Report on the Deliberation Results

June 3, 2015

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

[Brand name]	Farydak Capsules 10 mg
	Farydak Capsules 15 mg
[Non-proprietary name]	Panobinostat Lactate (JAN*)
[Applicant]	Novartis Pharma K.K.
[Date of application]	September 26, 2014

[Results of deliberation]
In the meeting held on May 28, 2015, 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 re-examination period is 10 years. The drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to:

1. Establish and appropriately implement a risk management plan.

2. Conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, to identify the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product, since only a limited number of Japanese patients participated in clinical studies of the product.

**Japanese Accepted Name (modified INN)*

Review Report

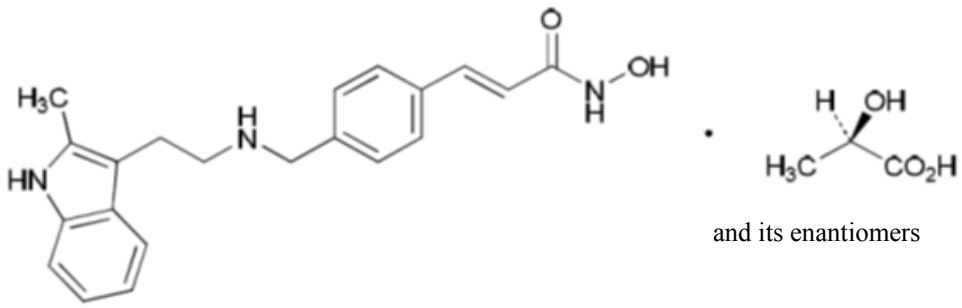
May 19, 2015

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Farydak Capsules 10 mg Farydak Capsules 15 mg
[Non-proprietary name]	Panobinostat Lactate
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	September 26, 2014
[Dosage form/Strength]	Capsules: Each capsule contains 12.576 mg of Panobinostat Lactate (equivalent to 10 mg of panobinostat) or 18.864 mg of Panobinostat Lactate (equivalent to 15 mg of panobinostat).
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



and its enantiomers

Molecular formula: $C_{21}H_{23}N_3O_2 \cdot C_3H_6O_3$
Molecular weight: 439.5
Chemical name:
(2*E*)-*N*-Hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl] prop-2-enamide mono[(2*RS*)-2-hydroxypropanoate]

[Items warranting special mention]
Orphan drug (Designation [26 yaku] No. 349, Notification No. 0917-6 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 17, 2014)

[Reviewing office] Office of New Drug V

Review Results

May 19, 2015

[Brand name]	Farydak Capsules 10 mg Farydak Capsules 15 mg
[Non-proprietary name]	Panobinostat Lactate
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	September 26, 2014

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with relapsed or refractory multiple myeloma has been demonstrated and its safety is acceptable in view of its observed benefits. Potential QT prolongation, bone marrow depression, hemorrhage, infection, hepatic dysfunction, renal dysfunction, diarrhea/nausea/vomiting/dehydration, and hypotension/orthostatic hypotension/syncope/loss of consciousness following the use of the product need to be further investigated via post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indication]
Relapsed or refractory multiple myeloma

[Dosage and administration]
In combination with bortezomib and dexamethasone, the usual adult dosage is 20 mg of panobinostat administered orally once daily 3 times a week for 2 weeks (Days 1, 3, 5, 8, 10, and 12), followed by a 9-day rest period (Days 13-21). The 3-week treatment cycle is repeated. The dose may be adjusted according to the condition of the patient.

[Conditions for approval]
The applicant is required to:
1. Establish and appropriately implement a risk management plan.

2. Conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, to identify the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product, since only a limited number of Japanese patients participated in clinical studies of the product.

Review Report (1)

April 10, 2015

I. Product Submitted for Registration

[Brand name]	Farydak Capsules 10 mg Farydak Capsules 15 mg
[Non-proprietary name]	Panobinostat Lactate
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	September 26, 2014
[Dosage form/Strength]	Capsules: Each capsule contains 12.576 mg of Panobinostat Lactate (equivalent to 10 mg of panobinostat) or 18.864 mg of Panobinostat Lactate (equivalent to 15 mg of panobinostat).
[Proposed indication]	Relapsed or refractory multiple myeloma
[Proposed dosage and administration]	In combination with other antineoplastic drugs, the usual adult dosage is 20 mg of panobinostat administered orally once daily 3 times a week for 2 weeks (Days 1, 3, 5, 8, 10, and 12), followed by a 9-day rest period (Days 13-21). The 3-week treatment cycle is repeated. The dose may be adjusted according to the condition of the patient.

II. Summary of the Submitted Data and Outline of the Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries, etc.

1.(1) Overview of the product submitted for registration

Deacetylase (DAC) is a family of enzymes that catalyzes deacetylation, i.e., removal of acetyl group from acetylated lysine residues in proteins such as nucleosome core histone (histone) and transcription factors. The deacetylation of histone by this enzyme family is considered to cause the condensation of the chromatin structure, resulting in the inhibition of gene transcription.

Panobinostat Lactate (hereinafter referred to as panobinostat), a low molecular weight compound discovered by Novartis (Switzerland), exhibits an inhibitory effect against DAC. The applicant considers that panobinostat inhibits tumor growth by causing cell cycle arrest and inducing apoptosis through the inhibition of deacetylation of histone or non-histone protein.

1.(2) Development history, etc.

For the clinical development of panobinostat monotherapy, a foreign phase I study (Study B2101) was initiated by Novartis (Switzerland) in [redacted], 20[redacted] involving patients with advanced solid cancer or non-Hodgkin's lymphoma. A foreign phase II study (Study B2203) was initiated in April 2007 involving patients with relapsed or refractory multiple myeloma (MM) who had received at least 2 prior regimens. However, these studies were terminated prematurely as the yielded data were not convincing enough to continue the studies.

Subsequently, nonclinical pharmacology studies showed that combination therapy with panobinostat, bortezomib (BTZ), and dexamethasone exhibited a more potent tumor growth inhibitory effect than panobinostat monotherapy [see "3.(i).A.(1).5) Inhibition of the growth of malignant tumor-derived cell strains"]. Therefore, the clinical development of the 3-drug combination therapy was undertaken. A foreign phase II study (Study B2207) began in October 2007 involving patients with relapsed or refractory MM who had received at least 1 regimen (excluding BTZ-refractory patients). A global phase III study (Study D2308) started in January 2010 involving patients with relapsed or refractory MM who had received at least 1 regimen (excluding BTZ-refractory patients). In addition, a foreign phase II study

(Study DUS71) started in June 2010 involving patients with relapsed and BTZ-refractory MM who had received at least 2 regimens.

Novartis (Switzerland) submitted a marketing application for panobinostat in the US in March 2014 and in the EU in May 2014, with pivotal data from Studies D2308 and DUS71. In the US, panobinostat was approved in February 2015 for the following indication: "FARYDAK, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials." In the EU, panobinostat is currently under review.

As of February 2015, panobinostat has not been approved in any country or region except the US.

In Japan, a phase I study (Study B1101) was initiated by the applicant in November 2006 involving patients with advanced solid cancer or cutaneous T-cell lymphoma in order to evaluate the safety of panobinostat monotherapy. The enrollment of patients in Study D2308 was started in [redacted] 20[redacted].

Based on the results of Studies D2308 and DUS71 as pivotal data, a marketing application for panobinostat was submitted in September 2014.

Panobinostat was designated as an orphan drug in September 2014 with the proposed indication of "relapsed or refractory multiple myeloma" (Designation [26 yaku] No. 349).

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white to slightly yellow or brownish powder. The general properties of the drug substance including the description, solubility, pH, melting point, dissociation constant, and hygroscopicity were determined. The drug substance is an anhydrate that does not show crystalline polymorphism. [redacted].

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

2.A.(1).2) Manufacturing process

[redacted].

[redacted].

2.A.(1).3) Control of drug substance

[redacted].

During the review, particle diameter was included as a specification.

2.A.(1).4) Stability of drug substance

The following table shows stability studies conducted on the drug substance. Photostability testing showed that the drug substance was photolabile.

Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage configuration	Storage period
Long-term	3 commercial scale batches	25°C	60%RH	Polyethylene bag + aluminum-laminated bag	24 months
Accelerated	3 commercial scale batches	40°C	75%RH		6 months

Based on the above, a retest period of 36 months has been proposed for the drug substance when stored at room temperature in a polyethylene bag and protected from light by the aluminum-laminated bag, according to the "Guideline on Evaluation of Stability Data," (PMSB/ELD Notification No. 0603004 dated June 3, 2003 [ICH Q1E guideline]). Long-term testing is to be continued up to [redacted] months.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is an immediate-release hard capsule containing 12.576 or 18.864 mg of the drug substance (10 or 15 mg of panobinostat, respectively).

[redacted].

2.A.(2).2) Manufacturing process

[redacted].

[redacted].

2.A.(2).3) Control of drug product

The proposed specifications for the drug product include content, description, identification (ultraviolet-visible spectrophotometry), purity (hydroxylamine, related substances [high performance liquid chromatography (HPLC)]), water content, uniformity of dosage units (content uniformity [HPLC]), dissolution (ultraviolet-visible spectrophotometry), and assay (HPLC).

2.A.(2).4) Stability of drug product

[redacted]. Photostability testing showed that the drug product was stable to light.

Stability studies of drug product

Content	Study	Primary batch	Temperature	Humidity	Storage configuration	Storage period
10 mg	Long-term	3 pilot-scale batches	25°C	60%RH	PTP package	24 months
	Accelerated	3 pilot-scale batches	40°C	75%RH		6 months
[redacted] mg	Long-term	3 pilot-scale batches	25°C	60%RH		24 months
	Accelerated	3 pilot-scale batches	40°C	75%RH		6 months

Based on these results, a shelf life of 36 months was proposed for the drug product when stored at room temperature in PTP (polyvinyl chloride/polychlorotrifluoroethylene film/aluminum foil), according to the ICH guidelines Q1E. Long-term testing will be continued up to [redacted] months.

2.B Outline of the review by PMDA

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

3. Non-clinical data

3.(i) Summary of pharmacology studies

In this section, the dose and concentration of panobinostat are expressed as the amount of panobinostat lactate salt unless specified otherwise.

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Inhibitory effect against histone deacetylase (HDAC) (Report RD-2008-51291)

The inhibitory effect of panobinostat lactate and vorinostat, a drug with HDAC-inhibiting activity, against 11 isoforms of recombinant human histone deacetylase (HDAC) was investigated (the table below).

Inhibitory effect of panobinostat lactate and vorinostat against HDAC isoforms

Isoform	IC_{50} (nmol/L)	
	Panobinostat lactate	Vorinostat
HDAC1	2.5 ± 0.9	75.5 ± 9.0
HDAC2	13.2 ± 2.5	362 ± 75
HDAC3	2.1 ± 0.7	57.4 ± 8.7
HDAC4	203 ± 53	15,056 ± 2195
HDAC5	7.8 ± 0.6	163 ± 24
HDAC6	10.5 ± 0.8	27.1 ± 5.2
HDAC7	531 ± 169	12,522 ± 4529
HDAC8	277 ± 20	1069 ± 150
HDAC9	5.7 ± 1.2	78.1 ± 9.5
HDAC10	2.3 ± 0.5	88.4 ± 9.3
HDAC11	2.7 ± 0.8	109 ± 3.5

Mean ± standard deviation (SD), $n \geq 4$

3.(i).A.(1).2) Acetylation-promoting effect (Report RD-2010-50113, RD-2010-50107)

i) *In vitro*

- The acetylation-promoting effect of panobinostat lactate on histone and tubulin was investigated by Western blotting in human cutaneous T-cell lymphoma-derived HuT78, HH, MJ, and HuT102 cell lines. Panobinostat lactate at concentrations of 0.5 to 500 nmol/L promoted the acetylation of histone H3 and H4 and of tubulin.

- The acetylation-promoting effect of panobinostat lactate on histone and tubulin was investigated by Western blotting in human Hodgkin's lymphoma-derived HD-MY-Z, L-428, and RPMI6666 cell lines. Panobinostat lactate promoted the acetylation of histone H3 and H4 at concentrations of 10 to 100 nmol/L and the acetylation of tubulin at concentrations of 50 to 100 nmol/L.

ii) *In vivo*

- Panobinostat lactate (19.8 mg/kg) was administered intravenously in a single dose to severe combined immunodeficiency (SCID) mice subcutaneously transplanted with a human colon cancer-derived HCT116 cell line. The effect of panobinostat lactate to promote the acetylation of histones within the tumor tissue was investigated by Western blotting. Panobinostat lactate promoted the acetylation of histone H4 within the tumor tissue.

- Panobinostat lactate (11.9 mg/kg) was administered intravenously once daily for 5 days to SCID mice subcutaneously transplanted with an HCT116 cell line. The effect of panobinostat lactate to promote the acetylation of histones within the tumor tissue was investigated by Western blotting. Panobinostat lactate caused a 10 to 20-fold increase from baseline in the level of acetylated histone H4 within the tumor tissue.

- Panobinostat lactate (1.2, 4, 11.9, 35.8, 59.6 mg/kg) was administered intravenously in a single dose to SCID mice subcutaneously transplanted with an HH cell line. The effect of panobinostat lactate to promote the acetylation of histones within the tumor tissue was investigated by Western blotting.

Panobinostat lactate caused a 15 to 20-fold increase in the level of acetylated histone H4 within the tumor tissue as compared with the control (no treatment) group.

3.(i).A.(1).3) Activation of the transcription of p21, a cell cycle arrest factor (Report RD-2008-51291, *Cancer Res.* 2006;66:5781-9 [Reference data])

Histone acetylation promoted by HDAC inhibition leads to the activation of transcription of a cell cycle arrest factor p21 (e.g., *Proc Natl Acad Sci USA.* 2004;101:1241-6). Transcriptional activation of p21 by panobinostat lactate was investigated by Western blotting in human multiple myeloma (MM)-derived MM1.S cell line. Panobinostat lactate increased the expression level of p21. Also, the concentration of panobinostat lactate or vorinostat to activate p21 promoter by 50%* (AC_{50}) was investigated by reporter assay. AC_{50} values of panobinostat lactate and vorinostat were 46 and 9800 nmol/L, respectively.

* Transcriptional activation by psammaplin A (positive control) was defined as 100%.

Since p21 inhibits the activity of cyclin-cyclin-dependent kinase (CDK) 2 complex and of cycline-CDK1 complex, it is considered to play an important role in cell cycle arrest in the G1 phase (*Cell.* 1993;75:805-16, *Cell.* 1995;82:675-84). Therefore, the activity of panobinostat lactate to arrest the cell cycle in an MM1.S cell line was investigated by flow cytometry. The percentage of cells in G0/G1 phase at 24 hours after treatment with panobinostat lactate (100 nmol/L) was 72.2%, showing an increase as compared with the control (no treatment) group (43.0%). The applicant explained that the results suggested the cell cycle-arresting activity of panobinostat lactate.

3.(i).A.(1).4) Apoptosis induction (Report RD-2008-51291, *Cancer Res.* 2006;66:5781-9 [Reference data], *Haematologica.* 2010;95:794-803 [Reference data])

Based on the following investigations, the applicant explained that panobinostat lactate has a more potent apoptosis-inducing effect on tumor cells and transformed cells than on normal cells.

