Also, because of the limited information on the safety of romidepsin in Japanese patient population, relevant information should be continuously collected after the market launch, and any new findings should be communicated to healthcare professionals in a timely manner.

In the following sections, PMDA reviewed the safety profile of romidepsin based mainly on the safety results in Studies 001 and 0002, with focus on adverse events that resulted in death, Grade ≥3 or serious adverse events with a high incidence, adverse events with a higher incidence in Study 001 than in Study 0002, adverse events listed in the labels approved in foreign countries, and overseas post-marketing information.

7.R.3.3 Bone marrow depression

The applicant's explanation about the incidences of romidepsin-induced bone marrow depression:
As adverse events related to bone marrow depression, preferred terms (PTs) coded to "Haematopoietic cytopenias" in standard Medical Dictionary for Regulatory Activities (MedDRA) queries (MedDRA SMQ; MedDRA/J ver. 18.1) were tabulated.

Table 19 shows the incidences of bone marrow depression in Studies 001 and 0002.

Table 19. Incidences of bone marrow depression (Studies 001 and 0002)

PT (MedDRA/J ver. 18.1)	Number of patients (%)			
	Study 001 N = 50		Study 0002 N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Bone marrow depression	50 (100)	46 (92.0)	75 (57.3)	51 (38.9)
Thrombocytopenia	49 (98.0)	19 (38.0)	53 (40.5)	32 (24.4)
Lymphopenia	44 (88.0)	37 (74.0)	5 (3.8)	4 (3.1)
Leukopenia	42 (84.0)	23 (46.0)	16 (12.2)	8 (6.1)
Neutropenia	40 (80.0)	27 (54.0)	39 (29.8)	26 (19.8)
Anaemia	17 (34.0)	6 (12.0)	33 (25.2)	14 (10.7)
Hb decreased	13 (26.0)	6 (12.0)	0	0
Febrile neutropenia	0	0	5 (3.8)	4 (3.1)
Pancytopenia	0	0	2 (1.5)	1 (0.8)
Microcytic anaemia	0	0	1 (0.8)	0

In Study 001, no fatal bone marrow depression nor serious bone marrow depression was observed. Bone marrow depression leading to treatment discontinuation was reported by 4 patients (8.0%; thrombocytopenia and neutropenia in 2 patients each). Bone marrow depression leading to treatment interruption was reported by 21 patients (42.0%; thrombocytopenia in 13 patients, neutropenia in 9

patients [a patient had more than 1 event]). Bone marrow depression leading to dose reduction was reported by 13 patients (26.0%; neutropenia in 8 patients, thrombocytopenia in 6 patients [a patient had more than 1 event]).

In Study 0002, no fatal bone marrow depression was observed. Serious bone marrow depression was reported by 13 of 131 patients (9.9%; febrile neutropenia in 4 patients, neutropenia in 3 patients, thrombocytopenia, leukopenia, and anaemia in 2 patients each, pancytopenia in 1 patient [a patient had more than 1 event]). A causal relationship to romidepsin could not be ruled out for febrile neutropenia in 3 patients, neutropenia in 3 patients, and thrombocytopenia, leukopenia, and anaemia in 2 patients each. Bone marrow depression leading to treatment discontinuation was reported by 5 patients (3.8%; thrombocytopenia in 3 patients, neutropenia, leukopenia, and febrile neutropenia in 1 patient each [a patient had more than 1 event]). Bone marrow depression leading to treatment interruption was reported by 33 patients (25.2%; thrombocytopenia in 23 patients, neutropenia in 15 patients, anaemia in 2 patients, leukopenia in 1 patient [some patients had more than 1 event]). Bone marrow depression leading to dose reduction was reported by 6 patients (4.6%; thrombocytopenia in 4 patients, neutropenia in 2 patients).

PMDA's view:
In Studies 001 and 0002, romidepsin-induced Grade ≥3 bone marrow depression was observed in many patients, and there were cases of serious bone marrow depression for which a causal relationship to romidepsin could not be ruled out. Taking account of these observations, caution should be exercised against bone marrow depression in romidepsin administration. Based on the above, information on the incidences of bone marrow depression in clinical studies should be provided to healthcare professionals and that advice should be appropriately provided to healthcare professionals using the package insert, etc., requiring the physician to conduct periodical haematology test during romidepsin administration and, if any abnormalities are observed, to take appropriate measures such as interruption or dose reduction of romidepsin.

7.R.3.4 Infection

The applicant's explanation about the incidences of romidepsin-induced infection:
As adverse events related to infection, PTs coded to "Infections and infestations" in MedDRA system organ class [SOC] (MedDRA/J ver. 18.1) were tabulated.

Table 20 shows the incidences of infection in Studies 001 and 0002.

Table 20. Incidences of infection reported by ≥2% of subjects in either study (Studies 001 and 0002)

PT (MedDRA/J ver. 18.1)	Number of patients (%)			
	Study 001 N = 50		Study 0002 N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infection	18 (36.0)	8 (16.0)	74 (56.5)	26 (19.8)
Nasopharyngitis	4 (8.0)	0	5 (3.8)	0
Influenza	3 (6.0)	0	4 (3.1)	1 (0.8)
CMV infection	2 (4.0)	2 (4.0)	0	0
Upper respiratory tract infection	2 (4.0)	0	12 (9.2)	2 (1.5)
Urinary tract infection	2 (4.0)	1 (2.0)	9 (6.9)	1 (0.8)
Bacterial infection	1 (2.0)	1 (2.0)	0	0
Hepatitis B	1 (2.0)	1 (2.0)	1 (0.8)	0
Pneumocystis jirovecii pneumonia	1 (2.0)	1 (2.0)	1 (0.8)	1 (0.8)
Pneumonia	1 (2.0)	1 (2.0)	9 (6.9)	7 (5.3)
Pneumonia bacterial	1 (2.0)	1 (2.0)		
Sepsis	1 (2.0)	1 (2.0)	7 (5.3)	7 (5.3)
Conjunctivitis	1 (2.0)	0	1 (0.8)	0
Cystitis	1 (2.0)	0	2 (1.5)	0
Cytomegalovirus viraemia	1 (2.0)	0	0	0
Infected dermal cyst	1 (2.0)	0	0	0
Infection	1 (2.0)	0	4 (3.1)	2 (1.5)
Oral herpes	1 (2.0)	0	5 (3.8)	0
Periodontitis	1 (2.0)	0	0	0
Sinusitis	1 (2.0)	0	3 (2.3)	0
Oral candidiasis	0	0	8 (6.1)	1 (0.8)
Cellulitis	0	0	6 (4.6)	5 (3.8)
Pharyngitis	0	0	6 (4.6)	0
Bronchitis	0	0	5 (3.8)	0
Rhinitis	0	0	5 (3.8)	0
Herpes zoster	0	0	4 (3.1)	0
Staphylococcal infection	0	0	3 (2.3)	2 (1.5)
Respiratory tract infection	0	0	3 (2.3)	1 (0.8)
Fungal infection	0	0	3 (2.3)	0
Gastroenteritis	0	0	3 (2.3)	0
Lower respiratory tract infection	0	0	3 (2.3)	0

In Study 001, fatal infection was reported by 1 patient (2.0%; pneumonia bacterial), but its causal relationship to romidepsin was ruled out. Serious infection was reported by 8 patients (16.0%; CMV infection in 2 patients, urinary tract infection, bacterial infection, hepatitis B, *Pneumocystis jirovecii* pneumonia, pneumonia, pneumonia bacterial, and sepsis in 1 patient each [a patient had more than 1 event]), and a causal relationship to romidepsin could not be ruled out for these adverse events except pneumonia bacterial. Infection leading to treatment discontinuation was reported by 4 patients (8.0%; CMV infection, bacterial infection, hepatitis B, pneumonia bacterial, and sepsis in 1 patient each [a patient had more than 1 event]). Infection leading to treatment interruption was reported by 4 patients (8.0%; influenza and upper respiratory tract infection in 2 patients each). Infection leading to dose reduction was reported by 1 patient (2.0%; *Pneumocystis jirovecii* pneumonia).

In Study 0002, fatal infection was reported by 5 patients (3.8%; pneumonia and sepsis in 2 patients each, candida sepsis and septic shock in 1 patient each [a patient had more than 1 event]), and a causal relationship of sepsis (in 1 patient) to romidepsin could not be ruled out. Serious infection was reported by 26 patients (19.8%; pneumonia in 7 patients, sepsis in 6 patients, cellulitis in 5 patients, urinary tract infection and staphylococcal infection in 2 patients each, oral candidiasis, herpes zoster, infection, respiratory tract infection, sinusitis, device related infection, viral upper respiratory tract infection, candida sepsis, erysipelas, peritonitis, *Pneumocystis jirovecii* pneumonia, and septic shock in 1 patient each [some patients had more than 1 event]). A causal relationship to romidepsin could not be ruled out for cellulitis in 4 patients, pneumonia in 3 patients, sepsis in 2 patients, urinary tract infection, staphylococcal infection, oral candidiasis, herpes zoster, infection, respiratory tract infection, and peritonitis in 1 patient each (including patients with more than 1 event). Infection leading to treatment discontinuation was reported by 6 patients (4.6%; pneumonia in 3 patients, sepsis in 2 patients, upper respiratory tract infection and candida sepsis in 1 patient each [a patient had more than 1 event]). Infection leading to treatment interruption was reported by 19 patients (14.5%; upper respiratory tract infection in 4 patients, pneumonia in 3 patients, cellulitis, bronchitis, and respiratory tract infection in 2 patients each, urinary tract infection, sepsis, herpes zoster, infection, influenza, gastroenteritis, lower

respiratory tract infection, application site infection, candida infection, erysipelas, hepatitis B, peritonitis, *Pneumocystis jirovecii* pneumonia, and RS virus infection in 1 patient each [some patients had more than 1 event]). Infection leading to dose reduction was reported by 1 patient (0.8%; influenza).

PMDA asked the applicant to explain the following issues in Studies 001, 0002, and NCI 1312:
(a) Screening and monitoring for opportunistic infection by CMV, Epstein-Barr virus (EBV), *Mycobacterium tuberculosis*, *Pneumocystis jiroveci*, and herpes zoster virus, and for infection by hepatitis B virus (HBV), and occurrences of romidepsin-induced opportunistic infection and HBV reactivation, and
(b) rules for prophylactic administration against infection and the state of the administration.

The applicant's response:
(a)
As for the screening and monitoring for infection, screening for HBV was performed only in Study 001, and patients positive for HBs antigen and patients positive for anti-HBs or anti-HBc antibody with a detectable level of HBV-deoxyribonucleic acid (DNA) were excluded from the study. Anti-HBs or anti-HBc antibody-positive patients were monitored for HBV DNA. Screening or monitoring for other infections was not performed in any of the studies.

As for HBV reactivation, of 16 patients who were positive for anti-HBs or anti-HBc antibody at the screening in Study 001 (12 patients positive for anti-HBs antibody, 13 patients positive for anti-HBc antibody [some patients were positive for both antibodies]), 2 patients showed positive conversion of HBV DNA and received entecavir hydrate.[21)] In Studies 0002 and NCI 1312, HBV test was not performed at the screening, precluding the identification of reactivation. In Study 0002, 1 patient experienced hepatitis B.

As for opportunistic infections (by CMV, EBV, *Mycobacterium tuberculosis*, *Pneumocystis jiroveci*, and herpes zoster virus), in addition to the events listed in Table 20, EBV virus infection (fatal) was reported by 1 patient with PTCL in Study NCI 1312. A causal relationship of the EBV infection to romidepsin could not be ruled out. In a foreign investigator-initiated clinical trial (Study RM-TCL-PI-0038) other than Studies 001, 0002, and NCI 1312, 2 patients with extranodal NK/T-cell lymphoma, nasal type, experienced serious hepatic failure caused by EBV reactivation, and the disease was fatal in one of them. Since the causal relationship to romidepsin could not be ruled out in either of the patients, patients with extranodal NK/T-cell lymphoma, nasal type, were removed from the inclusion criteria in the mid-course of the study in Study 001. In Study 001, EBV monitoring was not required, while liver function test was performed periodically. In Study 001, EBV infection was not observed.

(b)
In Study 001, prophylactic administration of ST combination product (combination product of sulfamethoxazole and trimethoprim) or anti-herpes virus drug was recommended for the prevention of infection in patients who showed CD4-positive T-lymphocyte count of ≤200/μL at least once. ST combination product was administered to 35 of 50 patients, and anti-herpes virus drug to 14 of 50 patients. *Pneumocystis jiroveci* infection was observed in none of patients who had received prophylactic treatment, while the infection was observed in 1 of 15 patients (6.7%) not receiving the prophylactic treatment. Herpes zoster was not observed in any of the patients regardless of the prophylactic treatment.

In Studies 0002 and NCI 1312, no prophylactic treatment against infection was required, and the detailed purposes of concomitant drugs used during the study period are unknown.

PMDA's view:
In Studies 001 and 0002, serious infection, including death, for which a causal relationship to romidepsin could not be ruled out was observed in multiple patients. Therefore, caution should be exercised against infection during romidepsin administration, and information on the incidences of infection in clinical studies should be provided to healthcare professionals. Taking account of the observation that reactivation of HBV and EBV occurred during treatment with romidepsin, PMDA concluded that appropriate advice should be provided to healthcare professionals using the package insert, etc.,

21) Entecavir hydrate was administered to 3 patients. One patient without positive conversion of HBV DNA was not monitored for HBV DNA but received prophylactic treatment with entecavir hydrate.

requiring the physician to check patients for HBV infection before administration of romidepsin and to pay attention to signs of HBV or EBV reactivation by periodical blood tests such as liver function test. Also, information on the safety measures taken against infection in clinical studies should be appropriately provided to healthcare professionals using materials.

7.R.3.5 Cardiac disorder

The applicant's explanation about the incidences of romidepsin-induced cardiac disorder:
As adverse events related to cardiac disorder, PTs coded to "Torsade de pointes/QT prolongation (wide)," "Other ischaemic heart disease (wide)," and "Myocardial infarction (wide)" in MedDRA SMQ (MedDRA/J ver. 18.1) and "Electrocardiogram repolarisation abnormality," "Electrocardiogram T wave biphasic," and "Electrocardiogram T wave amplitude decreased" in MedDRA PT were tabulated.

Table 21 shows the incidences of cardiac disorder in Studies 001 and 0002.

Table 21. Incidences of cardiac disorder (Studies 001 and 0002)

PT (MedDRA/J ver. 18.1)	Number of patients (%)			
	Study 001 N = 50		Study 0002 N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac disorder	8 (16.0)	3 (6.0)	9 (6.9)	4 (3.1)
Electrocardiogram QT prolonged	3 (6.0)	0	4 (3.1)	1 (0.8)
Angina pectoris	1 (2.0)	1 (2.0)	0	0
Cardio-respiratory arrest	1 (2.0)	1 (2.0)	0	0
Long QT syndrome	1 (2.0)	1 (2.0)	0	0
Electrocardiogram ST-T segment elevation	1 (2.0)	0	0	0
Electrocardiogram T wave inversion	1 (2.0)	0	1 (0.8)	0
Myocardial ischaemia	0	0	1 (0.8)	1 (0.8)
Subendocardial ischaemia	0	0	1 (0.8)	1 (0.8)
Syncope	0	0	1 (0.8)	1 (0.8)
Electrocardiogram T wave amplitude decreased	0	0	1 (0.8)	0
Electrocardiogram repolarisation abnormality	0	0	1 (0.8)	0

In Study 001, no fatal cardiac disorder occurred. Serious cardiac disorder was reported by 2 patients (4.0%; angina pectoris and cardio-respiratory arrest in 1 patient each), and a causal relationship of cardio-respiratory arrest (in 1 patient) to romidepsin could not be ruled out. Cardiac disorder leading to treatment discontinuation was reported by 1 patient (2.0%; cardio-respiratory arrest). There was no cardiac disorder leading to interruption or dose reduction of romidepsin.

In Study 0002, fatal cardiac disorder was reported by 1 patient (0.8%; subendocardial ischaemia), but a causal relationship to romidepsin was ruled out. Serious cardiac disorder was reported by 5 patients (3.8%; electrocardiogram QT prolonged, electrocardiogram T wave inversion, electrocardiogram repolarisation abnormality, subendocardial ischaemia, and syncope in 1 patient each), and a causal relationship to romidepsin could not be ruled out for these events except subendocardial ischaemia. Cardiac disorder leading to treatment discontinuation was reported by 2 patients (1.5%; electrocardiogram QT prolonged and electrocardiogram T wave amplitude decreased in 1 patient each). Cardiac disorder leading to treatment interruption was reported by 1 patient (0.8%; electrocardiogram repolarisation abnormality), and cardiac disorder leading to dose reduction was reported by 1 patient (0.8%; electrocardiogram QT prolonged).

Among the post-marketing use experiences in foreign countries (data cut-off date of February 11, 2017),[22)] cardiac disorder was reported by 112 patients. Fatal cardiac disorder occurred in 16 patients (sudden death in 5 patients, cardiac arrest and cardiopulmonary failure in 4 patients each, acute myocardial infarction, cardiac failure congestive, cardiogenic shock, myocardial infarction, and myocardial ischaemia in 1 patient each [some patients had more than 1 event]). A causal relationship to romidepsin could not be ruled out for sudden death in 3 patients, cardiopulmonary failure in 2 patients, and myocardial ischaemia in 1 patient. Serious cardiac disorder was reported by 105 patients. Serious cardiac disorder reported by ≥5 patients was electrocardiogram QT prolonged in 27 patients, syncope in 10 patients, myocardial infarction in 8 patients, electrocardiogram ST segment depression, electrocardiogram T wave inversion, oedema peripheral, and troponin I increased in 6 patients each, and

22) Includes patients other than patients with PTCL.

sudden death and ventricular tachycardia in 5 patients each. A causal relationship to romidepsin could not be ruled out for electrocardiogram QT prolonged in 14 patients, syncope, troponin I increased, and ventricular tachycardia in 4 patients each, electrocardiogram ST segment depression, electrocardiogram T wave inversion, and sudden death in 3 patients each, myocardial infarction in 2 patients, and oedema peripheral in 1 patient.

PMDA asked the applicant to explain the necessity for providing precautions against the risk of QT interval prolongation during treatment with romidepsin.

The applicant's response:
In Studies 001 and 0002, the following were required as safety measures against abnormal electrocardiogram (prevention of drug-induced Torsade de pointes and sudden death): (1) To confirm that serum potassium and magnesium levels are not less than the lower limit of the reference levels on the day of, or one day before, romidepsin administration and, if below the reference level, potassium and/or magnesium should be supplemented before romidepsin administration, and (2) to interrupt or reduce the dose of romidepsin when abnormal electrocardiogram such as QTc interval prolongation of >500 ms was observed. Taking account of these requirements and the occurrences of cardiovascular disorder in Japanese and foreign clinical studies and in post-marketing use experiences in foreign countries, the package insert should appropriately provide advice on the risk of abnormal electrocardiogram including QT interval prolongation.

PMDA's view:
In light of the observation that serious cardiac disorder, including death, for which a causal relationship to romidepsin could not be ruled out occurred in Japanese and foreign clinical studies and in post-marketing use experiences in foreign countries, it is necessary to pay attention to cardiac disorder during romidepsin administration. Therefore, information on the incidences of cardiac disorder in clinical studies, etc., should be provided to healthcare professionals using the package insert, etc. Since particular attention should be paid to QT interval prolongation, the package insert and other materials should be provided advice to physicians to perform periodical electrocardiography and electrolyte test (potassium, magnesium, etc.) before and during treatment with romidepsin so that appropriate measures, such as treatment interruption or dose reduction of romidepsin and supplementation of electrolytes, are taken in case of abnormality.

7.R.3.6 TLS
The applicant's explanation about the incidences of romidepsin-induced TLS:
As adverse events related to TLS, PTs coded to "Tumour lysis syndrome (narrow)" in MedDRA SMQ (MedDRA/J ver. 18.1) were tabulated.

In Study 001, TLS was reported by 3 of 50 patients (6.0%; TLS in 3 patients), and the event was Grade 3 in 1 patient. There was no TLS that was fatal, serious, or led to discontinuation, interruption, or dose reduction. A causal relationship to romidepsin could not be ruled out for Grade 3 TLS in 1 patient. The Grade 3 TLS occurred on Day 1, but resolved.

In Study 0002, TLS was reported by 2 of 131 patients (1.5%; TLS in 2 patients), and the event was Grade ≥3 in both patients. There was no fatal TLS. Serious TLS was reported by 2 patients (1.5%; TLS in 2 patients), and a causal relationship to romidepsin could not be ruled out for either of the events. TLS occurred on Day 1 or 2, but resolved. TLS leading to dose reduction was reported by 1 patient (0.8%), but there was no TLS leading to discontinuation or interruption of romidepsin.

Among the foreign post-marketing use experience (data cut-off date of February 11, 2017),[22)] TLS was reported by 14 patients. Fatal TLS was reported by 2 patients, and a causal relationship to romidepsin could not be ruled out in 1 patient. Serious TLS was reported by 14 patients, of these, a causal relationship to romidepsin could not be ruled out in 9 patients.

PMDA's view:
In foreign clinical studies and post-marketing use experiences, serious TLS, including death, for which a causal relationship to romidepsin could not be ruled out was observed in multiple patients. Therefore, attention should be paid to TLS during romidepsin administration, and information on the incidences of TLS in clinical studies, etc., should be provided to healthcare professionals. Also, appropriate

information should be provided to healthcare professionals using the package insert, etc., requiring the physician to perform periodical haematology test during romidepsin administration so that appropriate measures are taken in case of abnormality.

7.R.3.7 Hypersensitivity

The applicant' explanation about the incidences of hypersensitivity to romidepsin:
As adverse events related to hypersensitivity, PTs coded to "Anaphylactic reaction (wide)" or "Severe cutaneous adverse reactions (narrow)" in MedDRA SMQ (MedDRA/J ver. 18.1) and "Hypersensitivity" and "Drug hypersensitivity" in MedDRA PT were tabulated.