- Caspase 3/7 activity in the presence of panobinostat lactate was investigated in normal cells (human mammary gland epithelial cells [HMEC], human renal epithelial cells [HRE], human fetal pulmonary fibroblast-derived IMR-90 cell line, peripheral-blood mononuclear cells [PBMC]) and tumor cells (chronic myeloid leukemia-derived K562, HH, and HCT116 cell lines). Caspase 3/7 activity in tumor cells increased as compared with that in normal cells.

- Fluorescence microscopy was used to detect annexin V staining in the presence of panobinostat lactate in normal bronchial epithelial (NBE) cells and bronchial epithelial (BE) cells transformed by SV40/telomerase. BE cells were stained with annexin V (annexin V-positive) while NBE cells were not.

- Bone marrow cells isolated from patients with MM and normal bone marrow cell-derived lymphocytes and granulocytes were analyzed by flow cytometry for the percentage of annexin V-positive cells in the presence of panobinostat lactate. The percentage of annexin V-positive cells in plasmatocytes in MM patient-derived bone marrow cells increased in a panobinostat lactate concentration-dependent manner. Normal bone marrow cell-derived lymphocytes and granulocytes had a lower percentage of annexin V-positive cells than MM patient-derived bone marrow cells.

- Bone marrow cells isolated from patients with MM were analyzed by flow cytometry for the percentage of annexin V-positive cells in the presence of panobinostat lactate alone or in the presence of panobinostat lactate combined with bortezomib (BTZ). The percentage of annexin V-positive cells increased in cells treated with panobinostat lactate and BTZ, followed by cells treated with panobinostat lactate alone, as compared with untreated control cells.

- SCID mice subcutaneously transplanted with an MM1.S cell line were analyzed by immunostaining for the expression levels of active caspase 3, cleaved poly (ADP ribose) polymerase (cPARP), and Ki67 in the tumor tissue treated with panobinostat lactate alone or in combination with BTZ and dexamethasone (DEX). The expression levels of activated caspase 3 and cPARP increased, and the expression level of Ki67 decreased, in cells treated with the combination of 3 drugs, followed by

cells treated with panobinostat alone, as compared with cells treated with the vehicle (phosphate-buffered saline [PBS]).

3.(i).A.(1).5) Inhibition of the growth of malignant tumor-derived cell strains

i) *In vitro*

(a) Effect on MM-derived cell lines (Report RD-2013-50424, *Cancer Res.* 2006;66:5781-9 [Reference data])

The growth-inhibitory effect of panobinostat against various human tumor-derived cell lines (a panel of 472 cell lines) was investigated by measuring the levels of viable cell-derived ATP. Panobinostat showed a potent growth-inhibitory effect against all MM-derived cell lines investigated (KMS-12-BM, SK-MM-2, COLO677, KHM-1B, MOLP-8, L-363, KARPAS-620, AMO-1, KMM-1, KMS-11, KMS-26, LP-1, KE-97, OPM-2), as compared with cell lines derived from tumors other than MM.

The growth-inhibitory effect of panobinostat against MM cell lines (DEX-sensitive MM1.S cell line, DEX-resistant MM1.R cell line, melphalan-sensitive U226 cell line, melphalan-resistant U266LR7 cell line, and doxorubicin-sensitive U266DOX4 cell line) was investigated by measuring redox pigment. IC_{50} values of panobinostat against each cell line were 5.7, 6.5, 8.1, 24, and 45.5 nmol/L, respectively.

The growth-inhibitory effect of panobinostat in combination with BTZ, DEX, or melphalan against MM1.S cell line was investigated. BTZ, DEX, or melphalan was added to MM1.S cell line in the presence or absence of panobinostat (3 nmol/L). Panobinostat lactate potentiated the growth-inhibitory effect of BTZ, DEX, and melphalan.

(b) Effect on cell lines derived from tumors other than MM (Report RD-2008-51291)

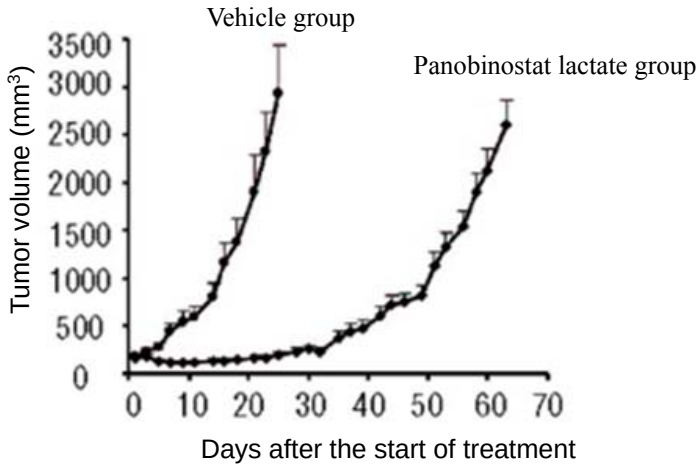
The growth-inhibitory effect of panobinostat against various human tumor-derived cell lines (a panel of 184 cell lines) was investigated by measuring redox pigment. A total of 21 cell lines were resistant to panobinostat (LD_{50}^{*} > 1000 nmol/L), whereas panobinostat lactate showed a potent growth-inhibitory effect (LD_{50} < 50 nmol/L) against most of the leukemia-derived cell lines (28 of 28 cell lines including JM1, MV-4-11, and CEM/C2), lymphoma-derived cell lines (15 of 19 cell lines including Toledo, HuT78, and HH), and small cell lung cancer-derived cell lines (17 of 18 cell lines including NCI-H1963, H209, and H211).

*Concentration that causes a 50% decrease in cell count from baseline

ii) *In vivo*

(a) Effect on an MM-derived cell line (Report *Cancer Res.* 2006;66:5781-9 [Reference data], *Haematologica.* 2010;95:794-803 [Reference data])

The tumor growth-inhibitory effect of panobinostat lactate was investigated in SCID mice subcutaneously transplanted with an MM1.S cell line. Starting from Day 45 to 50 after the transplantation (mean tumor volume, 167-193 mm^3), panobinostat lactate (10 mg/kg) was administered intraperitoneally 5 times a week for 3 weeks. After that, the dose was reduced to 5 mg/kg, and tumor volume was calculated. Tumor volume showed a statistically significant decrease in the panobinostat lactate group as compared with the vehicle (PBS) group (P < 0.05, one-way analysis of variance [ANOVA]) (the figure below).



Tumor growth-inhibitory effect of panobinostat lactate in mice subcutaneously transplanted with an MM1.S cell line
n ≥ 8, mean ± standard error

The tumor growth-inhibitory effect of panobinostat lactate was investigated in SCID mice intravenously transplanted with an MM1.S cell line expressing luciferase. Starting from Day 15 after the transplantation, panobinostat lactate (5, 10, 20 mg/kg) was administered intraperitoneally 5 times a week for 3 weeks. After that, the dose was reduced to 5 mg/kg, and tumor volume was calculated. A statistically significant decrease in the tumor volume was observed in the panobinostat lactate 10 and 20 mg/kg groups as compared with the vehicle (PBS) group ($P < 0.05$, one-way ANOVA).

The tumor growth-inhibitory effect of panobinostat lactate in combination with BTZ and DEX was investigated in SCID mice subcutaneously transplanted with an MM1.S cell line. Starting from Day 45 to 50 after the transplantation (mean tumor volume, 165-173 mm^3), panobinostat lactate (10 mg/kg) was administered intraperitoneally 5 times a week for 3 weeks. After that, the dose was reduced to 5 mg/kg. In addition, BTZ (0.1 mg/kg) and DEX (1 mg/kg) were administered intraperitoneally 5 times a week starting from the first day of panobinostat lactate administration, and tumor volume was calculated. A statistically significant decrease in tumor volume was observed in the groups treated with the dual combination of panobinostat lactate and BTZ or DEX as compared with the group treated with panobinostat lactate alone ($P < 0.05$, one-way ANOVA). Furthermore, the group treated with triple combination of panobinostat lactate, BTZ, and DEX showed a statistically significant decrease in tumor volume as compared with the groups treated with the dual combination of panobinostat lactate and BTZ or DEX ($P < 0.05$, one-way ANOVA).

(b) Effect on cell lines derived from tumors other than MM (Report RD-2001-50288, RD-2007-50247)

The tumor growth-inhibitory effect of panobinostat lactate was investigated in SCID mice subcutaneously transplanted with an HCT116 cell line. Starting from Day 13 after the transplantation (mean tumor volume, 100 mm^3), panobinostat lactate (5, 10, 20, 40 mg/kg) was administered intravenously 5 times a week for 3 weeks, and the tumor volume was calculated. A statistically significant decrease in tumor volume was observed in the panobinostat lactate group as compared with the vehicle (solution containing 0.06 mol/L lactic acid, 0.04 mol/L sodium hydroxide, and 5% glucose) group ($P < 0.001$, Student's t-test).

The tumor growth-inhibitory effect of panobinostat lactate was investigated in SCID mice subcutaneously transplanted with an HH cell line. Starting from Day 13 after the transplantation (mean tumor volume, 273 mm^3), panobinostat lactate (6.0, 11.9 mg/kg) was administered intravenously 5 times a week for 2 weeks, or panobinostat lactate (9.9, 14.9, 19.8 mg/kg) was administered intravenously 3 times a week for 2 weeks, and the tumor volume was calculated. A statistically significant decrease in tumor volume was observed in the groups receiving 6.0 or 11.9 mg/kg of panobinostat lactate 5 times a week for 2 weeks and in the groups receiving 14.9 or 19.8 mg/kg of panobinostat lactate 3 times a week

for 2 weeks as compared with the vehicle (10% aqueous solution of 2-hydroxypropyl-β-cyclodextrin) group ($P < 0.05$, one-way ANOVA).

3.(i).A.(2) Secondary pharmacodynamics

Effect on bone lesion (Report RD-2008-51313, *Haematologica.* 2010;95:794-803 [Reference data])

Using SCID mice intravenously transplanted with an MM1.S cell line expressing luciferase, the effect of panobinostat lactate on bone lesion was investigated by calculating the tibial spongy bone mass by imaging analysis. A statistically significant inhibition of decrease in the tibial spongy bone mass was observed in the panobinostat lactate group as compared with the vehicle (5% glucose solution) group ($P < 0.05$, Tukey test). Based on the above results, the applicant explained that panobinostat lactate is expected to inhibit MM-associated spongy bone injury.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effect on the central nervous system (Report 0280108)

Panobinostat free base (30, 60, 100 mg/kg) was administered intravenously in a single dose to mice (n = 10/group), and the effect of panobinostat free base on clinical signs and on behavior was investigated. Decreased locomotor activity, staggering gait, convulsions, and death were observed in the 60 and 100 mg/kg groups and decreased body temperature and decreased grip strength in the 100 mg/kg group. The applicant explained that it is not necessary to provide a caution for these observations in the clinical use of panobinostat lactate, for the following reasons: (i) AUC (463-533 ng·h/mL) following a single intravenous dose of 19.9 mg/kg of panobinostat free base is higher than clinical exposure ($AUC_{0\text{-}24h}$, 139 ng·h/mL*), and (ii) Panobinostat exposure following intravenous administration of panobinostat free base at a ≥30 mg/kg dose would be much more greater than clinical exposure.

* In a Japanese phase I study (Study B1101), a foreign phase I study (Study B2101), and a foreign phase I/II study (Study B2102), $AUC_{0\text{-}24h}$ following multiple oral doses of 20 mg of panobinostat 3 times a week (Days 1, 3, and 5 every week) in patients with solid cancer, non-Hodgkin's lymphoma, or hematological malignancy was 139 ng·h/mL (the geometric mean obtained by combined analysis of the 3 studies).

3.(i).A.(3).2) Effect on the cardiovascular system

i) Effect on hERG current (Reports 0870294, 0870532, 0970190)

The effect of panobinostat lactate and its metabolite M37.8 (reduced form of hydroxamic acid moiety) on hERG potassium current was investigated in human fetal kidney-derived HEK293 cell line introduced with human ether-a-go-go-related gene (hERG). IC_{50} of panobinostat lactate and M37.8 was 3.5 and 1.6 μmol/L, respectively.

ii) Effect on blood pressure and electrocardiogram, etc. (Reports RD-2001-50377 [Reference data], 0350418 [Reference data], 0618524 [Reference data], 0618523 [Reference data], 0618585 [Reference data], 0110024 [Reference data], 0210083, 0680202)

The electrophysiological effect of panobinostat lactate on the heart was investigated using isolated rabbit hearts. The results are shown below.

- In a specimen treated with panobinostat lactate (0.5, 1, 2, 5, 10 μmol/L), prolongation of action potential duration (APD) was observed at ≥2 μmol/L, and early after depolarization and Torsades de Pointes (TdP) were observed at 10 μmol/L.

- In 3 specimens treated with panobinostat lactate (0.2, 0.6, 2, 6, 20 μmol/L), APD prolongation was observed at ≥6 μmol/L and early afterdepolarization at 20 μmol/L. Similarly, in a specimen treated with panobinostat free base (0.5, 1, 2, 5 μmol/L), APD prolongation was observed at ≥2 μmol/L and early afterdepolarization at 5 μmol/L.

- In 3 specimens treated with panobinostat lactate (0.5, 1 μmol/L), APD prolongation, triangular action-potential configuration, decreased coronary perfusion rate, enhanced pacemaker activity, ventricular tachycardia, and ventricular fibrillation were observed at 1 μmol/L.

- In 3 specimens treated with M37.8 (0.3, 1, 3, 10, 30 μmol/L), APD prolongation was observed at ≥1 μmol/L, instability at 3 μmol/L, early afterdepolarization and reverse use-dependency at ≥10 μmol/L,

and triangular action-potential configuration, TdP, and delayed intraventricular conduction velocity at 30 μmol/L.

The effect of panobinostat lactate on electrocardiogram (ECG), heart rate, blood pressure, body temperature, locomotor activity, and pulse pressure was investigated in dogs. The results were as follows.

- Panobinostat free base was administered intravenously on Day 1 (0 mg/kg [vehicle]), Day 3 (1 mg/kg) and Day 8 (3 mg/kg) to 2 dogs. Prolongation of QT/QTc interval was observed.

- Panobinostat free base was administered intravenously on Day 1 (0 mg/kg [vehicle]), Day 8 (0.06 mg/kg), Day 15 (0.2 mg/kg), and Day 76 (0.6 mg/kg) to 4 dogs. Prolongation of QT/QTc interval was observed at 0.2 and 0.6 mg/kg.

- Panobinostat lactate (1.5 mg/kg) was administered orally on Day 1, Day 3, and Day 5 to 4 dogs. Prolongation of QT/QTc interval was observed.

Since prolonged QT/QTc was observed following the administration of panobinostat lactate both in the nonclinical study as described above and in clinical studies [see "4.(iii).B.(3).3) QT prolongation"], the applicant explained that healthcare professionals would be cautioned against this finding through the package insert, etc.