Table 22 shows the incidences of hypersensitivity in Studies 001 and 0002.

Table 22. Hypersensitivity reported by ≥2% of subjects in either study (Studies 001 and 0002)

PT (MedDRA/J ver. 18.1)	Number of patients (%)			
	Study 001 N = 50		Study 0002 N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypersensitivity	15 (30.0)	2 (4.0)	60 (45.8)	10 (7.6)
Rash	5 (10.0)	0	10 (7.6)	1 (0.8)
Hypotension	3 (6.0)	1 (2.0)	11 (8.4)	2 (1.5)
Cough	2 (4.0)	0	24 (18.3)	0
Face oedema	2 (4.0)	0	1 (0.8)	0
Cardio-respiratory arrest	1 (2.0)	1 (2.0)	0	0
Dyspnoea	1 (2.0)	0	17 (13.0)	3 (2.3)
Erythema	1 (2.0)	0	4 (3.1)	0
Oedema	1 (2.0)	0	6 (4.6)	0
Pruritus	1 (2.0)	0	12 (9.2)	0
Periorbital oedema	0	0	4 (3.1)	0
Hypersensitivity	0	0	3 (2.3)	1 (0.8)

In Study 001, there was no fatal hypersensitivity. Serious hypersensitivity was reported by 1 patient (2.0%; cardio-respiratory arrest), and a causal relationship of the event to romidepsin could not be ruled out. Hypersensitivity leading to treatment discontinuation was reported by 1 patient (2.0%; cardio-respiratory arrest). Hypersensitivity leading to treatment interruption was reported by 1 patient (2.0%; rash). There was no hypersensitivity leading to dose reduction.

In Study 0002, there was no fatal hypersensitivity. Serious hypersensitivity was reported by 5 patients (3.8%; dyspnoea in 3 patients, hypotension and hypersensitivity in 1 patient each), and a causal relationship to romidepsin could not be ruled out for these events except dyspnoea in 1 patient. Hypersensitivity leading to treatment discontinuation was reported by 2 patients (1.5%; dyspnoea in 2 patients, stridor and throat tightness in 1 patient each [some patients had more than 1 event]). Hypersensitivity leading to treatment interruption was reported by 1 patient (0.8%; hypersensitivity), and hypersensitivity leading to dose reduction was reported by 1 patient (0.8%; hypotension).

Among the post-marketing use experiences in foreign countries (data cut-off date of February 11, 2017),[22)] hypersensitivity was reported by 154 patients. Fatal hypersensitivity was reported by 15 patients (respiratory failure in 6 patients, dyspnoea and acute respiratory failure in 3 patients each, cardiovascular insufficiency, hypotension, respiratory arrest, and respiratory distress in 1 patient each [a patient had more than 1 event]), but a causal relationship to romidepsin was ruled out in all patients except 8 patients for whom no information on the causal relationship was available. Serious hypersensitivity was reported by 110 patients. Serious hypersensitivity reported by ≥5 patients was dyspnoea in 33 patients, hypotension in 30 patients, respiratory failure in 9 patients, cough in 8 patients, and rash in 5 patients. A causal relationship to romidepsin could not be ruled out for hypotension in 13 patients, dyspnea in 10 patients, cough in 2 patients, and rash in 1 patient.

PMDA's view:
In Japanese and foreign clinical studies and in the post-marketing use experiences in foreign countries, serious hypersensitivity for which a causal relationship to romidepsin could not be ruled out was observed in multiple patients. Therefore, attention should be paid to hypersensitivity during treatment with romidepsin and that information on the incidences of hypersensitivity in clinical studies, etc., should be appropriately provided to healthcare professionals using the package insert, etc.

7.R.3.8 Haemorrhage

The applicant's explanation about the incidences of romidepsin-induced haemorrhage:
As adverse events related to haemorrhage, PTs coded to "Haemorrhage terms (excl laboratory terms) (narrow)" in MedDRA SMQ (MedDRA/J ver. 18.1) were tabulated.

Table 23 shows the incidences of haemorrhage in Studies 001 and 0002.

Table 23. Haemorrhage reported by ≥2% of subjects in either study (Studies 001 and 0002)

PT (MedDRA/J ver. 18.1)	Number of patients (%)			
	Study 001 N = 50		Study 0002 N = 131	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Haemorrhage	5 (10.0)	0	10 (7.6)	3 (2.3)
Contusion	2 (4.0)	0	0	0
Conjunctival haemorrhage	1 (2.0)	0	0	0
Gastrointestinal haemorrhage	1 (2.0)	0	1 (0.8)	1 (0.8)
Haematochezia	1 (2.0)	0	0	0
Haemorrhage subcutaneous	1 (2.0)	0	0	0
Henoch-Schonlein purpura	1 (2.0)	0	0	0
Epistaxis	0	0	3 (2.3)	1 (0.8)

In Study 001, there was no fatal haemorrhage. Serious haemorrhage was reported by 1 patient (2.0%; gastrointestinal haemorrhage), but its causal relationship to romidepsin was ruled out. There was no haemorrhage that led to discontinuation, interruption, or dose reduction of romidepsin.

In Study 0002, fatal haemorrhage was reported by 1 patient (0.8%; gastrointestinal haemorrhage), but its causal relationship to romidepsin was ruled out. Serious haemorrhage was reported by 2 patients (1.5%; gastrointestinal haemorrhage and lower gastrointestinal haemorrhage in 1 patient each), and a causal relationship to romidepsin could not be ruled out for lower gastrointestinal haemorrhage. There was no haemorrhage that led to discontinuation, interruption, or dose reduction of romidepsin.

Among the post-marketing use experiences in foreign countries (data cut-off date of February 11, 2017),[22)] haemorrhage was reported by 51 patients. Fatal haemorrhage was reported by 11 patients (cerebral haemorrhage in 4 patients, haemorrhage intracranial in 2 patients, arterial haemorrhage, disseminated intravascular coagulation, gastric haemorrhage, gastrointestinal haemorrhage, and pulmonary haemorrhage in 1 patient each), and a causal relationship to romidepsin could not be ruled out for cerebral haemorrhage and disseminated intravascular coagulation in 1 patient each. Serious haemorrhage was reported by 45 patients. Haemorrhage reported by multiple patients was epistaxis in 5 patients, cerebral haemorrhage and pulmonary haemorrhage in 4 patients each, disseminated intravascular coagulation, gastric haemorrhage, gastrointestinal haemorrhage, and haematuria in 3 patients each, and melaena, rectal haemorrhage, arterial haemorrhage, haemorrhage intracranial, and subdural haematoma in 2 patients each. A causal relationship to romidepsin could not be ruled out for epistaxis, pulmonary haemorrhage, disseminated intravascular coagulation, and melaena in 2 patients each, and cerebral haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematuria, and subdural haematoma in 1 patient each.

PMDA's view:
There were only limited cases of haemorrhage for which a causal relationship to romidepsin could not be ruled out in the foreign clinical studies and in the foreign post-marketing use experiences. It is difficult to draw any clear conclusion on the relationship between romidepsin and haemorrhage. However, taking account of the observation that, in the Japanese and foreign clinical studies and in the foreign post-marketing use experiences, serious haemorrhage, including death, for which a causal relationship to romidepsin could not be ruled out was observed in multiple patients, attention should be paid to haemorrhage during romidepsin administration and that information on the incidences of haemorrhage in clinical studies, etc., should be appropriately provided to healthcare professionals using the packaging insert, etc.

7.R.3.9 Venous thromboembolism

The applicant's explanation about the incidences of romidepsin-induced venous thromboembolism:
As adverse events related to venous thromboembolism, PTs coded to "Embolic and thrombotic events, venous (narrow)" in MedDRA SMQ (MedDRA/J ver. 18.1) were tabulated.

In Study 001, no venous thromboembolism-related adverse events were observed.

In Study 0002, venous thromboembolism was reported by 8 of 131 patients (6.1%; deep vein thrombosis in 5 patients, pulmonary embolism in 3 patients, vena cava thrombosis in 1 patient [a patient had more than 1 event]). Except deep vein thrombosis and vena cava thrombosis in 1 patient each, all others were Grade ≥3 events. No fatal venous thromboembolism was observed. Serious venous thromboembolism was reported by 7 patients (5.3%; deep vein thrombosis in 5 patients, pulmonary embolism in 3 patients [a patient had more than 1 event]), and a causal relationship to romidepsin could not be ruled out for deep vein thrombosis and pulmonary embolism in 3 patients each (including a patient with more than 1 event). Deep vein thrombosis occurred on Day 3, 22, 23, 29, and 938 after the start of treatment, and was unresolved in 1 patient. Pulmonary embolism occurred on Day 29, 63, and 148, and was unresolved in 1 patient. Venous thromboembolism leading to discontinuation or interruption of romidepsin was reported by 1 patient each (0.8%; pulmonary embolism). There was no venous thromboembolism leading to dose reduction.

Among the post-marketing use experiences in foreign countries (data cut-off date of February 11, 2017),[22)] venous thromboembolism was reported by 43 patients. Fatal venous thromboembolism was reported by 3 patients (pulmonary embolism in 2 patients, venous thrombosis limb in 1 patient), but information on their causal relationship to romidepsin was not available. Serious venous thromboembolism was reported by 43 patients. Serious venous thromboembolism reported by multiple patients was pulmonary embolism in 24 patients, deep vein thrombosis in 17 patients, and jugular vein thrombosis in 2 patients, and a causal relationship to romidepsin could not be ruled out for pulmonary embolism in 12 patients, deep vein thrombosis in 4 patients, and jugular vein thrombosis in 2 patients.

PMDA's view:
There were only limited cases of venous thromboembolism for which a causal relationship to romidepsin could not be ruled out in the Japanese and foreign clinical studies and in the foreign post-marketing use experiences. It is difficult to draw any clear conclusion on the relationship between romidepsin and venous thromboembolism. However, taking account of the observation that, in the foreign clinical studies and in the foreign post-marketing use experiences, serious venous thromboembolism for which a causal relationship to romidepsin could not be ruled out was observed in multiple patients, attention should be paid to venous thromboembolism during romidepsin administration and that information on the incidences of venous thromboembolism in clinical studies, etc., should be appropriately provided to healthcare professionals using the packaging insert, etc.

7.R.4 Clinical positioning and indication

The proposed indication for romidepsin was "Relapsed or refractory peripheral T-cell lymphoma." The Precautions for Indications section contained the following requirements:

- The diagnosis of the disease to be treated with romidepsin should be performed by a physician with sufficient experience in pathological diagnosis or at a medical institution to which such physicians belong.

- The eligibility of patients for the use of romidepsin should be determined by a physician who has a good understanding of the efficacy and safety of romidepsin based on a thorough comprehension of the study data presented in the "Clinical Studies" section of the package insert, including the histopathological types of patients enrolled in the clinical studies.

As a result of the review of sections "7.R.2 Efficacy" and "7.R.3 Safety" and of the review described below, PMDA concluded that the package insert should include, in the "Clinical Studies" section, the histopathological type of the disease in patients enrolled in Study 001, and that the "Indications" and "Precautions for Indications" sections should be specified as proposed by the applicant.