3.(i).A.(3).3) Effect on the respiratory system (Report 0280118)

Panobinostat free base (1, 3, 10 mg/kg) was administered intravenously in a single dose to rats (n = 6/group), and the effect of panobinostat free base on tidal volume, respiratory rate, and minute ventilation volume was investigated. Panobinostat free base had no effect on these parameters.

3.(i).B Outline of the review by PMDA

Based on the submitted data and on the following review, PMDA has concluded that panobinostat lactate is effective for MM.

Mechanism of action of panobinostat lactate

The applicant explained the mechanism of action of panobinostat lactate as follows:

In light of the data submitted for this application and based on the following published articles, panobinostat lactate inhibits tumor growth by causing cell cycle arrest and apoptosis induction of MM cells through the mechanism that promotes (a) histone acetylation through inhibition of class I HDAC (HDAC1, 2, 3, 8), and (b) acetylation of non-histone proteins through inhibition of class IIb HDAC (HDAC6).

The following findings have been suggested:

- The expression of class I and II HDAC genes (HDAC4, 5, 6, 7, 9, 10) and HDAC1 and 6 proteins is increased in MM cell lines and human primary cultured MM cells (*Epigenetics.* 2014;9:1511-20).

- Class I HDAC is involved in histone acetylation and that HDAC6, a class IIb HDAC, is involved in the acetylation of non-histone proteins (*Proc Natl Acad Sci USA.* 2005;102:8567-72, *Oncogene.* 2007;26:5420-32, *Best Pract Res Clin Haematol.* 2007;20:797-816).

- Panobinostat lactate causes cell cycle arrest and apoptosis induction by promoting histone acetylation (*Cancer Res.* 2006;66:5781-9, *Haematologica.* 2010;95:794-803).

- Panobinostat lactate promotes acetylation of non-histone proteins involved in tumor formation, such as α-tubulin and heat shock protein (hsp) 90 (*Blood.* 2006;108:3441-9). The promotion of acetylation of α-tubulin and hsp 90 leads to the enhanced accumulation of ubiquitinated proteins within cells, resulting in the induction of apoptosis (*Proc Natl Acad Sci USA.* 2005;102:8567-72).

- It is reported that, in MM, the function of aggresome- and proteasome-mediated degradation pathways, mechanisms for degrading and eliminating abnormal proteins, are enhanced (*Proc Natl Acad Sci USA.* 2005;102:8567-72), and that the aggresome pathway is activated by HDAC6 (*Blood.*

2006;108:3441-9), which suggests that HDAC6 inhibition by panobinostat lactate suppresses the aggresome pathway, thereby inducing apoptosis (*Proc Natl Acad Sci USA.* 2005;102:8567-72).

PMDA considers as follows:
Study results showed that panobinostat lactate inhibited HDAC activity and suppressed the growth of MM cell lines. However, much remains unknown about the involvement of deacetylation of histone and non-histone proteins in the etiology of MM, about factors affected by the acetylation-promoting effect of panobinostat lactate, and about other aspects. Thus, it is unclear how panobinostat lactate-induced inhibition of HDAC activity is directly related with tumor growth inhibition, and the proposed mechanism of action of panobinostat lactate remains a matter of speculation. Nevertheless, the mechanism of action of panobinostat lactate is important as evidence to support the efficacy of panobinostat lactate. Therefore, relevant information should be continuously collected and new findings should be provided to healthcare professionals in an appropriate manner when available.

3.(ii) Summary of pharmacokinetic studies
In this section, the dose and concentration of panobinostat are expressed in the amount of the free base (hereinafter referred to as panobinostat).

3.(ii).A Summary of the submitted data
The pharmacokinetics (PK) of panobinostat in animals was investigated in mice, rats, rabbits, and dogs. Studies on plasma protein binding of panobinostat, drug-metabolizing enzymes, transporters, etc. were performed using biological samples derived from humans and animals.

3.(ii).A.(1) Absorption
3.(ii).A.(1).1) Single-dose administration
^{14}C-labeled panobinostat was administered intravenously in a single dose at 10, 0.5, and 8 mg/kg, or orally at 10, 1.5, and 40 mg/kg, to male rats, male dogs, and female rabbits, respectively, to investigate radioactivity in plasma and in blood as well as plasma panobinostat concentration (the table below). The absorption rates of ^{14}C-labeled panobinostat calculated from plasma radioactivity and panobinostat concentrations were 17%, 68%, and 62% in rats, dogs, and rabbits, respectively. Oral bioavailability (BA) of panobinostat was 6%, 52%, and 2.4%, respectively. CL of panobinostat was comparable to the hepatic blood flow in rabbits and dogs (4.2 and 1.9 L/h/kg, respectively) but exceeded the hepatic blood flow in rats (3.3 L/h/kg) (*Pharm Res.* 1993;10:1093-5). Taking account of these observations, the applicant explained that observed BA was lower than absorption rates for the following reasons:

- In rats with CL of panobinostat exceeding the hepatic blood flow, extrahepatic clearance is likely to be involved. When ^{14}C-labeled panobinostat (500 ng/mL) was added to rat plasma and the mixture was incubated at 37°C for 1 hour, 67% of ^{14}C-labeled panobinostat was degraded, suggesting that panobinostat is unstable in rat plasma. Thus, metabolism by plasma esterase is considered to contribute to the suggested extrahepatic clearance in rats.

- When panobinostat (1.5 ng/mL) was added to rabbit plasma and the mixture was incubated at room temperature, panobinostat remained stable up to 17 hours, suggesting that panobinostat is stable in rabbit plasma. Thus, in rabbits, intraintestinal metabolism or the first-pass effect is considered to be a major contributor to extrahepatic clearance.

PK parameters of radioactivity in each animal species

Animal species	Dose (route of administration)	Food	Sex	n	Sample	C_{max} (ngEq/mL)	T_{max} (h)	AUC_t (ngEq·h/mL)	$T_{1/2}$ (h)	Absorption rate (%)
Rats	10 mg/kg (i.v.)	Fed	Male	3	Plasma	2180 ± 226	0.083[*1]	6110 ± 470[*2]	30	-
					Blood	2650 ± 150	0.083[*1]	7510 ± 407[*2]	-	-
	10 mg/kg (i.v.)	Fed	Male	3	Plasma	3220[*3]	-	6120[*2, 3]	-	-
					Blood	3340[*3]	-	8030[*2, 3]	-	-
	10 mg/kg (p.o.)	Fed	Male	3	Plasma	92.6 ± 13.2	-	1042[*2]	-	17
					Blood	108 ± 33.1	0.5	1216[*2]	-	15
Dogs	0.5 mg/kg (i.v.)	Fasted	Male	2[*4]	Plasma	146, 176	-	2640, 2580[*5]	171, 112	-
					Blood	373, 357	-	6510, 6040[*5]	125, 180	
	1.5 mg/kg (p.o.)	Fasted	Male	3	Plasma	270 ± 35.5	1	5310 ± 991[*5]	-	68
					Blood	389 ± 93.2	1	6710 ± 982[*5]	-	36
Rabbits	8 mg/kg (i.v.)	Fed	Female	2	Plasma	15,400	-	80,100[*2]	19	-
					Blood	10,200	-	59,000[*2]	46	-
	40 mg/kg (p.o.)	Fed	Female	3	Plasma	8650 ± 2400	10 ± 20	249,000 ± 70,000[*6]	-	62
					Blood	6500 ± 1900	24	173,000 ± 53,000[*6]	-	59

Arithmetic mean ± SD, [*1] First measuring time point, [*2] $AUC_{0\text{-}96h}$, [*3] n = 1 (no blood sample was collected at the first sampling point in 2 animals.), [*4] Individual values, [*5] $AUC_{0\text{-}168h}$, [*6] $AUC_{0\text{-}72h}$, - Not calculated

PK parameters of panobinostat in each animal species

Animal species	Dose (route of administration)	Food	Sex	n	C_{max} (ng/mL)	T_{max} (h)	AUC_t (ng·h/mL)	$T_{1/2}$ (h)	CL (L/h/kg)	V_{ss} (L/kg)	Oral BA (%)
Rats	10 mg/kg (i.v.)	Fed	Male	3	787 ± 166	-	705 ± 131[*1]	-	-	-	-
	10 mg/kg (i.v.)	Fed	Male	3	1016	-	-	3.8 ± 1.4	22.1 ± 3.49	40.2 ± 16	-
	10 mg/kg (p.o.)	Fed	Male	3	BLQ	-	-	-	-	-	Approx 6[*2]
Dogs	0.5 mg/kg (i.v.)	Fasted	Male	2[*3]	67.9, 85.5	-	132, 118[*4]	22, 11	2.9, 3.8	52, 31	-
	1.5 mg/kg (p.o.)	Fasted	Male	3	95.2 ± 29.9	0.25 ± 0	226 ± 86[*4]	-	-	-	52 ± 19
Rabbits	8 mg/kg (i.v.)	Fed	Female	2[*3]	3640, 3570	-	2100, 2290[*5]	11, 25	3.8, 3.3	6.2, 12.9	-
	40 mg/kg (p.o.)	Fed	Female	3	103 ± 137	2.2 ± 3.3	260 ± 248[*5]	-	-	-	2.4

Arithmetic mean ± SD; BA, Bioavailability; BLQ, Below the lower limit of quantitation (2.50-1.00 ng/mL in each sample of 20-50 μL)
[*1] $AUC_{0\text{-}24h}$, [*2] Value estimated from urinary excretion rate in oral dose studies [see "3.(ii).A.(4) Excretion"], [*3] Individual values,
[*4] $AUC_{0\text{-}48h}$, [*5] $AUC_{0\text{-}168h}$, - Not calculated

3.(ii).A.(1).2) Repeat-dose administration

Panobinostat (10, 30, 75 mg/kg) was administered orally 3 times a week for 26 weeks to male and female rats under fed conditions and plasma concentration of panobinostat was investigated (the table below). C_{max} and $AUC_{0\text{-}24h}$ of panobinostat on Day 75 were similar to those on Day 173, suggesting that they reached a steady state by Day 75. In repeated administration, C_{max} and $AUC_{0\text{-}24h}$ of panobinostat increased more than dose-proportionally both in males and females, and no consistent sex difference was observed either in C_{max} or in $AUC_{0\text{-}24h}$. The applicant explained that the more than dose-proportional increase in panobinostat exposure (C_{max}, $AUC_{0\text{-}24h}$) was likely due to saturation of the panobinostat metabolism with increasing doses.

PK parameters of panobinostat (male and female rats, 26-week repeated oral administration)

Day of measurement	Dose (mg/kg)	C_{max} (ng/mL)		$AUC_{0\text{-}24h}$ (ng·h/mL)	
		Male	Female	Male	Female
1	10	2.06[*]	2.30	4.80	4.37
	30	9.37	9.49	41.5	22.3
	75	26.0	57.9	101	148
75	10	11.6	19.3	54.3	49.8
	30	95.5	72.5	296	212
	75	107	278	391	872
173	10	17.5	38.5	60.5	94.5
	30	89.9	172	266	313
	75	129	279	555	662

n = 3/measuring time point, [*] n = 2/measuring time point

Panobinostat (0.15, 0.5, 1.0 mg/kg) was administered orally for 39 weeks to male and female dogs under fed conditions, and plasma concentration of panobinostat was investigated (the table below). At all days of measurement, C_{max} and $AUC_{0\text{-}24h}$ of panobinostat were dose-proportional. There was no tendency toward the accumulation of panobinostat by repeated administration. No clear sex difference was observed either in C_{max} or in $AUC_{0\text{-}24h}$.

PK parameters of panobinostat (male and female dogs, 39-week repeated oral administration)

Day of measurement	Dose (mg/kg)	C_{max} (ng/mL)		$AUC_{0\text{-}24h}$ (ng·h/mL)	
		Male	Female	Male	Female
1	0.15	3.37 ± 1.11	3.73 ± 0.967	9.55 ± 4.99	11.7 ± 3.63
	0.5	9.47 ± 3.01	12.0 ± 7.20	35.9 ± 7.24	30.6 ± 18.1
	1.0	25.0 ± 3.76	37.9 ± 10.9	62.6 ± 4.53	85.5 ± 25.4
89	0.15	4.94 ± 2.24	4.44 ± 0.705	22.9 ± 5.71	19.7 ± 2.48
	0.5	16.7 ± 3.66	15.0 ± 4.17	62.6 ± 9.77	67.1 ± 33.7
	1.0	34.1 ± 8.90	31.8 ± 7.37	96.2 ± 14.5	95.5 ± 12.5
270	0.15	2.88 ± 0.835	3.36 ± 0.567	17.0 ± 4.95	13.5 ± 3.90
	0.5	14.1 ± 0.974	13.5 ± 4.33	61.0 ± 13.9	60.3 ± 15.9
	1.0	16.0 ± 9.20	24.2 ± 13.7	71.2 ± 37.3	91.8 ± 37.6

Arithmetic mean ± SD, n = 4

3.(ii).A.(1).3) *In vitro* membrane permeability

Permeability of panobinostat across the human gastrointestinal membrane was investigated using human colon cancer-derived Caco-2 cell line. In the presence of LY335979 (1 μmol/L), a P-glycoprotein (P-gp) inhibitor, the apparent permeability coefficients of ^{14}C-labeled panobinostat (5, 23 μmol/L) from the apical surface to the basal surface ($P_{app\ A\rightarrow B}$) were 29.5×10^{-5} and 36.1×10^{-5} cm/sec, respectively. In contrast, $P_{app\ A\rightarrow B}$ values of ^{14}C-labeled mannitol (3.8 μmol/L), the negative control, and ^{14}C-labeled propranolol (7.5 μmol/L), the positive control, were 6.8×10^{-5} and 80.8×10^{-5} cm/sec, respectively. Based on these results, the applicant explained that panobinostat has a moderate membrane permeability.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution

^{14}C-labeled panobinostat was administered orally in a single dose at 25 mg/kg to male and female albino and pigmented rats, and intravenously in a single dose at 10 mg/kg to male albino and pigmented rats, and tissue distribution of the radioactivity was investigated by quantitative whole-body autoradiography.

At 5 minutes after intravenous administration, radioactivity in most tissues was higher than that in the blood. High concentrations of radioactivity were detected in the renal medulla, renal cortex, and renal pelvis, in particular (112,000, 101,000, and 72,000 ng Eq/g, respectively). In contrast, little or no radioactivity was detected in the central nervous system. At 96 hours after administration, radioactivity was detectable in many tissues even, and the radioactivity level in the adrenal medulla was as high as 942 ng Eq/g. Radioactivity in the skin and uvea was detected only in pigmented rats, suggesting that panobinostat or its metabolite(s) was bound to melanin. However, radioactivity in these tissues was eliminated over time. The applicant explained that the binding of panobinostat or its metabolite(s) to melanin is reversible.

3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells

^{14}C-labeled panobinostat (0.1, 0.5, 1, 10, 100 μg/mL) was added to plasma samples of mice, rats, dogs, and humans, and the mixtures were incubated at 37°C for 3.5 hours, then binding of panobinostat to plasma or serum protein was investigated by ultracentrifugation. In all animal species tested, plasma protein binding rates of panobinostat were, being generally constant regardless of the panobinostat concentration, 59.9% in mice, 79.1% in rats, 78.7% in dogs, and 89.6% in humans (the mean binding rates at all concentrations tested).