7.R.4.1 Clinical positioning of romidepsin

Descriptions of romidepsin for the treatment of relapsed or refractory PTCL in the Japanese and foreign clinical practice guidelines and in the representative textbooks of hematology and clinical oncology are as shown below.[23)]

Clinical Practice Guidelines

- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas (NCCN Guidelines) (v3. 2016) recommends romidepsin monotherapy as a second-line treatment option for patients with PTCL regardless of indication for hematopoietic stem cell transplantation (Category 2A[24)]).

- European Society for Medical Oncology (ESMO) Guideline (*Ann Oncol*. 2015;26 [Suppl 5]:v 108-15): Romidepsin is approved for the treatment of relapsed or refractory PTCL in the US based on the data of phase II studies.

- National Cancer Institute Physician Data Query, Adult Non-Hodgkin Lymphoma Treatment (NCI-PDQ), USA (June 1, 2016): The response rate in patients with relapsed or refractory PTCL was similar (30%) to that with pralatrexate (unapproved in Japan) (level of evidence: 3iii Div[25)]).

Textbooks

- Williams Hematology, 9th Edition (USA, The McGraw-Hill Companies, Inc, 2015): In Studies 0002 and NCI 1312 in patients with relapsed or refractory PTCL, the response rate was 38% at the maximum, and median progression-free survival (PFS) in patients who showed complete response (15% of all patients studied) was 29 months. Romidepsin is approved in the US.

- Wintrobe's Clinical Hematology, 13th Edition (USA, Lippincott Williams & Wilkins, 2013): Romidepsin is an HDAC inhibitor and, in Study NCI 1312 in patients with relapsed or refractory PTCL, the response rate was 38% (CR 18%).

- DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 10th edition (USA, Lippincott Williams & Wilkins, 2014): In Study 0002 in patients with relapsed or refractory PTCL, the response rate to romidepsin was 25% to 30% with the median duration of the response being less than 18 months. Romidepsin is approved in the US.

PMDA asked the applicant to explain the clinical positioning of romidepsin in patients with relapsed or refractory PTCL.

The applicant's response:
Study 001 demonstrated the efficacy of romidepsin in patients with relapsed or refractory PTCL, based on which romidepsin is positioned as one of the treatment options for these patients.

Mogamulizumab (genetical recombination) (mogamulizumab) and brentuximab vedotin (genetical recombination) (brentuximab) are approved for the treatment of relapsed or refractory PTCL. However, since no clinical data are available on the direct comparison of the efficacy and safety between romidepsin and these drugs, the appropriate choice between these drugs is unclear currently. The applicant considered that an appropriate drug will be selected according to the disease conditions of individual patients, with consideration given to the mechanism of action of each drug.

PMDA accepted the explanation of the applicant.

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23) There was no description of romidepsin in Clinical Practice Guideline for Hematologic Malignancy 2013 Edition (Kanehara & Co., Ltd., 2013) or in New Clinical Oncology, Fourth revised edition, edited by Japanese Society of Medical Oncology (Nankodo Co., td., 2015) which is a representative clinical oncology textbook in Japan.

24) There is a unified consensus of NCCN that the intervention is appropriate, albeit based on the evidence of a relative low level.

25) Efficacy was evaluated by response rate in a non-consecutive case series.

7.R.4.2 Target patients and indication of romidepsin

The applicant's explanation about the target patients of romidepsin:

Tables 24 and 25 show the best overall response and response rate by histopathological type, evaluated by the central assessment, in patients enrolled in Studies 001 and 0002. Among patients with PTCL, patients with peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), or anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL) responded to romidepsin, suggesting that romidepsin is clinically useful in these patient groups.

Table 24. Best overall response and response rate by histopathological type in Study 001 (central assessment, phase I[26] and phase II parts of Study 001)

Histological type	Number of patients (%) N = 46	Best overall response						Response (CR + CRu + PR) (response rate [%])
		CR	CRu	PR	SD	PD	NE	
PTCL-NOS	20 (43.5)	5	0	4	3	2	6	9 (45.0)
AITL	20 (43.5)	5	0	4	4	5	2	9 (45.0)
ALK-negative ALCL	3 (6.5)	1	0	2	0	0	0	3 (100)
Transformed mycosis fungoides	1 (2.2)	0	0	0	0	0	1	0
ALK-positive ALCL	0	-	-	-	-	-	-	-
Extranodal NK/T-cell lymphoma, nasal type[27]	0	-	-	-	-	-	-	-
Enteropathy-associated T-cell lymphoma	0	-	-	-	-	-	-	-
Hepatosplenic T-cell lymphoma	0	-	-	-	-	-	-	-
Subcutaneous panniculitis-like T-cell lymphoma	0	-	-	-	-	-	-	-
Primary cutaneous gamma-delta T-cell lymphoma	0	-	-	-	-	-	-	-
Other[28]	2 (4.3)	0	0	0	2	0	0	0

Table 25. Best overall response and response rate by histopathological type in Study 0002 (central assessment, efficacy analysis population)

Histological type	Number of patients N = 130	Best overall response						Response (CR + CRu + PR) (response rate [%])
		CR	CRu	PR	SD	PD	NE	
PTCL-NOS	69 (53.1)	6	4	10	16	21	12	20 (29.0)
AITL	27 (20.8)	5	1	3	8	4	6	9 (33.3)
ALK-negative ALCL	21 (16.2)	4	0	1	5	5	6	5 (23.8)
Enteropathy-associated T-cell lymphoma	6 (4.6)	0	0	0	1	2	3	0
Subcutaneous panniculitis-like T-cell lymphoma	3 (2.3)	0	0	0	1	1	1	0
ALK-positive ALCL	1 (0.8)	0	0	0	0	1	0	0
Transformed mycosis fungoides	1 (0.8)	0	0	0	0	0	1	0
Extranodal NK/T-cell lymphoma, nasal type	1 (0.8)	0	0	0	0	1	0	0
Primary cutaneous gamma-delta T-cell lymphoma	1 (0.8)	0	0	0	1	0	0	0
Hepatosplenic T-cell lymphoma	0	-	-	-	-	-	-	-

PTCL is a histological type classified as mature T/NK cell neoplasm according to World Health Organization (WHO) classification (2008). Mature T/NK cell neoplasm is classified into 4 subtypes, "nodal," "extranodal," "leukemic," and "cutaneous," according to the site of the main lesion. Among the above subtypes, the histological types classified as "leukemic"[29] or "cutaneous"[30] were excluded from enrollment in Study 001 because of the difference in the treatment policy.

In an investigator-initiated study in patients with relapsed or refractory extranodal NK/T-cell lymphoma, nasal type (Study RM-TCL-PI-0038), hepatic failure caused by EBV reactivation was reported in 2

[26] Six patients in ITT population receiving romidepsin (14 mg/m^2) in phase I part

[27] Upon receiving the safety report of a Korean investigator-initiated study (Study RM-TCL-PI-0038) in patients with relapsed or refractory extranodal NK/T-cell lymphoma, nasal type, the study protocol was revised in the mid-course of the study period to exclude patients with this disease.

[28] Two patients diagnosed with PTCL by the investigator but not by the central pathological analysis ("double cancer of diffuse large B-cell lymphoma and AITL" and "follicular dendritic cell sarcoma" in 1 patients each).

[29] T-cell prolymphocytic leukemia, T-cell large granular lymphocytic leukemia, aggressive NK cell leukemia, and adult T-cell leukemia/lymphoma

[30] Mycosis fungoides, Sezary syndrome, and primary cutaneous CD30-positive T-cell lymphoproliferative disorders

patients. Therefore, patients with extranodal NK/T-cell lymphoma, nasal type, were excluded from the inclusion criteria in Study 001 in the mid-course of the study. Since fatal hepatic failure due to EBV reactivation was reported in these patients, the applicant considered inappropriate to include patients with extranodal NK/T-cell lymphoma, nasal type, in target patients for treatment with romidepsin.

On the other hand, it is considered acceptable to administer romidepsin to the following patients by taking account of the observations listed below: (1) Patients with PTCL of histopathological types who were enrolled in Study 001 or Study 0002 but did not respond to romidepsin (ALK-positive ALCL, enteropathy-associated T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, transformed mycosis fungoides, primary cutaneous gamma-delta T-cell lymphoma) and (2) patients with PTCL of histopathological type who were not enrolled in Study 001 or Study 0002 (hepatosplenic T-cell lymphoma):

- The tumor growth-suppressive effect of romidepsin is thought to be due to (1) cell cycle arrest caused by regulation of gene expression mediated by HDAC inhibition and (2) apoptosis induction. Therefore, romidepsin is expected to exhibit a tumor growth-suppressive effect against PTCL that shows increased expression levels of HDAC1, HDAC2, and HDAC6.
- Given that romidepsin showed a certain level of efficacy against PTCL-NOS, AITL, and ALK-negative ALCL, romidepsin is expected to be effective also in patients with PTCL of histopathological type who were (1) enrolled in Study 001 or Study 0002 but did not respond to romidepsin or (2) not enrolled in the above studies.

Based on the above, the histopathological types of patients enrolled in Study 001 and efficacy results by histopathological type are described in the Clinical Studies section of the package insert. Also, advice is provided in the Precautions for Indications section, requiring the physician to determine the eligibility of patients for the use of romidepsin upon thorough understanding of the efficacy and safety of romidepsin based on a good knowledge on the description in the "Clinical Studies" section. With the above precautions, the proposed indication was specified as "relapsed or refractory peripheral T-cell lymphoma."

PMDA's view:
PMDA generally accepted the explanation of the applicant regarding the target patients for treatment with romidepsin, taking account of the following points, in addition to the explanation of the applicant:

- There is no treatment that is expected to prolong OS of patients with PTCL. It is considered that different treatment policy is not required for different histological types [see Section 7.R.4.1].
- Due to the extremely limited number of patients with PTCL, it is practically impossible to conduct clinical studies to investigate the efficacy of romidepsin for each histological type.
- Romidepsin is used by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancy.

Based on the above, PMDA concluded that it is acceptable to indicate romidepsin for "relapsed or refractory peripheral T-cell lymphoma," as proposed by the applicant. However, taking account of the proposal that, in the pathological diagnosis of PTCL, histological typing should be performed by a hematopathologist (*J Clin Oncol*. 2008;26:4124-30, NCCN Guidelines), the histopathological types, etc., of patients enrolled in Study 001 should be described in the Clinical Studies section and that the following advice should be provided in the Precautions for Indications section of the package insert. In addition, fatal hepatic failure due to EBV reactivation was reported in patients with extranodal NK/T-cell lymphoma, nasal type, and as a result, patients with this disease were excluded from the inclusion criteria in the mid-course of Study 001. Since this is important information for the selection of patients eligible for the treatment with romidepsin, the advice should be appropriately provided to healthcare professionals using the package insert, etc.

- The diagnosis of the disease to be treated with romidepsin should be performed by a physician with sufficient experience in pathological diagnosis or at a medical institution to which such physicians belong.
- The eligibility of patients for the use of romidepsin should be determined by a physician who has a good understanding of the efficacy and safety of romidepsin based on a thorough comprehension of

the study data presented in the "Clinical Studies" section of the package insert, including the histopathological types of patients enrolled in the clinical studies.