^{14}C-labeled panobinostat (0.1, 0.5, 1, 10, 100 μg/mL) was added to blood samples of mice, rats, dogs, and humans, and the mixtures were incubated and subjected to a test for panobinostat distribution in blood cells. In all animal species tested, blood/plasma ratios of radioactivity were, being almost constant regardless of the panobinostat concentration, 1.7 in mice, 1.5 in rats, 2.2 in dogs, and 1.4 in humans (the mean blood/plasma ratios of radioactivity at all concentrations tested).

3.(ii).A.(2).3) Placental and fetal transfer

^{14}C-labeled panobinostat (100 mg/kg) was administered orally in a single dose to pregnant rats (on Gestation Days 12 and 17) to investigate plasma and tissue concentrations of panobinostat in maternal animals and fetuses. At 3 hours after administration on Gestation Day 12, radioactivity concentration in fetuses was 3 times plasma panobinostat concentration in the maternal animals.

The applicant explained that the above results suggested the placental transfer of panobinostat.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vitro* metabolism

Human liver microsomes were incubated with ^{14}C-labeled panobinostat (39 μmol/L) for 30 minutes to investigate metabolites of panobinostat. M24.2 (monohydroxide) was detected as the major metabolite, together with M9 (structure unidentified), M37.8 (reduced form of hydroxamic acid moiety), and M43.5 (hydrolysate of hydroxamic acid moiety).

The following studies were conducted to identify the isoforms of cytochrome P450 (CYP) involved in panobinostat metabolism in humans. Based on the results of these studies, the applicant explained that CYP3A4 plays a major role in the metabolism of panobinostat in humans.

- Recombinant human CYP isoforms (1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 4A11) were incubated with ^{14}C-labeled panobinostat (39 μmol/L) for 30 minutes. Panobinostat was metabolized only by CYP2C19, 2D6, and 3A4 expression systems. The intrinsic metabolic clearance (CL_{int}) were highest in CYP3A4 followed in decreasing order by CYP2D6 and CYP2C19 (0.602, 0.174, and 0.0466 mL/h/mg protein, respectively). M24.2, M9, and M43.5 were detected as major metabolites in the CYP3A4 expression system. M9, M24.2, and M24.2A (2-atom oxygen adduct) were detected in the CYP2C19 expression system, and M9, M24.2, M24.2A, and M43.5 in the CYP2D6 expression system.

- Human liver microsome samples were incubated with ^{14}C-labeled panobinostat (33 μmol/L) for 30 minutes in the presence of inhibitors of CYP1A2, 2C8, 2C9, 2C19, 2D6, and CYP3A. Metabolism of panobinostat was inhibited by 69% to 98% by CYP3A inhibitors (ketoconazole [KCZ], terfenadine, dexamethasone [DEX], troleandomycin, azamulin). In contrast, inhibitors of other CYP isoforms did not markedly inhibit the metabolism of panobinostat.

Human liver microsome samples were incubated with ^{14}C-labeled panobinostat (47 μmol/L) for 30 minutes in the presence of a glucuronidation cofactor (UDPGA). M34.4 (glucuronate conjugate) was detected as a metabolite of panobinostat. Recombinant human UDP-glucuronosyltransferase (UGT) isoforms (1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, 2B17) were incubated with ^{14}C-labeled panobinostat (47 μmol/L) for 30 minutes to identify UGT isoforms involved in M34.4 formation in humans. The results showed that UGT1A1, 1A3, 1A7, 1A8, 1A9, and 2B4 were involved in M34.4 formation.

3.(ii).A.(3).2) *In vivo* metabolism

^{14}C-labeled panobinostat (1.5, 10, 40 mg/kg) was administered orally in a single dose to rats, rabbits, and dogs to evaluate metabolites in plasma, urine, feces, and bile, as shown below.

- Major metabolites detected in plasma were M34.4 (glucuronate conjugate of panobinostat, corresponding to 50.2% of AUC of total radioactivity in plasma) and T27d (glucuronate conjugate of M43.5, 33.8%) in rats, P15.2 (glucuronate conjugate of hydroxylated M37.8, 76.7%) in rabbits, and M36.9 (carboxylate in two-carbon shortening of the hydroxamic acid-containing side chain, 50.1%-52.1%) in dogs.

- Metabolites with a high excretion rate in urine and feces up to 96 hours (rats) or 168 hours (rabbits, dogs) after administration were M40.8 (carboxylate in one-carbon shortening of the hydroxamic acid-containing side chain, 44.2% in feces) and M26.8 (hydroxylate of M37.8, 15.8% in feces) in rats, M36.9 (7.73% in urine, 6.34% in feces), P15.2 (5.86% in urine), M24.3 (intramolecularly

cyclized form of M36.9, 5.98% in feces), M26.8 (including T24.4 [reduced form of M26.8], 14.0% in feces), M37.8 (17.0% in feces), and M44.6 (reduced form of M43.5, 4.54% in feces) in rabbits, and M36.9 (22.6% in urine, 22.2% in feces) and M40.8 (9.60% in feces) in dogs.

- Metabolites with a high excretion rate in bile up to 72 hours after administration were M34.4 (32.5%) and P15.2 (8.39%) in rats.

- Unchanged panobinostat was almost undetectable in urine either in rats, rabbits, or dogs (<0.5% of total radioactivity administered).

- Fecal excretion rate of unchanged panobinostat was 7.5% in rats and 1.9% in dogs, while unchanged panobinostat was undetectable in rabbits.

3.(ii).A.(4) Excretion

^{14}C-labeled panobinostat (10 mg/kg) was administered in a single dose orally or intravenously to male rats, to investigate urinary and fecal excretion rates of radioactivity (as a percentage of administered radioactivity). Urinary and fecal excretion rates of radioactivity up to 96 hours after administration were 0.73% and 83.4%, respectively, following the oral administration and 12.5% and 80.9%, respectively, following the intravenous administration.

^{14}C-labeled panobinostat (10 mg/kg) was administered intravenously in a single dose to bile duct-cannulated male rats, and urinary, fecal, to investigate biliary excretion rates of radioactivity (as a percentage of administered radioactivity). Urinary, fecal, and biliary excretion rates of radioactivity up to 72 hours after administration were 31.4%, 9.89%, and 61.7%, respectively, with ≥95% of the administered dose being excreted in all studies.

^{14}C-labeled panobinostat was administered in a single dose orally at 40 mg/kg or intravenously at 8 mg/kg to female rabbits, to investigate urinary and fecal excretion rates of radioactivity (as a percentage of administered radioactivity). Urinary and fecal excretion rates of radioactivity up to 168 hours after administration were 24.2% and 62.3%, respectively, following the oral administration and 40.5% and 67.4%, respectively, following the intravenous administration.

^{14}C-labeled panobinostat was administered in a single dose orally at 1.5 mg/kg or intravenously at 0.5 mg/kg to male dogs, to investigate urinary and fecal excretion rates of radioactivity (as a percentage of administered radioactivity). Urinary and fecal excretion rates of radioactivity up to 168 hours after administration were 33.7% and 58.0%, respectively, following the oral administration and 32.8% and 49.1%, respectively, following the intravenous administration.

The excretion of panobinostat in milk was not investigated.

3.(ii).A.(5) Pharmacokinetic drug interactions

3.(ii).A.(5).1) Enzyme inhibition

Human liver microsomes and substrates of CYP isoforms (1A2, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5) were incubated in the presence of panobinostat (1-100 μmol/L). Panobinostat inhibited CYP3A4/5, CYP2C19, and CYP2D6 with IC_{50} of 15 to 75, 35, and 2 μmol/L (K_i, 0.167 μmol/L), respectively. Panobinostat at the maximum concentration tested did not show any clear inhibitory effect against the metabolism of the substrates of CYP1A2, CYP2C8, CYP2C9, or CYP2E1.

When panobinostat (20 mg) was administered orally in multiple doses to patients with MM, C_{max} of panobinostat was <40 ng/mL (approximately 0.11 μmol/L) [see "4.(ii).B.(1) Difference in PK of panobinostat between Japanese and non-Japanese patients"]. Based on these results, the applicant explained that, in clinical use, panobinostat is unlikely to inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5, but it may possibly inhibit CYP2D6.

Since panobinostat inhibited CYP3A4/5 in a time-dependent manner (K_I and kinact were 12.0 μmol/L and 0.0228 min^{-1}, respectively), the effect of 3-time-weekly dose of panobinostat (20 mg) on the PK of midazolam was investigated based on the physiological pharmacokinetic model (software used, Simcyp

ver13.1). Increases in C_{max} and AUC_{inf} of midazolam in combination with panobinostat were estimated to be approximately 4%. This model was constructed to simulate the plasma panobinostat concentrations observed following panobinostat monotherapy (10-80 mg) or combination therapy with KCZ in Studies B1101, B2101, B2102, and B2110. Based on these results, the applicant explained that combination of panobinostat with a CYP3A substrate is unlikely to cause pharmacokinetic interactions.

3.(ii).A.(5).2) Enzyme induction

Human liver cells were treated with panobinostat (0.01-1 μmol/L) for 3 days to investigate mRNA levels and enzyme activity of CYP isoforms (1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 3A4/5) and mRNA level of UGT1A1. Treatment with panobinostat did not increase the mRNA levels or enzyme activity of any CYP isoforms tested. Panobinostat did not increase the mRNA level of UGT1A1.

When panobinostat (20 mg) was administered orally in multiple doses to patients with MM, C_{max} of panobinostat was <40 ng/mL (approximately 0.11 μmol/L) [see "4.(ii).B.(1) Difference in PK of panobinostat between Japanese and non-Japanese patients"]. Based on these results, the applicant explained that panobinostat is unlikely to induce pharmacokinetic interactions mediated by induction of drug-metabolizing enzymes in clinical use.

3.(ii).A.(5).3) Transporters

P-gp- or multidrug resistance-associated protein (MRP) 2-mediated transport of ^{14}C-labeled panobinostat (5, 23 μmol/L) was investigated in a Caco-2 cell line. The efflux ratios of panobinostat (5, 23 μmol/L) were 15 and 14, respectively, in the absence of a P-gp or MRP2 inhibitor, and decreased to 1.5 to 1.3, respectively, in the presence of a P-gp inhibitor (LY335979, 1 μmol/L), but were 23 and 25, respectively, in the presence of an MRP2 inhibitor (MK571, 10 μmol/L).

These results suggested that panobinostat serves as a substrate for P-gp. However, studies on the mass balance of panobinostat and on metabolites showed that ≥87% of the administered radioactivity was recovered in urine and feces, and unchanged panobinostat accounted for ≤3.3% of the administered dose both in urine and in feces [see "4.(ii).A.(3).5) Foreign phase I study"]. This indicates that panobinostat is absorbed efficiently from the gastrointestinal tract and P-gp-mediated efflux into gastrointestinal lumen does not limit the absorption of panobinostat. Based on these findings, the applicant explained that there is little need of conducting a clinical study to investigate pharmacokinetic interactions between panobinostat and P-gp inhibitors.

The applicant also explained as follows: C_{max} of panobinostat following multiple oral doses of panobinostat (20 mg) in patients with MM was <40 ng/mL (approximately 0.11 μmol/L) [see "4.(ii).B.(1) Difference in PK of panobinostat between Japanese and non-Japanese patients"]. This finding and study results listed below suggest that pharmacokinetic interactions mediated by the inhibition of the following transporters by panobinostat are unlikely to occur in clinical use of panobinostat: P-gp, breast cancer resistance protein (BCRP), organic anion transporter (OAT) 1 and 3, organic cation transporter (OCT) 1 and 2, and human organic anion transport polypeptide (OATP) 1B1 and 1B3.

- The inhibitory effect of panobinostat (0.1-100 μmol/L) against P-gp-mediated rhodamine 123 transport was investigated in a human breast cancer MDA435T0.3 cell line expressing human P-gp. Panobinostat did not show any clear inhibitory effect against P-gp even at the maximum concentration tested.

- The inhibitory effect of panobinostat (0.1-25 μmol/L) against BCRP-mediated Bodipy FL prazosin (BDP) transport was investigated in a human ovarian cancer-derived IGROV1 cell line expressing human BCRP. Panobinostat did not show any clear inhibitory effect against BCRP even at the maximum concentration tested.

- The inhibitory effect of panobinostat (0.1-400 μmol/L) against OATP-, OAT-, or OCT-mediated transport of the substrate* of each transporter was investigated in an HEK293 cell line expressing human OATP1B1 or OATP1B3, OAT1 or OAT3, or OCT1 or OCT2. Panobinostat inhibited the transport of substrates for OATP1B1 and 1B3, OAT3, and OCT1 and 2, and IC_{50} values were 51.0,

94.1, 21.7, 4.4, and 60.0 μmol/L, respectively. In contrast, panobinostat did not show any clear inhibitory effect against OAT1 even at the maximum concentration tested.

* The following substrates were used for each transporter: ^{3}H-labeled estradiol-17β-glucuronide for OATP1B1 and OATP1B3, ^{3}H-labeled *p*-aminohippuric acid for OAT1, ^{3}H-labeled estrone-3-sulfate for OAT3, and ^{3}H-labeled N-methyl 4-phenylpyridinium for OCT1 and OCT2.

Human liver cells were treated with panobinostat (0.01-1 μmol/L) for 3 days to investigate mRNA levels of P-gp and MRP2. Panobinostat did not increase the mRNA level of either molecule investigated.

The applicant explained that pharmacokinetic interactions mediated by panobinostat-induced transporters are unlikely to occur in the clinical use of panobinostat, in light of the fact that C_{max} of panobinostat following multiple oral panobinostat (20 mg) in patients with MM was <40 ng/mL (approximately 0.11 μmol/L) [see "4.(ii).B.(1) Difference in PK of panobinostat between Japanese and non-Japanese patients"].

3.(ii).B Outline of the review by PMDA

Based on the submitted data and the following discussion, PMDA concluded that the applicant's explanation about the absorption, distribution, metabolism, and excretion of panobinostat and on the pharmacokinetic interactions are acceptable.

Tissue distribution

It is suggested that panobinostat or its metabolite(s) has a high affinity for melanin [see "3.(ii).A.(2).1) Tissue distribution"]. PMDA asked the applicant to explain safety concerns about the distribution of panobinostat or its metabolite(s) in melanin-containing tissues in clinical use.

The applicant responded as follows:

Panobinostat or its metabolite(s) distributed in melanin-containing tissue is unlikely to cause any significant adverse events in clinical use, for the following reasons.

- In the repeat-dose toxicity study in dogs, no toxicity findings suggestive of the effect of panobinostat or its metabolite(s) on melanin-containing tissues such as those in the eyes and skin were observed [see "3.(iii).A.(2) Repeat-dose toxicity"].

- In the global phase III study (Study D2308), no clear difference was observed between the panobinostat and placebo groups either in the incidence of skin and subcutaneous tissue disorders (panobinostat, 28.3%; placebo, 24.4%) or in the incidence of ocular tissue disorders (panobinostat 21.3%; placebo 22.5%). In the Japanese patients in Study D2038, the incidence of skin and subcutaneous tissue disorders was higher in the panobinostat group (77.8%) than in the placebo group (37.5%). However, there was no clear difference between the two groups in the incidence of events for which a causal relationship to panobinostat could not be ruled out (panobinostat, 27.8%; placebo, 18.8%). Grade ≥3 events were not observed in either group.

PMDA considers as follows:

The explanation of the applicant is acceptable. However, the following information should be appropriately communicated to healthcare professionals through information materials etc.: (1) panobinostat or its metabolite(s) has a high affinity for melanin, and (2) the incidence of skin and subcutaneous tissue disorders was higher in the panobinostat group than in the placebo group in Japanese patients.

3.(iii) Summary of toxicology studies

In this section, the dose and concentration of panobinostat are expressed in the amount of the free base.

3.(iii).A Summary of the submitted data

3.(iii).A.(1) Single-dose toxicity

3.(iii).A.(1).1) Single intravenous dose toxicity study in mice

Panobinostat (10, 50, 75, 100 mg/kg) or vehicle (20% propylene glycol/80% buffer*) was administered intravenously in a single dose to mice (ICR, n = 3-5/sex/group). Death occurred in 2 of 5 males in the

75 mg/kg group and in 2 of 3 males and 3 of 5 females in the 100 mg/kg group. The 2 dead animals in the 100 mg/kg group were found to have their lungs turned dark red or red. Changes in clinical signs observed were eyelid ptosis, decreased locomotor activity, and decreased feces in the ≥50 mg/kg groups, swollen muzzle in the 75 mg/kg group, and laboured respiration, saltatory spasm, sedation, muscular relaxation, hunchback position, and enophthalmos in the 100 mg/kg group. Hind limb disorder, muscular tremor, disturbance of consciousness, and mild decrease in locomotor activity were observed immediately after administration in all groups including the vehicle group, but they were considered to be due to the administration of a large volume of vehicle.

Accordingly, the approximate lethal dose of panobinostat was determined to be 50 to 75 mg/kg in males and 75 to 100 mg/kg in females.

* 0.1 mol/L lactic acid, 4.3% mannitol, and 1 mol/L sodium hydroxide (38 mL/L).

3.(iii).A.(1).2) Single intravenous dose toxicity study in rats

Panobinostat (1, 10, 50, 100 mg/kg) or vehicle (20% propylene glycol/80% buffer*) was administered intravenously in a single dose to rats (Wistar Hannover, n = 5/sex/group). Death or moribund sacrifice occurred in 2 of 5 females in the 50 mg/kg group and in 5 of 5 males and 5 of 5 females in the 100 mg/kg group. In the 1 mg/kg group, death occurred in 1 of 5 females, but was considered unrelated to the administration of panobinostat because no death or moribundity was observed in the 10 mg/kg group or in other rats in the 1 mg/kg group. Dead or moribund-sacrificed animals showed decreased locomotor activity, decreased body temperature, decreased righting reflex, recumbency, eyelid ptosis, abnormal feces, tremor, hemorrhage in thoracic and abdominal cavity, red discoloration/mottling of the lungs, edema of mesentery, mottling of the kidneys, and decreased size of spleen. Findings in surviving animals were red urine in the 1 and 10 mg/kg groups, decreased body weight at 3 days after administration in the ≥10 mg/kg groups, and moist fur, eyelid ptosis, and decreased body weight in the 50 mg/kg group.

Accordingly, the approximate lethal dose of panobinostat was determined to be 50 to 100 mg/kg in males and 10 to 50 mg/kg in females.

* 0.1 mol/L lactic acid, 4.3% mannitol, and 1 mol/L sodium hydroxide (38 mL/L).

3.(iii).A.(2) Repeat-dose toxicity

3.(iii).A.(2).1) Four-week repeated oral dose toxicity study with 3 times a week administration in rats

Panobinostat (3, 10, 30 mg/kg/day) or vehicle (purified water) was administered orally 3 times a week (Days 1, 3, and 5 every week) for 4 weeks to rats (Wistar Hannover, n = 10-16/sex/group). Separately, rats in the vehicle and 30 mg/kg group (6 males and 6 females per group) were to undergo a 4-week recovery period to investigate reversibility.

Findings were decreased thyroid weight in the ≥3 mg/kg groups, decreased platelet count, decreased spleen weight, decreased thyroid follicular colloid, and vacuolization of follicular epithelial cells in the ≥10 mg/kg groups, and reduced body weight gain, decreases in white blood cell count and lymphocyte count, decreased thymus size, decreases in pituitary and thymus weights, thinning of thymic cortex, and decreased extramedullary hemopoiesis in the spleen in the 30 mg/kg group. All these conditions were reversible after the recovery period.

The no-observed-adverse-effect level (NOAEL) could thus not be determined in this study; instead, the maximum tolerated dose was determined to be 30 mg/kg/day.

3.(iii).A.(2).2) Thirteen-week repeated oral dose toxicity study with 3 times a week administration in rats

Panobinostat (10, 30, 100 mg/kg/day) or vehicle (0.5% hydroxypropylcellulose) was administered orally 3 times a week (Days 1, 3, and 5 every week) for 13 weeks to rats (Wistar Hannover, n = 10-16/sex/group). Separately, rats in the vehicle and 100 mg/kg groups (6 males and 6 females per group), were to undergo a 4-week recovery period to investigate reversibility.

Findings in the ≥10 mg/kg groups were reduced body weight gain, decreased food consumption, decreased erythrocyte indices (mean cell hemoglobin, mean cell hemoglobin concentration, mean cell volume), decreases in neutrophil count and lymphocyte count, decreases in creatine phosphokinase, myocardial-bound creatine kinase, and potassium, increases in phosphate and total bilirubin, decreased granulocyte series cells/erythroblast series cells ratio on bone marrow smear test, decreased triiodothyronine (T3), increased troponin I, bone marrow atrophy, and pigmentation of spleen. Findings in the ≥30 mg/kg groups were increased blood calcium, decreases in thymus, adrenal, submandibular gland, and liver weights, and thymic atrophy. Findings in the 100 mg/kg group were decreased body weight, decreases in red blood cell count, hematocrit (Ht), hemoglobin (Hb), and platelet count, granulocyte hypoplasia and suppression of maturation on bone marrow smear test, decreases in thyroxine (T4) and thyroid-stimulating hormone (TSH), decreased urine specific gravity, increased urine volume, decreased thymic size, red discoloration of mesenteric lymph node, decreased prostate weight, hyperostosis in femoral bone marrow space, erythrophagocytosis in mesenteric lymph node, lymphocyte depletion in mandibular lymph node, and atrophy of splenic lymphatic tissue, and increased number of females showing histological picture of estrus in the vagina. All findings except pigmentation of the spleen were reversible or tended to be reversible. One male in the 100 mg/kg group showed adhesion and bulging of the lungs, mass in the stomach mass, multiple abscesses in the lungs, pericarditis, peritonitis, and degeneration of seminiferous epithelium in the testes, but their causal relationship to panobinostat was unclear.

Animals in the recovery group showed decreased submandibular gland weight, decreased prostate weight, spleen pigmentation, etc., but other conditions observed after the treatment period were reversible or tended to be reversible.

The NOAEL could thus not be determined in this study. Instead, the maximum tolerated dose was determined to be 100 mg/kg/day.

3.(iii).A.(2).3) Twenty six-week repeated oral dose toxicity study with 3 times a week administration in rats

Panobinostat (10, 30, 75 mg/kg/day) or vehicle (0.5% hydroxyethyl cellulose on Days 1, 3, and 59, 0.5% hydroxypropylcellulose on other days) was administered orally 3 times a week (Days 1, 3, and 5 every week) for 26 weeks to rats (Wistar Hannover, n = 20-30/sex/group). Clinical chemistry included a test for thyroid gland function and for troponin. Separately, rats in the vehicle and 75 mg/kg groups (10 males and 10 females per group), were to undergo a 4-week recovery period to investigate reversibility.

Death occurred in 1 of 40 animals in the 30 mg/kg group, but the cause of the death was not identified. In the 75 mg/kg group, 1 of 60 animals showed abnormal gait and was sacrificed moribund. Findings in the ≥10 mg/kg groups were reduced body weight gain, maturation arrest of granulocyte series cells and increases in eosinophil series cell ratio and in granulocyte series cell/erythroblast series cell ratio on bone marrow smear test, decreases in prostate, submandibular gland, and thymus weights, splenic hemosiderin deposition, hypertrophy of follicular epithelial cells in the thyroid gland, and atrophy of fatty marrow in bone, and the increased number of females showing histological picture of estrus in the vagina. Findings in the ≥30 mg/kg groups were decreases in food consumption and body weight, decreases in white blood cell count, neutrophil count, lymphocyte count, monocyte count, eosinophil count, and platelet count, increased troponin I, decreases in adrenal, spleen, and liver weights, thymic atrophy, and atrophy of male mammary gland. Findings in the 75 mg/kg group were decreases in Ht, Hb, and erythrocyte indices, increased reticulocyte count, increased urine volume, decreased urine specific gravity, red discoloration of mesenteric lymph node, decreased thymic size, increased ovary weight, atrophy of germinal center of mandibular lymph node, erythrophagocytosis in mesenteric lymph node, and atrophy of periarterial lymphatic sheath in the spleen.

In this study and in the 13-week repeated oral dose toxicity study with 3 times a week administration in rats [see "3.(iii).A.(2).2) Thirteen-week repeated oral dose toxicity study with 3 times a week administration in rats"], increased troponin I was observed, but without any change in the troponin T level or histopathological changes. This suggested that the observed increase in troponin I did not clearly indicate cardiac toxicity of panobinostat. Therefore, the applicant considered that the finding was of little toxicological significance.

Animals in the recovery group showed decreased lymphocyte count, decreases in weights of the submandibular gland, thymus, adrenal, and spleen, increased splenic hemosiderin, and hypertrophy of follicular epithelial cells in the thyroid gland, but other findings observed after the treatment period were reversible or tended to be reversible. Thyroid follicular cell adenoma was observed in 1 of 10 males in the recovery group. The applicant explained that although the involvement of panobinostat in the occurrence of thyroid follicular cell adenoma cannot be excluded, the symptom was more likely to be spontaneous rather than due to panobinostat, for the following reasons.

- Thyroid follicular cell adenoma occurs spontaneously in aged rats (*Toxicol Sci.* 1998;45,1-8).
- Thyroid follicular cell adenoma occurred in only 1 animal in all toxicity studies using rats and dogs.
- Despite positive results obtained in genotoxicity studies, there were no findings suggestive of carcinogenicity of panobinostat in any tissues or organs except the thyroid gland. This suggests that the genotoxicity of panobinostat is unlikely to be involved in the occurrence of thyroid follicular cell adenoma.
- The thyroid hormone level remained unchanged after a 23 week-treatment with panobinostat in this study.

Thus, the NOAEL could not be determined in this study; instead, the maximum tolerated dose was determined to be 75 mg/kg/day.

$AUC_{0\text{-}24h}$ (608.5 ng·h/mL) at the maximum tolerated dose of 75 mg/kg/day was approximately 4.38 times the clinical exposure,* whereas $AUC_{0\text{-}24h}$ (77.5 ng·h/mL) at 10 mg/kg/day was below the clinical exposure.

* In the Japanese phase I study (Study B1101), the foreign phase I study (Study B2101), and the foreign phase I/II study (Study B2102), $AUC_{0\text{-}24h}$ following multiple oral doses of 20 mg panobinostat 3 times a week (Days 1, 3, and 5 in each week) in patients with solid cancer, non-Hodgkin's lymphoma, or hematological malignancy was 139 ng·h/mL (the geometric mean obtained by combined analysis of the results of the 3 studies).

3.(iii).A.(2).4) Dose escalation and 5-day repeated oral dose toxicity studies in dogs (Reference data, non-GLP study)

In the dose escalation study, panobinostat was administered orally at 3 mg/kg/day on Day 1 and at 10 mg/kg/day on Day 5 to beagle dogs (n = 1/sex). The used vehicle was 20% propylene glycol/80% buffer.* After administration at 10 mg/kg, the animals showed increased body temperature, muscle stiffness, dehydration, tonic convulsion, tremor, recumbency, decreased locomotor activity, irregular breathing, diarrhea, and no-feces. The female was sacrificed moribund on Day 7, and the male on Day 9, because of the poor clinical conditions.

Based on the above, the approximate lethal dose was determined to be ≥3 mg/kg and <10 mg/kg in this study.

* 0.1 mol/L lactic acid, 4.3% mannitol, and 1 mol/L sodium hydroxide (38 mL/L).

In the repeat-dose study, panobinostat (3 mg/kg/day) was administered orally for 5 days to beagle dogs (n = 2/sex/group). The vehicle was 20% propylene glycol/80% buffer.* One male died before the administration on Day 5. Observed changes in clinical signs were decreased locomotor activity, ataxic gait, decreased body temperature, diarrhea, soft feces, salivation, and vomiting, which were observed mostly on Day 5. In addition, decreases in body weight and food consumption, increases in erythrocyte count, Ht, and Hb as well as decreased lymphocyte count on hematology were observed, and little or no monocytes, eosinophils, or basophils were identified. The bone marrow smear test performed on 1 animal showed little or no erythropoiesis, indicating severe myelopoietic suppression. Other findings were reddening of gastrointestinal mucosa and lymph nodes, bone marrow cell depletion, epithelial necrosis and decreased goblet cell count in the gastrointestinal tract, vacuolated renal tubules and protein

cast in the kidneys, the increased number of atretic follicles in the ovary, endometrial atrophy, epithelial thinning of the prostate, cell depletion, necrosis, and bleeding of lymph nodes, thymic atrophy, and decreased mucin and atrophy of exocrine glands.

Thus, the NOAEL could not be determined in this study.

* 0.1 mol/L lactic acid, 4.3% mannitol, and 1 mol/L sodium hydroxide (38 mL/L).

3.(iii).A.(2).5) Four-week repeated oral dose toxicity study with 3 times a week administration in dogs

Panobinostat (0.15, 0.5, 1.5 mg/kg/day) or vehicle (purified water) was administered orally 3 times a week (Days 1, 3, and 6 every week) for 4 weeks to beagle dogs (n = 3-5/sex/group). Separately, dogs in the vehicle and 1.5 mg/kg groups (2 males and 2 females per group) were to undergo a 4-week recovery period to investigate reversibility.

Findings in the ≥0.15 mg/kg groups were decreased thyroid weight, decreased thyroid follicular colloid, vacuolization of follicular epithelial cells of thyroid gland, atrophy of gastric cardiac gland, and thymic atrophy. Findings in the ≥0.5 mg/kg groups were increased creatinine, increased granulocyte series cell/erythroblast series cell ratio on bone marrow smear test, and splenic lymphocyte depletion. Findings in the 1.5 mg/kg group were decreased body weight, decreased lymphocyte count, prolonged activated partial thromboplastin time (APTT), decreased cholesterol, decreased size of prostate, decreases in kidney, spleen, prostate, and testis weights, lymphocyte depletion in mesenteric lymph nodes and submandibular lymph nodes, debris in duodenal and jejunal crypts and expanded crypts, atrophy of ileal lymphatic tissue and of gastric pyloric gland, decreased bone marrow cell count, epithelial thinning of prostate, increased debris in epididymal lumen, and degeneration of testicular seminiferous epithelium.