7.R.5 Dosage and administration

The proposed dosage and administration for romidepsin was "The usual adult dosage is 14 mg/m^2 (body surface area) of romidepsin administered as an intravenous infusion over 4 hours on Days 1, 8, and 15, followed by a rest period (Days 16-28). This 28-day cycle is repeated. The dose may be reduced according to the patient's condition." The following descriptions were included in the Precautions for Dosage and Administration section:

- The efficacy and safety of romidepsin in combination with other antineoplastic drugs have not been established.

- Method for the reconstitution of the solution for injection and the duration of infusion

- Criteria for treatment interruption, dose reduction, and discontinuation of romidepsin in patients experiencing an adverse drug reaction

As a result of the review presented in Sections "6.R.1 Romidepsin administration in patients with hepatic impairment," "7.R.2 Efficacy," and "7.R.3 Safety" and of the review described below, PMDA concluded that the dosage and administration should be specified as proposed by the applicant, and that the following statements should be included in the Precautions for Dosage and Administration section of the package insert of romidepsin.

[Precautions for Dosage and Administration]

- The efficacy and safety of romidepsin in combination with other antineoplastic drugs have not been established.

- Increases in blood romidepsin concentrations in patients with hepatic impairment were reported in a clinical study. Dose reduction should be considered in such patients, and the patients should be carefully monitored for adverse events.

- In case of an adverse drug reaction associated with romidepsin, treatment interruption, dose reduction, or discontinuation should be considered based on the following criteria.

Criteria for treatment interruption, dose reduction, or discontinuation in patients experiencing an adverse drug reaction

Adverse drug reaction		Measures to be taken
Platelet count decreased	Platelet count <50,000/μL	Interrupt treatment with romidepsin until platelet count returns to ≥75,000/μL or baseline. After resolution of the event, treatment may be resumed at the initial dose.
	Platelet count <50,000/μL again, or <25,000/μL, which requires platelet transfusion	Interrupt treatment with romidepsin until platelet count returns to ≥75,000/μL or baseline. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with romidepsin if the platelet count decreased again after dose reduction.
Neutrophil count decreased	Neutrophil count <1000/μL	Interrupt treatment with romidepsin until neutrophil count returns to ≥1500/μL or baseline. After resolution of the event, treatment may be resumed at the initial dose.
	Neutrophil count <1000/μL again, or <500/μL accompanied by pyrexia (temperature ≥38.5°C)	Interrupt treatment with romidepsin until neutrophil count returns to ≥1500/μL or baseline. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with romidepsin if the neutrophil count decreased again after dose reduction.
Non-hematological toxicity*	Grade 3 non-hematological toxicity	Interrupt treatment with romidepsin until the toxicity returns to Grade ≤1 or baseline. After resolution of the event, treatment may be resumed at the initial dose.
	Recurrence of Grade 3 non-hematological toxicity, or Grade 4 non-hematological toxicity	Interrupt treatment with romidepsin until the toxicity returns to Grade ≤1 or baseline. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with romidepsin if the toxicity recurs after dose reduction.
QTc interval	>500 ms	Interrupt treatment with romidepsin. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with romidepsin if the event recurs after dose reduction.
Arrhythmia	Sinus tachycardia (>140/min), atrial dysrhythmia (supraventricular tachycardia, atrial fibrillation, atrial flutter), heart rate increased (>120/min and higher than the previous level by >20/min), ventricular tachycardia (≥3 irregular heartbeats in a row)	Interrupt treatment with romidepsin. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with romidepsin if the event recurs after dose reduction.

* Grade is based on CTCAE.

7.R.5.1 Dosage and administration of romidepsin

The applicant's explanation about the justification for the dosage and administration of romidepsin:
In Study T-95-0022 in patients with advanced solid cancer, romidepsin was administered on Days 1, 8, and 15 of a 28-day cycles. MTD was determined to be 13.3 mg/m^2. Subsequently, Study NCI 1312 in patients with relapsed or refractory PTCL or CTCL was conducted in which romidepsin (14 mg/m^2) was administered on Days 1, 8, and 15 of a 28-day cycles. The study did not show any clear tolerability problem. Based on these results, Study 0002 in patients with relapsed or refractory PTCL was conducted using the same dosage regimen as those used in Study NCI 1312. In the study, romidepsin exhibited a certain level of efficacy.

As for the dosage regimen of romidepsin in Japanese patients, since phase I part of Study 001 demonstrated the tolerability of romidepsin (9 or 14 mg/m^2) when administered using the same dosing schedule as that used in Study 0002, the same dosage regimen as in Study 0002 was used in phase II part. In the study, romidepsin demonstrated a certain level of efficacy [see Section 7.R.2.1].

Based on the above, the proposed dosage and administration of romidepsin was specified according to the dosage regimen used in Study 001.

PMDA accepted the explanation of the applicant.

7.R.5.2 Romidepsin dose adjustment

The applicant's explanation about the dose adjustment of romidepsin:
In Studies 001 and 0002, the criteria for treatment interruption, dose reduction, and discontinuation were specified, and the study results confirmed the clinical benefits of romidepsin when romidepsin was

administered in accordance with these criteria. Therefore, the following criteria for treatment interruption, dose reduction, and discontinuation were specified in the Precautions for Dosage and Administration section by referring to the criteria used in Studies 001 and 0002, with the following changes:

- Platelet count: In Study 0002, romidepsin was to be interrupted until platelet count returned to ≥50,000/μL or baseline, whereas in Study 001, romidepsin was to be interrupted until platelet count returns to ≥75,000/μL or baseline. The same criterion for platelet count was selected as that in Study 001.
- Non-hematological toxicity: The reduction of the dose of romidepsin was permitted (1) in case of the onset of a Grade 1 or Grade 2 adverse event (in Studies 001 and 0002), or (2) at the resumption of administration of romidepsin after treatment interruption due to Grade 3 adverse event (in Study 001), provided that the resumption of romidepsin at the initial dose was considered by the investigator to seriously affect the quality of life (QOL) of the patient. This criterion was not included because appropriate judgment would be made by healthcare professionals.
- Cardiovascular disorder: The criteria in Studies 001 and 0002 specified that, treatment with romidepsin should be interrupted when T wave inversion (≥4 mm) or ST depression (≥2 mm) is observed, and may be resumed at the reduced dose of 10 mg/m^2 after resolution of the event, and that romidepsin should be interrupted or discontinued in case where the event recurs or dose not resolve. However, there were no patients in whom the dose of romidepsin was interrupted, reduced, or discontinued due to cardiovascular disorder. Romidepsin was interrupted, reduced in dose, or discontinued in 4 patients who had atrial fibrillation in study 001 and in 1 patient each who had ventricular extrasystoles and tachycardia in Study 0002. Advising physicians to perform periodical electrocardiogram would lead to taking appropriate measures, as necessary, including treatment interruption, dose reduction, and discontinuation of romidepsin. Only QTc prolongation was included in the criteria because the event requires particular attention during romidepsin treatment.

PMDA's view:
PMDA generally accepted the explanation of the applicant. As for cardiovascular disorder, there were patients who underwent dose adjustment because of arrhythmia. Therefore, the criteria for interruption, dose reduction, and discontinuation due to arrhythmia stipulated in Study 001 should be included as a guide in the Precautions for Dosage and Administration section of the package insert.

7.R.5.3 Concomitant use with other antineoplastic drugs

The applicant explained that since there are no data from clinical studies in patients with relapsed or refractory PTCL receiving romidepsin in combination with other antineoplastic drugs, neither efficacy nor safety of such concomitant use has been established, and that relevant advice will be provided in the Precautions for Dosage and Administration section of the package insert.

PMDA accepted the explanation of the applicant.

7.R.6 Post-marketing investigations

The applicant's explanation about the plan for the post-marketing surveillance:
In order to evaluate the safety, etc., of romidepsin in the post-marketing clinical setting, the applicant plans to conduct a post-marketing surveillance covering all patients treated with romidepsin.

The following key survey items for the post-marketing surveillance were selected taking account of the results of Studies 001 and 0002 and of the incidence and seriousness of adverse events reported: Bone marrow depression, infection, and abnormal electrocardiogram (QT interval prolongation, abnormal T wave, and abnormal ST segment).

The planned sample size was 100 patients, based on the occurrences of abnormal electrocardiogram (QT interval prolongation, abnormal T wave, and abnormal ST segment), the least frequent adverse event among the key survey items. Given the occurrences of the above key survey items in clinical studies, it is expected that the above number of patients will also allow the collection of enough data on key survey items other than abnormal electrocardiogram (QT interval prolongation, abnormal T wave, and abnormal ST segment).

The follow-up period was 24 weeks (6 treatment cycles) based on the results of Studies 001 and 0002, with the following taken into consideration: (1) Most of the first episode of the events included in the key survey items were observed within 24 weeks and (2) the incidence of any adverse events did not show clear tendency of increase with treatment period.

PMDA's view:
Because of the limited safety data currently available on the use of romidepsin in Japanese patients with relapsed or refractory PTCL, a post-marketing surveillance should be conducted, and safety data obtained from the surveillance should be provided to healthcare professionals without delay. However, there is little need to conduct the surveillance covering all patients receiving romidepsin provided that information is collected and provided in an appropriate manner, taking account of the following: (a) Since the approval of romidepsin in the US[31)] in November 2009, use experiences in approximately 9000 patients have been collected in foreign countries by November 2016, and (b) other anti-neoplastic drugs with HDAC-inhibitory activity similar to that of romidepsin have been approved in Japan, and a certain level of use experiences have been collected.

The key survey items for the post-marketing surveillance should include bone marrow depression, infection, QT interval prolongation, and hypersensitivity, which are adverse events requiring particular attention in administering romidepsin as judged from the results of clinical studies, etc.

The planned sample size should be reexamined, also taking into consideration the comparison of safety information on the incidences of the key survey items obtained from Studies 001 and 0002 with the information available from this surveillance.

The follow-up period proposed by the applicant is acceptable, taking account of the fact that the first episode of most of the adverse events, including the key survey items, occurred within 24 weeks (within 6 cycles) after the start of romidepsin treatment and that the incidence of any adverse events did not show clear tendency of increase after 24 weeks (6 cycles).

7.3 Adverse events, etc. reported in clinical studies

Deaths reported in clinical data submitted for safety evaluation were described in Section "7.1 Evaluation data" and in Section "7.2 Reference data." Major adverse events other than death were as follows.

7.3.1 Japanese phase I/II study (Study 001)

Adverse events were observed in all 50 patients, and a causal relationship of adverse events to the study drug could not be ruled out in any of the patients. Table 26 shows adverse events reported by ≥20% of subjects.

31) Approved for the indication for the treatment of CTCL.

Table 26. Adverse events reported by ≥20% of subjects

SOC PT (MedDRA/J ver. 18.1)	Number of patients (%) N = 50 All Grades	 Grade ≥3
All adverse events	50 (100)	46 (92.0)
Blood and lymphatic system disorders		
Thrombocytopenia	49 (98.0)	19 (38.0)
Lymphopenia	44 (88.0)	37 (74.0)
Leukopenia	42 (84.0)	23 (46.0)
Neutropenia	40 (80.0)	27 (54.0)
Anaemia	17 (34.0)	6 (12.0)
Gastrointestinal disorders		
Nausea	27 (54.0)	0
Vomiting	21 (42.0)	0
Diarrhoea	18 (36.0)	0
Constipation	16 (32.0)	1 (2.0)
General disorders and administration site conditions		
Pyrexia	33 (66.0)	3 (6.0)
Fatigue	16 (32.0)	2 (4.0)
Malaise	13 (26.0)	2 (4.0)
Metabolism and nutrition disorders		
Decreased appetite	28 (56.0)	5 (10.0)
Hypokalaemia	10 (20.0)	0
Hypophosphataemia	10 (20.0)	5 (10.0)
Nervous system disorders		
Dysgeusia	31 (62.0)	0
Investigations		
Hb decreased	13 (26.0)	6 (12.0)
ALT increased	10 (20.0)	2 (4.0)
Weight decreased	10 (20.0)	1 (2.0)

Serious adverse events were reported by 15 of 50 patients (30.0%). The serious adverse events observed were CMV infection and pyrexia in 2 patients (4.0%) each, akathisia, bacterial infection, hepatitis B, *Pneumocystis jirovecii* pneumonia, pneumonia, pneumonia bacterial, sepsis, urinary tract infection, angina pectoris, cardiac failure acute, cardio-respiratory arrest, multi-organ failure, dehydration, hyperkalaemia, cancer pain, diffuse large B-cell lymphoma, tumour associated fever, altered state of consciousness, depressed level of consciousness, retinal detachment, gastrointestinal haemorrhage, hepatic function abnormal, and pleural effusion in 1 patient (2.0%) each. Of these, a causal relationship to the study drug could not be ruled out for CMV infection and pyrexia in 2 patients each, and bacterial infection, hepatitis B, *Pneumocystis jirovecii* pneumonia, pneumonia, sepsis, urinary tract infection, multi-organ failure, cardio-respiratory arrest, retinal detachment, hyperkalaemia, and diffuse large B-cell lymphoma in 1 patient each.

Adverse events leading to discontinuation of the study drug were reported by 13 of 50 patients (26.0%). They were neutropenia, thrombocytopenia, and atrial fibrillation in 2 patients (4.0%) each, and cardio-respiratory arrest, supraventricular extrasystoles, bacterial infection, CMV infection, hepatitis B, pneumonia bacterial, sepsis, hyperkalaemia, hypokalaemia, hypomagnesaemia, hypophosphataemia, and multi-organ failure in 1 patient (2.0%) each. Of these, a causal relationship to the study drug could not be ruled out for these adverse events except pneumonia bacterial in 1 patient.

7.3.2 Foreign phase II study (Study 0002)

Adverse events were reported by 128 of 131 patients (97.7%), and adverse events for which a causal relationship to the study drug could not be ruled out were reported by 126 of 131 patients (96.2%). Table 27 shows adverse events reported by ≥20% of subjects.

Table 27. Adverse events reported by ≥20% of subjects

SOC PT (MedDRA/J ver. 18.1)	Number of patients (%) N = 131 All Grades	 Grade ≥3
All adverse events	128 (97.7)	89 (67.9)
Gastrointestinal disorders		
Nausea	77 (58.8)	3 (2.3)
Vomiting	51 (38.9)	6 (4.6)
Diarrhoea	47 (35.9)	3 (2.3)
Constipation	39 (29.8)	1 (0.8)
General disorders and administration site conditions		
Fatigue	54 (41.2)	8 (6.1)
Pyrexia	47 (35.9)	8 (6.1)
Blood and lymphatic system disorders		
Thrombocytopenia	53 (40.5)	32 (24.4)
Neutropenia	39 (29.8)	26 (19.8)
Anaemia	33 (25.2)	14 (10.7)
Metabolism and nutrition disorders		
Decreased appetite	46 (35.1)	3 (2.3)
Nervous system disorders		
Dysgeusia	27 (20.6)	0

Serious adverse events were reported by 61 of 131 patients (46.6%). Serious adverse events reported by ≥2 patients were pyrexia in 11 patients (8.4%), pneumonia in 7 patients (5.3%), sepsis and vomiting in 6 patients (4.6%) each, cellulitis and deep vein thrombosis in 5 patients (3.8%) each, abdominal pain and febrile neutropenia in 4 patients (3.1%) each, chest pain, dehydration, dyspnoea, pulmonary embolism, and neutropenia in 3 patients (2.3%) each, urinary tract infection, staphylococcal infection, hyponatraemia, TLS, colitis, hypoxia, anaemia, autoimmune haemolytic anaemia, leukopenia, thrombocytopenia, mental status changes, renal failure acute, and renal failure in 2 patients (1.5%) each. Of these, a causal relationship to the study drug could not be ruled out for pyrexia in 8 patients, vomiting in 6 patients, cellulitis in 4 patients, pneumonia, febrile neutropenia, neutropenia, pulmonary embolism, and deep vein thrombosis in 3 patients each, sepsis, chest pain, dehydration, hyponatraemia, TLS, anaemia, leukopenia, thrombocytopenia, abdominal pain, colitis, mental status changes, and dyspnoea in 2 patients each, and urinary tract infection, staphylococcal infection, renal failure acute, and renal failure in 1 patient each.

Adverse events leading to discontinuation of the study drug were reported by 25 of 131 patients (19.1%). Adverse events leading to discontinuation of the study drug reported by ≥2 patients were thrombocytopenia and pneumonia in 3 patients (2.3%) each, and sepsis, fatigue, and dyspnea in 2 patients (1.5%) each. Of these, a causal relationship to the study drug could not be ruled out for thrombocytopenia in 3 patients, fatigue and dyspnoea in 2 patients each, and pneumonia and sepsis in 1 patient each.

7.3.3 Foreign phase I study (Study T-95-0077)

Adverse events[32)] were reported by 41 of 45 patients (91.1%), and adverse events for which a causal relationship to the study drug could not be ruled out were reported by 41 of 45 patients (91.1%). Adverse events reported by ≥20% of subjects were nausea in 33 patients (73.3%), vomiting in 30 patients (66.7%), asthenia in 27 patients (60.0%), pyrexia in 25 patients (55.6%), decreased appetite in 21 patients (46.7%), myocardial ischaemia in 19 patients (42.2%), hypocalcaemia in 15 patients (33.3%), leukopenia in 13 patients (28.9%), headache in 12 patients (26.7%), dysgeusia in 11 patients (24.4%), and constipation and thrombocytopenia in 9 patients (20.0%) each.

Adverse events leading to discontinuation of the study drug were reported by 3 patients (6.7%). They were haemoptysis, spleen disorder, and infection in 1 patient each. Of these, a causal relationship to the study drug could not be ruled out for spleen disorder and infection in 1 patient each.

7.3.4 Foreign phase I study (Study T-95-0022)

Adverse events[32)] were reported by all of 42 patients, and a causal relationship of adverse events to the study drug could not be ruled out in any of the patients. Adverse events reported by ≥20% of subjects

[32)] In this study, information on the seriousness of adverse events was not collected.

were nausea in 33 patients (78.6%), asthenia in 31 patients (73.8%), decreased appetite in 23 patients (54.8%), anaemia and vomiting in 22 patients (52.4%) each, hyperglycaemia in 20 patients (47.6%), thrombocytopenia and weight decreased in 15 patients (35.7%) each, pyrexia in 12 patients (28.6%), blood ALP increased and blood urea increased in 11 patients (26.2%) each, chest pain in 10 patients (23.8%), and back pain and arthralgia in 9 patients (21.4%) each.

Adverse events leading to discontinuation of the study drug were reported by 10 patients (23.8%). The adverse events leading to discontinuation of the study drug reported by ≥2 patients were asthenia in 4 patients (9.5%), and its causal relationship to the study drug could not be ruled out.

7.3.5 Foreign phase I study (Study ROMI-ADVM-001)

Adverse events were reported by all 15 patients, and adverse events for which a causal relationship to the study drug could not be ruled out were reported by 14 of 15 patients (93.3%). Adverse events reported by ≥2 patients were nausea in 11 patients (73.3%), vomiting and decreased appetite in 8 patients (53.3%) each, fatigue in 7 patients (46.7%), headache in 5 patients (33.3%), constipation in 3 patients (20.0%), and abdominal pain upper, diarrhoea, asthenia, general physical health deterioration, dysgeusia, arthralgia, pneumonia, and urinary tract infection in 2 patients (13.3%) each.

Serious adverse events were reported by 4 patients (26.7%). The serious adverse events observed were general physical health deterioration and pneumonia in 2 patients (13.3%) each, and atrial fibrillation and bile duct cancer in 1 patient (6.7%) each. Of these, a causal relationship of atrial fibrillation to the study drug could not be ruled out.

An adverse event leading to discontinuation of the study drug was reported by 1 patient (6.7%). The event was pneumonia, and its causal relationship to the study drug was ruled out.

7.3.6 Foreign phase I study (Study ROMI-ADVM-002)

Adverse events were reported by 13 of 14 patients (92.9%), and adverse events for which a causal relationship to the study drug could not be ruled out were reported by 13 of 14 patients (92.9%). Adverse events reported by ≥2 patients were nausea in 10 patients (71.4%), vomiting and fatigue in 7 patients (50%) each, decreased appetite in 6 patients (42.9%), diarrhoea and thrombocytopenia in 5 patients (35.7%) each, anaemia and anxiety in 3 patients (21.4%) each, and constipation, hypokalaemia, arthralgia, musculoskeletal discomfort, musculoskeletal pain, and dysgeusia in 2 patients (14.3%) each.

Serious adverse events were reported by 2 patients (14.3%). The serious adverse events observed were anaemia in 2 patients (14.3%) and thrombocytopenia, melaena, nausea, vomiting, and fatigue in 1 patient (7.1%) each. Of these, a causal relationship to the study drug could not be ruled out for thrombocytopenia, nausea, vomiting, and fatigue in 1 patient each.

There was no adverse event leading to discontinuation of the study drug.

7.3.7 Foreign phase I study (Study GPI-06-0005)

Adverse events were reported by all 29 patients, and a causal relationship of adverse events to the study drug could not be ruled out in any of the patients. Adverse events reported by ≥20% of subjects in either of the treatment periods (13 patients in the first period, 16 patients in the second period) were vomiting NOS in 12 patients (92.3%), nausea and fatigue in 10 patients (76.9%) each, inappetence in 8 patients (61.5%), constipation and dysgeusia in 7 patients (53.8%) each, anaemia NOS in 6 patients (46.2%), diarrhoea NOS and headache in 5 patients (38.5%) each, abdominal pain NOS, dyspepsia, pyrexia, dizziness, back pain, and visual acuity reduced in 3 patients (23.1%) each in the first period; and nausea in 12 patients (75.0%), vomiting NOS and fatigue in 11 patients (68.8%) each, anaemia NOS in 9 patients (56.3%), diarrhoea NOS and inappetence in 7 patients (43.8%) each, constipation and thrombocytopenia in 6 patients (37.5%) each, dizziness in 5 patients (31.3%), oedema peripheral, dysgeusia, muscle spasms, pain in extremity, dyspnoea, and cough in 4 patients (25.0%) each in the second period.