Animals in the recovery group showed decreased testicular weight, lymphocyte depletion in the spleen and submandibular lymph nodes, decreased bone marrow cell count, decreased thyroid follicular colloid, increased debris in epididymal lumen, and degeneration of testicular seminiferous epithelium. Other findings observed after the treatment period were reversible or tended to be reversible.

Thus, the NOAEL could not be determined in this study.

3.(iii).A.(2).6) Thirteen-week repeated oral dose toxicity study with 3 times a week administration in dogs

Panobinostat (0.15, 0.5, 1.5/1.0 mg/kg/day) or vehicle (water for injection) was administered orally 3 times a week (Days 1, 3, and 5 every week) for 13 weeks to beagle dogs (n = 4-6/sex/group). In the 1.5/1.0 mg/kg/day group, decreased body weight was observed after administration at 1.5 mg/kg/day, whereupon the dose was reduced to 1.0 mg/kg/day from Day 43. Separately, dogs in the vehicle and 1.5/1.0 mg/kg groups (2 males and 2 females per group) were to undergo a 4-week recovery period to investigate reversibility.

Findings in the ≥0.5 mg/kg groups were decreased body weight, decreases in white blood cell count, lymphocyte count, eosinophil count, basophil count, red blood cell count, Ht, Hb, and erythrocyte indices, increased reticulocyte count (Week 13 of administration), decreased alkaline phosphatase (ALP), and lymphocyte depletion in the submandibular lymph nodes and mesenteric lymph nodes. Findings in the 1.5/1.0 mg/kg group were liquid stool/soft stools and emaciation, decreased food consumption, transient decrease in reticulocyte count (only at Week 4 of administration), increased platelet count, prolonged APTT, decreases in alanine aminotransferase (ALT) and cholesterol, increased potassium, decreased T3, and decreased sperm count in epididymis. Also, 1 male in the 1.5/1.0 mg/kg group showed decreased size and atrophy of the thymus, reddening of the lungs, and acute multifocal pneumonia.

Animals in the recovery group showed decreases in white blood cell count, lymphocyte count, eosinophil count, basophil count, red blood cell count, Ht, Hb, erythrocyte indices, ALP, and ALT. Other findings observed after the treatment period were reversible or tended to be reversible.

Based on the above, the NOAEL in this study was determined to be 0.15 mg/kg/day.

3.(iii).A.(2).7) Thirty-nine-week repeated oral dose toxicity study with 3 times a week administration in dogs

Panobinostat (0.15, 0.5, 1.0 mg/kg/day) or vehicle (water for injection) was administered orally 3 times a week (Days 1, 3, and 5 every week) for 39 weeks to beagle dogs (n = 4-6/sex/group). Separately, dogs in the vehicle and 1.0 mg/kg groups (2 males and 2 females per group) were to undergo a 4-week recovery period to investigate reversibility.

Decreased ALP was observed in the ≥0.15 mg/kg groups, but the applicant considered that it was of little toxicological significance because the change was not an increase but a decrease. Findings in the ≥0.5 mg/kg groups were decreases in red blood cell count, Ht, Hb, and erythrocyte indices, decreased cholesterol, and decreases in thymus, thyroid, and spleen weights. Findings in the 1.0 mg/kg group were decreases in lymphocyte count, eosinophil count, and basophil count, prolonged APTT, increased reticulocyte count, increased aspartate aminotransferase, decreased ALT, immature granulocytes on bone marrow smear test, increased lung weight, increased frequency of inflammatory change in pulmonary interstitium, lymphocyte depletion in mesenteric lymph nodes, and increased splenic hemosiderin. Decreased size and retraction of the thymus were observed in all treatment groups including the vehicle group, but thymic atrophy was observed only in the panobinostat groups.

The applicant considered that a causal relationship between panobinostat and the inflammatory change of pulmonary interstitium cannot be excluded, but the condition is more likely an accidental change for the following reasons and therefore is not relevant to humans.

- No evidence was found for injuries of alveolar epithelial cells or vascular endothelial cells and immune cell activation, which are generally considered as causes of drug-induced interstitial pneumonia (*Respiratory Research.* 2012:13:1-9).

- Inflammatory changes in the lungs are spontaneous pathologic conditions commonly observed in dogs (Toxicologic Pathology [CRC Press, 2013]).

Animals in the recovery group showed decreases in red blood cell count, Ht, Hb, erythrocyte indices, lymphocyte count, eosinophil count, and cholesterol, as well as retraction of thymus. Other conditions observed after the treatment period were reversible or tended to be reversible.

The applicant considered that prolonged APTT observed in this study and other repeat-dose toxicity studies in dogs [see "3.(iii).A.(2).5) Four-week repeated oral dose toxicity study with 3 times a week administration in dogs" and "3.(iii).A.(2).6) Thirteen-week repeated oral dose toxicity study with 3 times a week administration in dogs"] was of little toxicological significance because there were no findings suggestive of hemorrhage and because the changes were reversible.

Accordingly, the NOAEL in this study was determined to be 0.15 mg/kg/day, and the maximum tolerated dose to be 1.0 mg/kg/day.

In the study, $AUC_{0\text{-}24h}$ was 15.25 ng·h/mL at the NOAEL and was 81.5 ng·h/mL at the maximum tolerated dose. These values were approximately 0.11 and 0.59 times the clinical exposure[*], respectively.

[*] In the Japanese phase I study (Study B1101), the foreign phase I study (Study B2101), and the foreign phase I/II study (Study B2102), $AUC_{0\text{-}24h}$ following multiple oral doses of 20 mg panobinostat 3 times a week (Days 1, 3, and 5 every week) in patients with solid cancer, non-Hodgkin's lymphoma, or hematological malignancy was 139 ng·h/mL (geometric mean obtained by combined analysis of the 3 studies).

3.(iii).A.(3) Genotoxicity

All of the following *in vitro* genotoxicity studies suggested genotoxicity of panobinostat. Therefore, no *in vivo* study was conducted.

A bacterial reverse mutation assay showed mutation-inducing activity of panobinostat. A comet assay in mouse lymphoma-derived L5178Y cells showed DNA-injuring activity of panobinostat. A

chromosomal aberration assay in human peripheral lymphocytes showed an increased frequency of endoreduplication.

p21is a cyclin-dependent kinase inhibitor. Increased p21 expression leads to cell cycle arrest. When the cell cycle is resumed by subsequent p21 inactivation, abnormal mitosis and endoreduplication are induced (*Oncogene.* 2000;19:2165-70). Therefore, the applicant explained that endoreduplication may have been induced by a p21-inducing effect of panobinostat [see "3.(i).A.(1).3) Activation of the transcription of p21, a cell cycle arrest factor"].

3.(iii).A.(4) Carcinogenicity

Since panobinostat is used to treat relapsed or refractory MM, no carcinogenicity test was performed.

3.(iii).A.(5) Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in rats and embryo-fetal development studies in rats and rabbits were conducted as reproductive and developmental toxicity studies. In a tissue distribution study, fetal transfer of panobinostat was confirmed [see "3.(ii).A.(2).3) Placental and fetal transfer"]. Since panobinostat is used to treat relapsed or refractory MM, a study on effects on pre- and postnatal development, including maternal function, was not conducted.

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats

Panobinostat (10, 30, 100 mg/kg/day) or vehicle (0.5% hydroxypropylcellulose) was administered orally to male rats (Wistar Hannover, n = 25/group) 3 times a week (Days 1, 3, and 5 every week) from 4 weeks before mating until necropsy after the mating period, and to female rats (Wistar Hannover, n = 25/group) 3 times a week (Days 1, 3, and 5 every week) from 2 weeks before mating, during the mating period, and on Gestation Days 0, 3, and 6. Female rats were necropsied on Gestation Day 13.

In male rats, 1 of 25 rats in the 30 mg/kg group died, but the cause of death was not identified. Observed changes in clinical signs were reduced body weight gain and decreased food consumption in the ≥10 mg/kg groups, and decreased body weight, salivation, dehydration, decreased locomotor activity, emaciation, hunchback position, and piloerection in the 100 mg/kg group. In animals in the 100 mg/kg group, decreased size of prostate gland was observed, while no change was observed in the weight of male reproductive organ or in sperm analysis.

In female rats, observed changes in clinical signs were reduced body weight gain and decreased food consumption in the ≥30 mg/kg groups and decreased body weight in the 100 mg/kg group. No toxicologically significant changes were observed in the estrous cycle, days until mating, copulation index, or fertility index.

Effects of panobinostat on early embryonic development included the increased number of early resorptions, increased post-implantation loss, and decreased live embryos in the ≥30 mg/kg groups.

Thus, in this study, the NOAEL could not be determined for male animals, but it was determined to be 10 mg/kg/day for female animals and for early embryonic development.

3.(iii).A.(5).2) Embryo-fetal development studies

i) Study for effects on embryo-fetal development in rats

Panobinostat (30, 100, 300 mg/kg/day) or vehicle (0.5% hydroxypropylcellulose) was administered orally to pregnant rats (Wistar Hannover, n = 22/group) from Gestation Day 6 to Gestation Day 17.

In the 100 mg/kg group, 2 maternal animals died on Gestation Day 11, and 7 animals were sacrificed moribund between Gestation Day 12 and Gestation Day 18 because of poor clinical conditions. In the 300 mg/kg group, 1 animal died on Gestation Day 9. All surviving animals in the 300 mg/kg group were necropsied from Gestation Day 7 to Gestation Day 10 because decreased locomotor activity, debility, a marked decrease in body weight and food consumption, etc. were observed within 4 days after start of administration. Findings were as follows: in the ≥30 mg/kg groups, decreased body weight, decreased food consumption, and atrophy/necrosis of thymic lymphatic tissue; in the 100 mg/kg group, decreased locomotor activity, partial eyelid closure, debility, emaciation, red vaginal secretion and pallor of skin,

enlarged adrenals, dark/pale discoloration of heart and liver, retraction and bulging of liver and stomach, gastric nodule, bacterial colonies in heart and liver, duodenal ulcer and necrosis, adrenal cortex hyperplasia, hepatic necrosis, and cardiac degeneration and necrosis; in the 100 and 300 mg/kg groups, dark/pale discoloration of the adrenals, duodenum, stomach, and thymus, hypertrophy of the duodenum and stomach, bacterial colonies in the duodenum and stomach, hemorrhage and inflammation of the duodenum, erosion, hemorrhage, and ulcer of the stomach, adrenal hemorrhage, and lymphatic tissue hypertrophy in lymph nodes; and, in the 300 mg/kg group, duodenal erosion and gastric edema.

Effects on embryo-fetal development were total desorption of embryos in 1 animal of the 30 mg/kg group and in all animals in the 100 mg/kg group. In the 30 mg/kg group, the increased number of early resorptions, increased post-implantation loss, decreased number of live fetuses, and decreased fetal weight were observed. In addition, an examination of fetuses showed the increased number of presacral vertebral bones and increased number of fetuses with extra ribs and unossification/incomplete ossification/bipartite ossification (including bifurcation) of sternebrae.

Thus, the NOAEL could not be determined either for maternal animals or for embryofetal development in this study.

In a separate study, C_{max} (15.8 ng/mL) and AUC (124 ng·h/mL) following administration to pregnant rats at 30 mg/kg/day were approximately 0.73 and 0.89 times, respectively, the clinical exposure.*

* In the Japanese phase I study (Study B1101), the foreign phase I study (Study B2101), and the foreign phase I/II study (Study B2102), C_{max} and $AUC_{0\text{-}24h}$ following multiple oral doses of 20 mg panobinostat 3 times a week (Days 1, 3, and 5 every week) in patients with solid cancer, non-Hodgkin's lymphoma, or hematological malignancy were 21.6 ng/mL and 139 ng·h/mL, respectively (geometric mean obtained by combined analysis of the 3 studies).

ii) Study for effects on embryo-fetal development in rabbits

Panobinostat (10, 40, 80 mg/kg/day) or vehicle (0.5% hydroxypropylcellulose) was administered orally to pregnant rabbits (New Zealand White, n = 22/group) from Gestation Day 7 to Gestation Day 19.

In the 80 mg/kg group, 2 maternal animals died on Gestation Day 19, and 1 animal was sacrificed moribund on Gestation Day 18 because of poor clinical conditions. The dead animals showed abnormal gait, decreased body temperature, decreases in locomotor activity and muscle tone, tremor, debility, convulsion, panting/laboured respiration, and dark discoloration of the gastrointestinal tract (stomach, duodenum, jejunum, ileum, cecum, and colon). In the 80 mg/kg group, 1 animal had an abortion. Changes in clinical signs of surviving animals were decreased amount of feces and food consumption observed in the ≥40 mg/kg groups.

Effects on embryo-fetal development were total resorption of embryos in 1 animal of the 80 mg/kg group and decreased fetal weight in the ≥40 mg/kg/day groups. The examination of fetuses showed incomplete ossification of hyoid bone and unossification/incomplete ossification/bipartite ossification (including bifurcation) of sternebrae in the ≥40 mg/kg groups and incomplete ossification of seventh cervical rib (partial ossification), intraparietal bone, and pubic bone, and the increased number of fetuses with extra sternebrae and 13th rib in the 80 mg/kg group.

Based on the result, the NOAEL was determined to be 10 mg/kg/day both for maternal animals and for embryo-fetal development in this study.

C_{max} (15.1 ng/mL) and AUC (49.6 ng·h/mL) at the NOAEL for maternal animals and embryo-fetal development were approximately 0.70 and 0.36 times, respectively, the clinical exposure.*

* In the Japanese phase I study (Study B1101), the foreign phase I study (Study B2101), and the foreign phase I/II study (Study B2102), C_{max} and $AUC_{0\text{-}24h}$ following multiple oral doses of 20 mg panobinostat 3 times a week (Days 1, 3, and 5 every week) in patients with solid cancer, non-Hodgkin's lymphoma, or hematological malignancy were 21.6 ng/mL and 139 ng·h/mL, respectively (geometric mean obtained by combined analysis of the 3 studies).

The studies on embryo-fetal development showed the effects of panobinostat on embryos and fetuses as described. The applicant explained that the data of studies on embryo-fetal development would be included in the package insert to raise caution, and that the use of panobinostat by pregnant and lactating women would be restricted.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Repeated oral dose toxicity study with 3 times a week administration for 5, 12, or 26 days in rats

This study was conducted to investigate the effect of panobinostat on the thyroid gland, using an antithyroid agent propylthiouracil as the positive control.

Panobinostat (75 mg/kg/day) or vehicle (0.5% hydroxypropylcellulose) was administered orally 3 times a week (Days 1, 3, and 5 every week) for 5, 12, or 26 days to male rats (Wistar Hannover, n = 90/group). Male rats in the positive control group (Wistar Hannover, n = 90/group) received propylthiouracil (10 mg/kg) orally once daily for 5, 12, or 26 days.