Serious adverse events were reported by 5 patients (38.5%) in the first period and 8 patients (50.0%) in the second period. The serious adverse events observed were pneumonia NOS in 2 patients (15.4%),

and nausea, vomiting NOS, pneumonia bacterial NOS, hydronephrosis, hip fracture, aspiration pneumonitis, skin haemorrhage, abnormal behavior NOS, and syncope in 1 patient (7.7%) each in the first period; and atrial fibrillation and diarrhoea NOS in 2 patient (12.5%) each, and nausea, vomiting NOS, rectal haemorrhage, hydronephrosis, pericardial effusion, fatigue, mental status changes, malignant neoplasm progression, febrile neutropenia, dehydration, and arthralgia in 1 patient (6.3%) each in the second period. Of these, a causal relationship to the study drug could not be ruled out for nausea, vomiting NOS, pneumonia bacterial NOS, skin haemorrhage, syncope, and abnormal behaviour NOS in 1 patient each in the first period; and for atrial fibrillation in 2 patients, and febrile neutropenia, dehydration, nausea, vomiting NOS, diarrhoea NOS, and fatigue 1 patient each in the second period.

Adverse events leading to discontinuation of the study drug were reported by 1 patient (7.7%) in the first period and 3 patients (18.8%) in the second period. They were skin haemorrhage in 1 patient (7.7%) in the first period and arthralgia, atrial fibrillation, diarrhoea NOS, and fatigue in 1 patient (6.3%) each in the second period. Of these, a causal relationship to the study drug could not be ruled out for skin haemorrhage in 1 patient in the first period and for atrial fibrillation, diarrhoea NOS, and fatigue in 1 patient each in the second period.

7.3.8 Foreign phase II study (Study NCI 1312)

Adverse events were reported by all 47 patients with PTCL,[33)] and a causal relationship to the study drug could not be ruled out in any of them. Table 28 shows adverse events reported by ≥20% of subjects.

[33)] Patients with PTCL or CTCL were enrolled in the study, and total of 47 patients with PTCL were included in the safety analysis population.

Table 28. Adverse events reported by ≥20% of patients with PTCL

SOC PT (MedDRA/J ver. 18.1)	Number of patients (%) N = 47	
	All Grades	Grade ≥3
All adverse events	47 (100)	40 (85.1)
Blood and lymphatic system disorders		
Thrombocytopenia	34 (72.3)	17 (36.2)
Neutropenia	31 (66.0)	22 (46.8)
Anaemia	29 (61.7)	13 (27.7)
Leukopenia	26 (55.3)	21 (44.7)
Lymphopenia	19 (40.4)	18 (38.3)
General disorders and administration site conditions		
Fatigue	35 (74.5)	9 (19.1)
Pyrexia	22 (46.8)	8 (17.0)
Gastrointestinal disorders		
Nausea	35 (74.5)	3 (6.4)
Constipation	19 (40.4)	1 (2.1)
Vomiting	19 (40.4)	4 (8.5)
Diarrhoea	17 (36.2)	1 (2.1)
Metabolism and nutrition disorders		
Hypocalcaemia	28 (59.6)	7 (14.9)
Hypoalbuminaemia	24 (51.1)	5 (10.6)
Decreased appetite	21 (44.7)	1 (2.1)
Hyperglycaemia	18 (38.3)	4 (8.5)
Hypomagnesaemia	15 (31.9)	0
Hyperuricaemia	14 (29.8)	3 (6.4)
Hyponatraemia	10 (21.3)	3 (6.4)
Hypophosphataemia	10 (21.3)	6 (12.8)
Investigations		
Electrocardiogram T wave amplitude decreased	32 (68.1)	0
AST increased	18 (38.3)	6 (12.8)
ALT increased	17 (36.2)	7 (14.9)
Nervous system disorders		
Headache	16 (34.0)	1 (2.1)
Dysgeusia	13 (27.7)	0
Infections and infestations		
Infection	10 (21.3)	6 (12.8)
Respiratory, thoracic and mediastinal disorders		
Cough	10 (21.3)	0
Dyspnoea	10 (21.3)	2 (4.3)
Vascular disorders		
Hypotension	13 (27.7)	5 (10.6)
Hepatobiliary disorders		
Hyperbilirubinaemia	14 (29.8)	4 (8.5)

Serious adverse events were reported by 30 of 47 patients (63.8%). Serious adverse events reported by ≥2 patients were pyrexia in 8 patients (17.0%), AST increased and hypotension in 6 patients (12.8%) each, disease progression, anaemia, thrombocytopenia, and ALT increased in 5 patients (10.6%) each, infection, dehydration, and dyspnoea in 4 patients (8.5%) each, hypocalcaemia, hyperbilirubinaemia, hypoxia, lymphopenia, and neutropenia in 3 patients (6.4%) each, and device related infection, ventricular arrhythmia, hyperuricaemia, hypoalbuminaemia, syncope, vomiting, pneumonitis, febrile neutropenia, leukopenia, hypersensitivity, packed red blood cell transfusion, and platelet transfusion in 2 patients (4.3%) each. Of these, a causal relationship to the study drug could not be ruled out for these adverse events except disease progression in 4 patients and pyrexia in 1 patient.

Adverse events leading to discontinuation of the study drug was reported by 13 of 47 patients (27.7%). Adverse events leading to discontinuation of the study drug reported by ≥2 patients were disease progression in 4 patients (8.5%), thrombocytopenia in 3 patients (6.4%), and ALT increased in 2 patients (4.3%). Of these, a causal relationship to the study drug could not be ruled out for these adverse events except disease progression in 3 patients.

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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted product application documents. The following findings were noted at a participating medical institution and the sponsor site, although they did not significantly affect the overall evaluation of the study. These were notified to the head of the medical institution and the applicant (sponsor) for corrective action to be taken.

Findings requiring corrective action

Medical institution

- Protocol deviation (partly missing 12-lead electrocardiograms, noncompliance with the rules related to the criteria for the start of the study drug administration, noncompliance with the rules related to the interruption of the study drug, noncompliance with the criteria for the resumption of the study drug after treatment interruption)

Sponsor

- Delay in periodical report of safety information to investigators and the heads of medical institutions

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

On the basis of the data submitted, PMDA has concluded that romidepsin has efficacy in the treatment of relapsed or refractory PTCL and that romidepsin has acceptable safety in view of its benefits. Istodax contains a new active ingredient, romidepsin, which is considered to suppress tumor growth by inhibiting deacetylation of histones and other proteins, thereby inducing cell cycle arrest and apoptosis. Thus, Istodax is of clinical significance because it offers a new treatment option for patients with relapsed or refractory PTCL. The efficacy, indication, post-marketing investigations, etc., should be further evaluated.

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

Review Report (2)

May 8, 2017

Product Submitted for Approval

Brand Name	Istodax Injection 10 mg
Non-proprietary Name	Romidepsin
Applicant	Celgene K.K.
Date of Application	September 2, 2016

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 a certain level of efficacy of romidepsin was demonstrated by the data from the phase II part of the Japanese phase I/II study in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) (Study ROMI-TCL-001 [Study 001]), because the response rate [95% CI] assessed centrally according to the modified International Workshop Response Criteria for non-Hodgkin's lymphomas (mIWC) 1999, the primary endpoint, was 42.5% [27.2%, 57.8%] which was significantly greater than the pre-defined threshold response rate (10%).

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

1.2 Safety

As a result of the review in Section "7.R.3 Safety" of the Review Report (1), PMDA has concluded that adverse events requiring particular attention during treatment with romidepsin are bone marrow depression, infection, cardiac disorders (abnormal electrocardiogram such as prolonged QT interval, in particular), tumour lysis syndrome (TLS), hypersensitivity, haemorrhage, and venous thromboembolism.

PMDA also concluded that romidepsin is well tolerated provided that appropriate measures, such as monitoring and management of adverse events as well as treatment interruption, dose reduction, and discontinuation of romidepsin, are taken by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancy.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- If cautions are provided against bone marrow depression including thrombocytopenia, then there is little need to provide precautions against the risk of haemorrhage in the package insert. On the other hand, since haemorrhage is caused also by factors other than thrombocytopenia (e.g., tissue infiltration of tumor, use of corticosteroid), a relationship between thrombocytopenia and haemorrhage should be investigated and, based on the results, appropriate advice should be provided.

- A particular attention should be paid to romidepsin-induced reactivation of Epstein-Barr virus (EBV). Information on the incidence of the EBV reactivation in clinical studies should be communicated to healthcare professionals. In addition, the package insert and other materials should provide advice to ensure that physicians closely monitor each patient's conditions, for example, by performing periodical liver function test and, in case of any abnormality, take appropriate measures.

PMDA asked the applicant to explain the relationship between romidepsin-induced haemorrhage and thrombocytopenia.

The applicant's response:
In Study 001, haemorrhage was reported by 5 of 50 patients (10.0%), and thrombocytopenia was reported by 49 of 50 patients (98.0%). Of the 49 patients experiencing thrombocytopenia, 4 (8.2%) showed haemorrhage. There was only 1 patient without thrombocytopenia, and this patient had haemorrhage (1 of 1 patient, 100%). Serious or Grade ≥3 haemorrhage was reported by 1 patient (2.0%), and platelet count[34)] at the onset of haemorrhage was $22.5 \times 10^4/mm^3$.

In the foreign phase II study (Study GPI-06-0002 [Study 0002]), haemorrhage was reported by 10 of 131 patients (7.6%), and thrombocytopenia was reported by 53 of 131 patients (40.5%). Of the 53 patients who showed thrombocytopenia, 6 (11.3%) showed haemorrhage. Of the 78 patients who did not show thrombocytopenia, 4 (5.1%) showed haemorrhage. Serious or Grade ≥3 haemorrhage was reported by 4 patients (3.1%), and platelet count[34)] at the onset of haemorrhage was $4.1 \times 10^4/mm^3$, $4.6 \times 10^4/mm^3$, $8.6 \times 10^4/mm^3$, and $11.2 \times 10^4/mm^3$, respectively.

Thus, although there are limitations to accurate evaluation due to the limited number of patients who had haemorrhage in Study 001 or Study 0002, there is currently no tendency strongly suggestive of a relationship between haemorrhage and thrombocytopenia.

PMDA accepted the explanation of the applicant.

Based on the above, PMDA instructed the applicant to ensure that healthcare professionals are informed of the incidence of haemorrhage in clinical studies, including the results of the investigation on the relationship between haemorrhage and thrombocytopenia, and to provide appropriate precautions against EBV reactivation. The applicant agreed to the instruction.

1.3 Clinical positioning and indication

As a result of the review in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), PMDA considered that romidepsin is positioned as an option for the treatment of relapsed or refractory PTCL. PMDA therefore concluded that romidepsin should be indicated for "relapsed or refractory peripheral T-cell lymphoma," as proposed by the applicant, with the following precautionary statement included in the Precautions for Indications section, together with the description of the histopathological types of patients enrolled in Study 001 in the Clinical Studies section of the package insert.