In both the panobinostat and propylthiouracil groups, reduced body weight gain, decreases in body weight and food consumption were observed. The test for thyroid gland function showed a mild increase in TSH and a mild decrease in T3, T4, and free T4 in the panobinostat group, but these changes were not statistically significant except the change in T4 on Day 26. Necropsy showed decreased size of thymus and atrophy/necrosis of lymphatic tissue in thymus in the group receiving panobinostat for 26 days. Gene expression analysis (non-GLP study) in the panobinostat group showed changes in gene expression associated with histone, histone acetylase, DNA repair, stress/oxidative stress, cell cycle regulation, and apoptosis. In the propylthiouracil group, in contrast, the test for thyroid gland function showed a statistically significant increase in TSH and decreases in T3, T4, and free T4, as well as thyromegaly, hypertrophy of anterior pituitary gland, and hypertrophy/hyperplasia of follicular epithelial cells in the thyroid gland. Gene expression analysis showed induction of genes related to mitosis/cell growth, iodine transport, neovascularization, and vascular remodeling in the thyroid gland; genes related to secretory cells/thyroid-stimulating hormone-producing cells in the pituitary gland; and genes coding for enzymes involved in glucuronidation reaction of T4-T3 in the liver.

The applicant explained that panobinostat is considered to affect the thyroid gland by a mechanism different from that of propylthiouracil because this study revealed that (1) rats receiving panobinostat showed only mild changes in the thyroid hormone level, and that (2) the changes in gene expression pattern in the liver, thyroid gland, and pituitary gland differed between the panobinostat and propylthiouracil groups.

3.(iii).A.(6).2) Evaluation of the safety of impurities

Among the impurities contained in the drug substance or the drug product of panobinostat, Impurity A (acceptance criterion of the drug substance, ≤[redacted]%) and 315-02 (acceptance criterion of the drug substance, ≤[redacted]%; acceptance criterion of the drug product, ≤[redacted]%) need to be evaluated for safety. ("Guidelines on Impurities in New Drug Substances" [PMSB/ELD Notification No. 1216001, dated December 16, 2002] and "Guidelines on Impurities in New Drug Products" [PMSB/ELD Notification No. 0624001, dated June 24, 2003]).

In the 13-week repeat-dose toxicity study in rats [see "3.(iii).A.(2).2) Thirteen-week repeated oral dose toxicity study with 3 times a week administration in rats], the amounts of Impurity A and 315-02 administered to animals ([redacted] and [redacted] mg/m^2, respectively) were greater than the maximum intake at clinical doses ([redacted] and [redacted] mg/m^2, respectively). The impurity 315-02 was detected as metabolite M43.5 in rats, dogs, and humans [see "3.(ii).A.(3) Metabolism"]. Based on these facts, Impurity A and 315-02 were considered safe up to the upper limit of the acceptance criteria.

Genotoxicity of the above 2 impurities was evaluated by *in silico* analysis using DEREK (v9.0.0 or v.12.0.0) and MCASE (v.1.9 or v2.2.0.36). The results did not suggest genotoxicity of either impurity.

Hydroxylamine, an impurity contained in panobinostat, is shown to be genotoxic and was reported to be carcinogenic in a long-term study using rodents (Hydroxylamine Free Base 50% Safety data sheet

[BASF, 2005]). The maximum intake of hydroxylamine in clinical dose, calculated from the acceptance criterion of the impurity in the drug substance and the drug product (≤[redacted] ppm), is [redacted] μg/day. The acceptance criterion was considered appropriate because the maximum intake is <1.5 μg/day, the Threshold of Toxicological Concern with a lifetime cancer risk of <1 in 100,000 people (ICH M7 Harmonised Tripartite Guideline [ICH, 2014]).

3.(iii).A.(6).3) *In vitro* phototoxicity

An *in vitro* 3T3 NRU phototoxicity test was conducted on panobinostat. Cells were irradiated with UVA (4.6 ± 0.3 J/cm^2) for 45 minutes in the presence of panobinostat at a concentration of 0.158 to 500 μg/mL (Experiment 1) or 0.0632 to 200 μg/mL (Experiment 2). In Experiment 1, the mean photo effect (MPE) was 0.079 and photo-irritation factor (PIF) could not be determined because of the failure to obtain an appropriate regression curve. In Experiment 2, MPE was 0.027 and PIF was 1.3, showing panobinostat to be non-phototoxic.

3.(iii).A.(6).4) Local lymph node assays

Local lymph node assays were conducted in mice to investigate the skin-sensitizing effect of panobinostat.

(a) Local lymph node assay in mice (maximum concentration, 10%)

Panobinostat (1%, 5%, 10% solution) or vehicle (mixture of 40% N,N-dimethylacetamide, 30% acetone, and 30% ethanol) was applied to the back of the bilateral auricles of female mice (CBA/Ca, n = 6/group) for 3 days, and the auricles were collected at 24 hours after the final application. Animals in the ≥5% groups showed reduced body weight gain, hunchback position, and auricular erythema and swelling. Animals in the 10% group showed increased auricular thickness. The weight of regional lymph nodes of auricle and cell count increased in the 1% group but decreased in the ≥5% groups in a concentration-dependent manner. The results in the ≥5% groups were considered to be due to the systemic toxicity-induced suppression of lymph node activation.

The above results showed that panobinostat at a 1% concentration activated the lymph nodes, whereas panobinostat at a ≥5% concentration showed systemic toxicity. This precluded the evaluation of dose response relationship of lymph node activation. Therefore, an additional local lymph node assay was conducted with the maximum panobinostat concentration of 1%, as described in the following section (b).

(b) Local lymph node assay in mice (maximum concentration, 1%)

Panobinostat (0.1%, 1% solution) or vehicle (mixture of 40% N,N-dimethylacetamide, 30% acetone, and 30% ethanol) was applied to the back of the bilateral auricles of female mice (CBA/Ca, n = 6/group) for 3 days, and the auricles were collected at 24 hours after the final application. Animals in the 1% group showed reduced body weight gain. Animals in the ≥0.1% groups showed increased auricle weight and a trend toward increased auricle thickness. Animals in the ≥0.1% groups also showed a dose-dependent increase in the weight of regional lymph nodes of auricle and cell count.

The above results were subjected to assessment of the extent of skin irritation and lymph node activation according to the 3-grade (strong, moderate, weak) evaluation method (*Arch Toxicol.* 2001;74:733-44). Panobinostat was classified as a substance with a strong skin irritating effect and with a moderate lymph node activating effect.

3.(iii).B Outline of the review 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 concerns about the clinical use of panobinostat.

Effect on female reproductive organs

The 13- and 26-week repeated oral dose toxicity studies in rats showed an increase in the number of animals showing histological picture of estrus in the vagina. The 5-day repeat-dose toxicity study in dogs showed endometrial atrophy and an increase in the number of atretic follicles [see "3.(iii).A.(2) Repeat-dose toxicity"]. Therefore, PMDA asked the applicant to explain the possibility of panobinostat affecting the female reproductive organs.

The applicant responded as follows:
A study using human choriocarcinoma-derived JAR cell line reported that trichostatin A (a HDAC inhibitor) enhanced the activity of the promotor of luteinizing hormone receptor (LHR), thereby promoting the expression of the receptor gene (*J Steroid Biochem Mol Biol.* 2003;85:401-14). These results suggest that panobinostat increased LHR expression in follicles, luteal bodies, etc., which in turn activated the signal transduction mediated by luteinizing hormone (LH), leading to failure to maintain the normal estrous cycle by LH and follicle stimulating hormone (FSH), thus affecting the female reproductive organ in rats and dogs.

The applicant considered the findings on the female reproductive organ in rats are unlikely to be seen on the female reproductive organ of humans for the following reasons.

- No related histopathological changes were observed in the uterus.

- In the study of fertility and early embryonic development to implantation in rats [see "3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats"], no effect on female fertility was observed even in the maximum dose (100 mg/kg) group with an exposure ($AUC_{0\text{-}24h}$, 763 ng·h/mL) approximately 5 times the clinical exposure ($AUC_{0\text{-}24h}$, 139 ng·h/mL).

- The finding in female rats (an increase in the number of animals showing histological picture of estrus in the vagina) may be due to the detection of a minor disturbance of the estrous cycle, because the finding was not observed in dogs, and because the estrous cycle is shorter in rats (4-6 days) than in dogs (approximately 6 months). The estrous cycle in humans (approximately 28 days) is longer than that in rats.

Since the abnormalities of the female reproductive organs of dogs observed in the 3 mg/kg/day group were mild, the applicant considers that panobinostat is unlikely to have similar effects on the female reproductive organs of humans.

PMDA considers as follows:
PMDA accepted the explanation of the applicant on the findings of the female reproductive organ of rats. However, the findings of the female reproductive organs of dogs should be provided appropriately to healthcare professionals through the package insert, etc. for the following reasons: (a) a causal relation of the abnormalities to panobinostat could not be ruled out, (b) the NOAEL for the abnormalities could not be determined, and (c) reversibility was not investigated.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

The pharmacokinetics (PK), etc. of panobinostat were investigated using the following formulations: injectable solution of panobinostat lactate, capsules containing panobinostat lactate monohydrate as the drug substance (monohydrate capsules; 5, 20 mg), and capsules containing panobinostat lactate anhydrate (hereinafter referred to as panobinostat) as the drug substance (anhydrate capsules; 5, 15, 20 mg) (the table below). The to-be-marketed formulations are anhydrate capsules 10 and 15 mg.

Formulations used in clinical studies

Formulation	Studies
Injectable solution	Japanese phase I study (A1101), foreign phase I study (A2101), foreign phase I/II study (A2102)
Monohydrate capsules (5, 20 mg)	Japanese phase I study (B1101), foreign phase I studies (B2101, B2108), foreign phase I/II study (B2102)
Anhydrate capsules (5, 15, 20 mg)	Foreign phase I studies (B2109,* B2110,* B2111,* B2206,* B2207,* X2101, X2105), Japanese phase II study (B1201*), foreign phase II studies (B2201,* B2202,* B2203,* B2211,* E2214,* DUS71), foreign phase III study (D2308)

* Only 5 and 20 mg capsules were used.

4.(i).A.(1) Assay

Human plasma was assayed for panobinostat and metabolite M37.8 (reduced form of hydroxamic acid moiety) and human urine for panobinostat by LC-MS/MS. The lower limits of quantitation are shown in the following table.

Lower limit of quantitation of the analytical method used in each clinical study

Analyte (sample)	Lower limit of quantitation (ng/mL)	Studies
Panobinostat (plasma)	0.5	A1101, A2101, A2102, B1101, B1201, B2101, B2102, B2109, B2110, B2111, B2202, B2206, B2211, E2214
	0.1	B2108, B2203, D2308
	0.5 or 0.1*	B2201, B2207, X2101, X2105
Panobinostat (urine)	0.5	X2105
M37.8 (plasma)	0.1	B2108, B2201, B2203, X2101, X2105

* Samples obtained in the early stage of studies were measured by an assay method with the lower limit of quantitation of 0.5 ng/mL. The assay method was then switched to a new one with the lower limit of quantitation of 0.1 ng/mL during the studies. The interchangeability of both assay methods was confirmed.

4.(i).A.(2) Foreign phase I study (5.3.1.1-1, Study B2111 [2007 to February 2011])

A cross-over study was conducted to investigate the food effect on the PK of panobinostat using anhydrate capsules in 36 patients with advanced solid cancer (36 patients included in PK analysis).

One treatment cycle consisted of 21 days. Panobinostat (20 mg) was administered once daily orally on Days 1, 4, 8, 11, 15, and 18. On Days 1, 8, and 15 in Cycle 1, panobinostat was administered under fasting conditions, after an ordinary meal (total calorie, approximately 500 kcal, of which approximately 175 kcal was in the form of lipids), or after a high-fat meal (total calorie, approximately 1000 kcal, of which approximately 500 kcal was in the form of lipids).

PK parameters of panobinostat following administration under fasting conditions, after an ordinary meal and after a high-fat meal are shown in the following table. The median T_{max} of panobinostat increased following administration after an ordinary meal or high-fat meal as compared with that after fasted administration. The ratios [90% confidence interval (CI)] of the geometric means of C_{max} and AUC_{inf} of panobinostat following administration after an ordinary meal relative to those after fasted administration were 0.64 [0.50, 0.81] and 0.86 [0.75, 1.00], respectively. The geometric mean ratios [90% CI] for C_{max} and AUC_{inf} of panobinostat following administration after a high-fat meal relative to those after fasted administration were 0.56 [0.45, 0.70] and 0.84 [0.74, 0.96], respectively.

PK parameters of panobinostat following administration under fasted or fed conditions

Condition for administration	n*1	C_{max} (ng/mL)	T_{max}*2 (h)	$T_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (h·ng/mL)	AUC_{inf} (h·ng/mL)
Fasted	33	22.7 ± 19.6	1.5 (0.5, 6.0)	14.5 ± 4.7*3	126.3 ± 77.3*6	176.4 ± 103.2*7
After ordinary meal	31	13.7 ± 8.9	2.5 (0.5, 6.0)	15.7 ± 7.7*4	96.2 ± 55.7*3	152.7 ± 89.9*8
After high-fat meal	34	11.9 ± 7.57	4.0 (1.0, 8.1)	13.7 ± 4.9*5	93.7 ± 54.7	143.9 ± 84.7*9

Mean ± SD, *1 Patients with missing values were excluded from PK analysis. *2 Median (range), *3 n = 28, *4 n = 26, *5 n = 29, *6 n = 31, *7 n = 24, *8 n = 19, *9 n = 25

4.(i).A.(3) Discussion by the applicant on the effect of formulations on the PK of panobinostat

Panobinostat in 10 mg, 15 mg, and 20 mg anhydrate capsules are proportionally formulated, and their bioequivalence has been confirmed by dissolution test. In a comparison with a 10 mg anhydrate capsule, a 5 mg anhydrate capsule corresponds to "Level formulation change" according to the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012). However, a study for bioequivalence was not conducted for the following reasons.

- In the global phase III study (Study D2308), 5 mg anhydrate capsules were to be used only when the dose of panobinostat was reduced to the minimal unit dose (10 mg). After all, they were actually used only in 74 of 381 patients (19.4%) for the purpose of dose reduction to 10 mg.

- A dissolution test was performed with 5 mg and 10 mg anhydrate capsules under the testing conditions stipulated as the specifications for 10 mg anhydrate capsules. The mean dissolution rates of 5 mg and 10 mg capsules in [redacted] minutes were ≥85% ([redacted]% and [redacted]%, respectively). Also, in all vessels tested (12 vessels each for 5 mg and 10 mg anhydrate capsules), the dissolution rate was within ± 15% from the mean dissolution rate. These results showed that the dissolution behavior was equivalent for 5 mg and 10 mg anhydrate capsules.

4.(i).B Outline of the review by PMDA

4.(i).B.(1) Food effect

In the foreign phase I study, C_{max} of panobinostat decreased after fed administration as compared with that after fasted administration [see "4.(i).A.(2) Foreign phase I study]. PMDA asked the applicant to explain the effect of food on the efficacy and safety of panobinostat.

The applicant responded as follows:
C_{max} of panobinostat tended to be lower after fed administration than after fasted administration. However, taking account of the following points, food-induced change in C_{max} is not clinically significant, and therefore panobinostat may be administered regardless of food intake.