Precautions for Indications

- The diagnosis of the disease to be treated with romidepsin should be performed by a physician with sufficient experience in pathological diagnosis or at a medical institution to which such physicians belong.

- The eligibility of patients for the use of romidepsin should be determined by a physician who has a good understanding of the efficacy and safety of romidepsin based on a thorough comprehension of the study data presented in the "Clinical Studies" section of the package insert, including the histopathological types of patients enrolled in the clinical studies.

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

Based on the above, PMDA instructed the applicant to specify the indication as above and provide the above precautionary statement in the Indications and Precautions for Indications sections of the package insert, to which the applicant agreed.

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 concluded that the following dosage and administration of romidepsin is appropriate, as proposed by the

34) Platelet count immediately before or after the occurrence of haemorrhage (if the count before the first dose of romidepsin was "the count immediately before," then the count observed at the time closest to the time of haemorrhage after romidepsin administration)

applicant: "The usual adult dosage is 14 mg/m^2 (body surface area) of romidepsin administered as an intravenous infusion over 4 hours on Days 1, 8, and 15, followed by a rest period (Days 16-28). This 28-day cycle is repeated. The dose may be reduced according to the patient's condition," with the following precautionary statements included in the Precautions for Dosage and Administration section of the package insert.

Precautions for Dosage and Administration

- The efficacy and safety of romidepsin in combination with other antineoplastic drugs have not been established.

- Increases in blood romidepsin concentrations in patients with hepatic impairment were reported in a clinical study. Dose reduction should be considered in such patients, and the patients should be carefully monitored for adverse events.

- In case of an adverse drug reaction associated with romidepsin, treatment interruption, dose reduction, or discontinuation should be considered based on the following criteria.

Criteria for treatment interruption, dose reduction, or discontinuation in patients experiencing an adverse drug reaction

Adverse drug reaction		Measures to be taken
Platelet count decreased	Platelet count <50,000/μL	Interrupt treatment with romidepsin until platelet count returns to ≥75,000/μL or baseline. After resolution of the event, treatment may be resumed at the initial dose.
	Platelet count <50,000/μL again, or <25,000/μL, which requires platelet transfusion	Interrupt treatment with romidepsin until platelet count returns to ≥75,000/μL or baseline. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with romidepsin if the platelet count decreased again after dose reduction.
Neutrophil count decreased	Neutrophil count <1000/μL	Interrupt treatment with romidepsin until neutrophil count returns to ≥1500/μL or baseline. After resolution of the event, treatment may be resumed at the initial dose.
	Neutrophil count <1000/μL again, or <500/μL accompanied by pyrexia (temperature ≥38.5°C)	Interrupt treatment with romidepsin until neutrophil count returns to ≥1500/μL or baseline. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with romidepsin if the neutrophil count decreased again after dose reduction.
Non-hematological toxicity*	Grade 3 non-hematological toxicity	Interrupt treatment with romidepsin until the toxicity returns to Grade ≤1 or baseline. After resolution of the event, treatment may be resumed at the initial dose.
	Recurrence of Grade 3 non-hematological toxicity, or Grade 4 non-hematological toxicity	Interrupt treatment with romidepsin until the toxicity returns to Grade ≤1 or baseline. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with romidepsin if the toxicity recurs after dose reduction.
QTc interval	>500 ms	Interrupt treatment with romidepsin. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with romidepsin if the event recurs after dose reduction.
Arrhythmia	Sinus tachycardia (>140/min), atrial dysrhythmia (supraventricular tachycardia, atrial fibrillation, atrial flutter), heart rate increased (>120/min and higher than the previous level by >20/min), ventricular tachycardia (≥3 irregular heartbeats in a row)	Interrupt treatment with romidepsin. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with romidepsin if the event recurs after dose reduction.

* Grade is based on CTCAE.

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

Based on the above, PMDA instructed the applicant to specify the Dosage and Administration and Precautions for Dosage and Administration sections as above. The applicant agreed to the instruction.

1.5 Risk management plan (draft)

The applicant plans to conduct a post-marketing surveillance covering all patients treated with romidepsin, so as to evaluate the safety, etc., of romidepsin in the post-marketing clinical setting. The surveillance will be conducted with the planned sample size of 100 patients and the follow-up period of 24 weeks (6 cycles).

As a result of the review in Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA concluded that the applicant should conduct a post-marketing surveillance to evaluate the safety, etc., of romidepsin in the post-marketing clinical setting in Japan and to provide safety information thus obtained to healthcare professionals without delay. PMDA also concluded that there is little necessity to conduct the post-marketing surveillance as an all-case surveillance on the premise that information is collected and provided in an appropriate manner. This is because (a) romidepsin has already been used in approximately 9000 patients outside Japan, and (b) in Japan, other histone deacetylase (HDAC)-inhibitors, as is the case with romidepsin, are approved as antineoplastic agents, resulting in the use of such drug products in certain number of patients.

Also, PMDA concluded that the surveillance plan should be designed as follows:

- Key survey items should include bone marrow depression, infection, QT interval prolongation, and hypersensitivity which are adverse events requiring particular attention in administering romidepsin as judged from their incidences in clinical studies, etc.
- The planned sample size should be reexamined, also taking into consideration the comparison of the incidences of events included in the key survey items between the safety data from Studies 001 and 0002 and the information available from this surveillance.
- There is no problem with specifying the follow-up period of 24 weeks, as proposed by the applicant, because of the fact that most of the events included in the key survey items occurred within 24 weeks after the start of treatment with romidepsin.

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

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

The applicant's response:

- The surveillance will be conducted not as an all-case surveillance but as a post-marketing surveillance covering patients with relapsed or refractory PTCL who are treated with romidepsin.
- The key survey items will include bone marrow depression, infection, QT interval prolongation, and hypersensitivity.
- The planned sample size will be 130 patients, taking into account that the key survey items include some adverse events reported in clinical studies.

PMDA accepted the response of the applicant.

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

Table 29. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Bone marrow depression • Infection (including reactivation of hepatitis B virus and EBV) • QT interval prolongation • TLS • Hypersensitivity	• Cardiac disorders (e.g., ventricular arrhythmia, ischemic heart disease) • Haemorrhage • Venous thromboembolism • Use in patients with hepatic impairment	• NA
Efficacy specification		
• Efficacy in routine clinical use		

Table 30. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing surveillance • Post-marketing clinical study (extension study of Study 001)	• Information provision based on the early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals

Table 31. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety, etc., of romidepsin in the post-marketing clinical setting
Survey method	Central registry system
Population	Patients with relapsed or refractory PTCL treated with romidepsin
Observation period	24 weeks (6 cycles)
Planned sample size	130 patients
Main survey items	Key survey items: Bone marrow depression, infection, QT interval prolongation, and hypersensitivity Other survey items: Patient characteristics (age, histopathological type, medical history, complications, etc.), treatment history, status of treatment with romidepsin, concomitant drugs, adverse events, clinical efficacy, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved with the indication and dosage and administration as proposed by the applicant, with the following condition of approval, provided that appropriate advice is included in the package insert and information concerning the proper use of romidepsin is provided appropriately to healthcare professionals in the post-marketing setting, and that the proper use of romidepsin is ensured under the supervision of a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancy at a medical institution capable of adequately responding to emergencies. Since romidepsin 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 classified as powerful drugs and poisonous drugs, respectively.

Indication

Relapsed or refractory peripheral T-cell lymphoma

Dosage and Administration

The usual adult dosage is 14 mg/m^2 (body surface area) of romidepsin administered as an intravenous infusion over 4 hours on Days 1, 8, and 15, followed by a rest period (Days 16-28). This 28-day cycle is repeated. The dose may be reduced according to the patient's condition.

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Warning

Istodax should be administered only to patients considered to be eligible for the therapy with Istodax by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancy at a medical institution capable of properly responding to emergencies. Patients or their families should be thoroughly informed of the efficacy and risks of the therapy before the start of therapy. Informed consent should be obtained before the start of administration of Istodax.

Contraindications

1. Patients with a history of hypersensitivity to any of the ingredients of Istodax

2. Pregnant women or women of childbearing potential

Precautions for Indications

1. The diagnosis of the disease to be treated with Istodax should be made by a physician with sufficient experience in pathological diagnosis or at a medical institution to which such physicians belong.

2. The eligibility of patients for the use of Istodax should be determined by a physician who have a good understanding of the efficacy and safety of Istodax based on a thorough comprehension of the study data presented in the "Clinical Studies" section of the package insert, including the histopathological types of patients enrolled in the clinical studies.

Precautions for Dosage and Administration

1. The efficacy and safety of romidepsin in combination with other antineoplastic drugs have not been established.

2. Increases in blood romidepsin concentrations in patients with hepatic impairment were reported in a clinical study. Dose reduction should be considered in such patients, and the patients should be carefully monitored for adverse events.

3. In patients experiencing an adverse reaction associated with the use of Istodax, treatment interruption, dose reduction, or discontinuation should be considered based on the following criteria.

Criteria for treatment interruption, dose reduction, or discontinuation in patients experiencing an adverse drug reaction

Adverse reaction		Measures to be taken
Platelet count decreased	Platelet count <50,000/μL	Interrupt treatment with Istodax until platelet count returns to ≥75,000/μL or baseline. After resolution of the event, treatment may be resumed at the initial dose.
	Platelet count <50,000/μL again, or <25,000/μL, which requires platelet transfusion	Interrupt treatment with Istodax until platelet count returns to ≥75,000/μL or baseline. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with Istodax if the platelet count decreased again after dose reduction.
Neutrophil count decreased	Neutrophil count <1000/μL	Interrupt treatment with Istodax until neutrophil count returns to ≥1500/μL or baseline. After resolution of the event, treatment may be resumed at the initial dose.
	Neutrophil count <1000/μL again, or <500/μL accompanied by pyrexia (temperature ≥38.5°C)	Interrupt treatment with Istodax until neutrophil count returns to ≥1500/μL or baseline. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with Istodax if the neutrophil count decreased again after dose reduction.
Non-hematological toxicity*	Grade 3 non-hematological toxicity	Interrupt treatment with Istodax until the toxicity returns to Grade ≤1 or baseline. After resolution of the event, treatment may be resumed at the initial dose.
	Recurrence of Grade 3 non-hematological toxicity, or Grade 4 non-hematological toxicity	Interrupt treatment with Istodax until the toxicity returns to Grade ≤1 or baseline. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with Istodax if the toxicity recurs after dose reduction.
QTc interval	>500 ms	Interrupt treatment with Istodax. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with Istodax if the event recurs after dose reduction.
Arrhythmia	Sinus tachycardia (>140/min), atrial dysrhythmia (supraventricular tachycardia, atrial fibrillation, atrial flutter), heart rate increased (>120/min and higher than the previous level by >20/min), ventricular tachycardia (≥3 irregular heartbeats in a row)	Interrupt treatment with Istodax. After resolution of the event, treatment may be resumed at a dose of 10 mg/m^2. Discontinue treatment with Istodax if the event recurs after dose reduction.

* Grade is based on CTCAE.