- The decrease in C_{max} after fed administration is thought to have been caused by the decreased absorption rate of panobinostat because of delay in the delivery of panobinostat to the absorption site due to the decreased gastric emptying rate following food intake.

- In Japanese patients in the global phase III study (Study D2308), no correlation was observed between the C_{max} and efficacy of panobinostat [see "4.(ii).A.(9).1) Relationship between exposure and efficacy"].

- In the foreign phase I study (Study B2111) conducted to investigate the effect of food on the PK of panobinostat, no clear difference was observed in the incidence of adverse events between fed and fasted administration.

PMDA accepted the explanation of the applicant.

4.(i).B.(2) Effect of gastrointestinal pH on PK of panobinostat

PMDA asked the applicant to explain the effect of increased gastrointestinal pH, caused by low gastric acid, proton pump inhibitors, or other factors, on the PK of panobinostat.

The applicant responded as follows:
In light of the following observations, increased gastrointestinal pH associated with low gastric acid, the administration of proton pump inhibitors, or other factors is unlikely to affect the PK of panobinostat.

- The solubility of panobinostat was investigated over the physiological pH range (1.2, 2.0, 4.5, 6.0, 6.8, 7.6). The solubility was ≥0.261 mg/mL within the pH range of 1.2 to 6.8, except pH 7.6 at which panobinostat showed the lowest solubility (0.064 mg/mL). In the administration of the maximum unit dose (20 mg), solubility of ≥0.08 mg/mL is required for panobinostat to be completely dissolved in 250 mL of water in the gastrointestinal tract. Therefore, within the intended clinical dose range, the dissolution of panobinostat from the formulation will not be affected by pH change within 1.2 to 6.8.

- At pH 7.5, the maximum amount of panobinostat that can be dissolved in 250 mL of water is 16 mg, suggesting that panobinostat may be difficult to dissolve from the formulation under weakly acidic conditions. However, intragastric pH exceeds pH 7 only for 1 to 2 hours after administration of proton pump inhibitors, etc. (e.g., *J Clin Biochem Nutr.* 2014;55:178-83).

- In Study D2308, no clear difference was observed in the efficacy or safety of panobinostat between patients receiving concomitant drugs that increase intragastric pH such as proton pump inhibitors (319 patients in the panobinostat group, 269 patients in the placebo group) and patients receiving no such concomitant drugs (62 patients in the panobinostat group, 108 patients in the placebo group).

PMDA considers as follows:
The use of panobinostat with concomitant drugs that increase gastrointestinal pH such as proton pump inhibitors may decrease the absorption of panobinostat. This finding should be provided appropriately to healthcare professionals through reference materials. Information on the safety, etc. of panobinostat used in combination with such drugs should be further collected after the market launch, and new findings should be provided to healthcare professionals in an appropriate manner once available.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The PK of panobinostat in cancer patients was investigated following the administration of panobinostat alone and in combination with ketoconazole (KCZ), dextromethorphan hydrobromide hydrate (DM), dexamethasone (DEX), lenalidomide hydrate (lenalidomide), or bortezomib (BTZ).

4.(ii).A.(1) Japanese clinical studies

4.(ii).A.(1).1) Japanese phase I study (5.3.3.2.4, Study B1101 [November 2006 to May 2008])

An open-label study was conducted to investigate the PK, etc. of panobinostat in 14 patients with advanced solid cancer or cutaneous T-cell lymphoma (CTCL) (13 patients included in the PK analysis). One treatment cycle consisted of 28 days. Panobinostat (10, 15, 20 mg) was administered orally once daily 3 times a week, to measure the plasma panobinostat concentration (the table below). The ratios of AUC on Day 15 to that on Day 1 were 1.23 to 1.89. The applicant explained that the limited number of patients in the study precluded a conclusion on the relationship between the dose of panobinostat and the PK parameters.

PK parameters of panobinostat

Dose (mg)	n	Day of measurement	C_{max} (ng/mL)	T_{max} [*1] (h)	$T_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (h·ng/mL)	AUC_{inf} (h·ng/mL)	CL/F (L/h)
10	3	1	20.5 (92.2)	1.0 (0.5, 2.0)	9.27, 22.3[*2]	36.5, 146[*2]	44.6, 214[*2]	46.7, 224[*2]
		15	19.4 (94.3)	1 (0.5, 4.0)	18.4 (34.0)	89.1 (67.4)	107, 247[*2]	40.4, 93.6[*2]
15	4	1	16.6 (68.8)	1.2 (0.5, 4.0)	9.16 (43.0)	67.4 (45.4)	79.0 (56.7)	230 (44.0)
		15	14.4 (29.5)	1.5 (0.4, 2.0)	17.8 (30.8)	88.5 (29.1)	133 (26.3)[*3]	118 (23.2)[*3]
20	6	1	10.8 (28.0)	1.5 (0.5, 3.0)	12.8 (40.0)	66.5 (43.2)	91.3 (47.7)[*3]	263 (54.6)[*3]
		15	11.6 (52.5)	2.0 (0.5, 8.0)	18.4 (27.2)[*4]	87.9 (46.4)	153 (37.6)[*5]	150 (45.8)[*5]

Arithmetic mean (coefficient of variation [CV]%), [*1] Median (range), [*2] Individual values, [3*] n = 3, [*4] n = 5, [*5] n = 4

4.(ii).A.(1).2) Japanese phase I study (5.3.3.2.1, Study A1101 [July 2008 to [redacted] 2009])

An open-label study was conducted to investigate the PK, etc. of panobinostat in 14 patients with advanced solid cancer. One treatment cycle consisted of 21 days. Panobinostat (10, 15, 20 mg/m^2) was administered intravenously once daily on Day 1 and Day 8 in each cycle, to measure plasma panobinostat concentration. The PK parameters of panobinostat following single-dose administration are shown in the following table. The applicant explained that the limited number of patients in the study precluded a conclusion on the relationship between the dose of panobinostat and the PK parameters.

PK parameters of panobinostat following single-dose administration

Dose (mg/m^2)	n	C_{max} (ng/mL)	T_{max} [*1] (h)	$T_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (h·ng/mL)	AUC_{inf} (h·ng/mL)	CL (L/h)
10	3	272 (15.7)	0.5 (0.5, 0.5)	16.8 (7.0)	220 (14.5)	274 (13.3)	54.1 (10.4)
15	3	496 (45.6)	0.5 (0.5, 0.5)	14.8, 19.0[*2]	483 (49.0)	385, 482[*2]	49.8, 57.6[*2]
20	8	493 (30.0)	0.5 (0.5, 0.6)	18.5 (11.5)	465 (21.0)	607 (21.8)	54.0 (23.7)

Arithmetic mean (CV%), [*1] Median (range), [*2] Individual values

4.(ii).A.(1).3) Japanese phase II study (5.3.5.4.1, Study B1201 [[redacted] 2008 to [redacted] 20[redacted]])

An open-label study was conducted to investigate the PK, etc. of panobinostat in 4 patients with CTCL or adult T cell leukemia (ATL). One treatment cycle consisted of 28 days. Panobinostat (20 mg) was administered orally once daily 3 times a week, to measure plasma panobinostat concentration (the table below). No clear accumulation of panobinostat with multiple administration was observed.

PK parameters of panobinostat

Day of measurement	n	C_{max} (ng/mL)	T_{max}^{*} (h)	$AUC_{0\text{-}24h}$ (h·ng/mL)	AUC_{inf} (h·ng/mL)
1	4	9.88 (32.0)	3.0 (1.6, 3.2)	115 (25.0)	121 (24.4)
8	3	10.4 (89.4)	3.0 (1.0, 3.0)	-	102 (86.7)

Arithmetic mean (CV%), - Not calculated, * Median (range)

4.(ii).A.(2) Global study

Global phase III study (5.3.5.1.1, Study D2308 [January 2010 – ongoing (data cut-off, September 10, 2013)])

A randomized, double-blind, placebo-controlled study was conducted to investigate the efficacy, safety, and PK of panobinostat in 768 patients with relapsed or refractory MM (13 patients included in the PK analysis).

One treatment cycle consisted of 21 days. Panobinostat (20 mg) was administered orally once daily 3 times a week for 2 weeks, followed by a 1-week washout period. BTZ (1.3 mg/m^2) was administered intravenously once daily on Days 1, 4, 8, and 11, and DEX (20 mg) orally once daily on Days 1, 2, 4, 5, 8, 9, 11, and 12. Data for PK parameter calculation were obtained in 13 of 18 Japanese patients receiving panobinostat. The PK data are shown in the following table.

PK parameters of panobinostat

Day of measurement	n	C_{max} (ng/mL)	T_{max}^{*} (h)	$AUC_{0\text{-}24h}$ (h·ng/mL)	AUC_{inf} (h·ng/mL)	$T_{1/2}$ (h)
1	13	10.8 (52.8)	2.00 (0.5, 4.0)	66.5 (33.8)	81.8 (34.5)	90.9 (35.0)
8	12	16.4 (41.4)	2.00 (0.5, 4.0)	98.4 (26.0)	123 (27.4)	141 (28.5)

Arithmetic mean (CV%), * Median (range)

4.(ii).A.(3) Foreign clinical studies

4.(ii).A.(3).1) Foreign phase I study (5.3.3.2.2, Study A2101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted to investigate the PK, etc. of panobinostat in 86 patients with advanced solid cancer or malignant lymphoma (76 patients included in PK analysis).

Panobinostat was administered by any of the following methods: (a) in each 21-day treatment cycle, panobinostat (1.2, 2.4, 4.8, 7.2, 9.0 mg/m^2) was administered intravenously once daily from Day 1 to Day 3 and from Day 8 to Day 10, (b) in each 28-day treatment cycle, panobinostat (2.4, 4.8, 9.6, 15.0, 20.0 mg/m^2) was administered intravenously once daily from Day 1 to Day 3 and from Day 15 to Day 17, or (c) in each 28-day treatment cycle, panobinostat (10, 15, 20 mg/m^2) was administered intravenously once daily on Days 1, 8, and 15. Plasma panobinostat concentration was measured in treated patients.

The PK parameters of panobinostat following a single-dose administration of panobinostat at 1.2 to 20 mg/m^2 are shown in the following table, with C_{max} and AUC_{inf} of panobinostat being generally dose-proportional within the dose range studied. In the once daily administration of panobinostat at 7.2 and 9.0 mg/m^2, the ratios of the geometric mean of AUC on Day 3 relative to that on Day 1 were 0.98 to 1.41, showing no clear accumulation of panobinostat with multiple administration.

PK parameters of panobinostat following single-dose administration

Dose (mg/m^2)	n	C_{max} (ng/mL)	T_{max}[*1] (h)	$T_{1/2}$ (h)	AUC_{0-24h} (h·ng/mL)	AUC_{inf} (h·ng/mL)	CL (L/h)
1.2[*8]	2	33.7, 40.9	0.5, 0.5	-	-	-	-
2.4	4	62.3 (9.6)	0.5 (0.3, 0.5)	-	-	-	-
4.8	4	78.8 (73.4)	0.5 (0.5, 0.8)	-	-	-	-
7.2	6[*9]	252 (14.6)	0.5 (0.5, 0.5)	9.8 (22.4)[*2]	234 (32.7)[*2]	258 (33.1)[*2]	55.6 (38.6)[*2]
9.0	8	291 (39.9)	0.5 (0.5, 0.6)	9.1 (27.8)[*3]	355 (27.8)	416 (21.2)[*3]	41.4 (29.6)[*3]
9.6[*8]	1	59.2	0.6				
10	7[*10]	419 (52.4)	0.5 (0.3, 0.6)	14.8 (21.4)	426 (22.0)	518 (21.9)	36.9 (21.8)
15	11	619 (25.1)	0.6 (0.3, 0.7)	14.6 (36.1)[*4]	749 (37.4)[*5]	913 (38.7)[*4]	35.7 (38.5)[*4]
20	31	784 (44.7)	0.5 (0.3, 0.7)	17.1 (27.4)[*6]	821 (37.5)[*7]	1041 (38.2)[*6]	45.2 (43.7)[*6]

Arithmetic mean (CV%), - Not calculated, [*1] Median (range), [*2] n = 5, [*3] n = 7, [*4] n = 9, [*5] n = 10, [*6] n = 26, [*7] n = 28, [*8] Individual values, [*9] One patient with abnormal C_{max} value (>2000 ng/mL) was excluded. [*10] One patient without the PK data was excluded.

4.(ii).A.(3).2) Foreign phase I/II study (5.3.3.2.3, Study A2102 [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted to investigate the PK, etc. of panobinostat in 15 patients with advanced hematological malignancy. In each 21-day treatment cycle, panobinostat (4.8, 7.2, 9.0, 11.5, 14.0 mg/m^2) was administered intravenously once daily from Day 1 to Day 7, to measure plasma panobinostat concentration. The PK parameters of panobinostat following a single-dose administration are shown in the following table. C_{max} and AUC_{inf} of panobinostat were generally dose-proportional within the dose range investigated. The ratios of the geometric mean of AUC on Day 5 or 7 relative to the value on Day 1 were 1.5 to 2.3, showing no clear accumulation of panobinostat with multiple administrations.

PK parameters of panobinostat following single-dose administration

Dose (mg/m^2)	n	C_{max} (ng/mL)	T_{max}[*1] (h)	$T_{1/2}$ (h)	AUC_{inf} (h·ng/mL)	CL (L/h)
4.8	3	182 (34.4)	0.4 (0.3, 0.5)	9.9, 11.3[*2]	182, 215[*2]	22.4, 26.3[*2]
7.2	3	121 (8.3)	0.5 (0.3, 0.7)	6.5, 9.5[*2]	153, 157[*2]	45.7, 47.2[*2]
9.0[*2]	1	201	0.5	13.9	241	37.4
11.5	3	249 (59.1)	0.5 (0.3, 0.6)	10.1, 15.5[*2]	315, 449[*2]	39.4 (39.3)
14.0	5	566 (79.7)	0.5 (0.3, 0.5)	12.0 (23.6)[*3]	460 (52.8)[*3]	36.4 (43.9)[*3]

Arithmetic mean (CV%), [*1] Median (range), [*2] Individual values, [*3] n = 4

4.(ii).A.(3).3) Foreign phase I study (5.3.3.2.5, Study B2101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted to investigate the PK, etc. of panobinostat in 95 patients with advanced solid cancer or non-Hodgkin's lymphoma (94 patients were included in the PK analysis). In each 28-day treatment cycle, (a) panobinostat (10, 15, 20, 30 mg) was administered orally once daily 3 times a week, (b) panobinostat (30, 45 mg) was administered orally once daily 3 times every other week, or (c) panobinostat (30, 45, 60 mg) was administered orally once daily twice a week, to measure plasma panobinostat concentration. The PK parameters of panobinostat following a single-dose administration of panobinostat at 10 to 60 mg are shown in the following table, with C_{max} and AUC_{inf} of panobinostat being generally dose-proportional within the dose range investigated.

PK parameters of panobinostat following single-dose administration

Dose (mg)	n	C_{max} (ng/mL)	T_{max}[*1] (h)	$T_{1/2}$ (h)	AUC_{0-24h} (h·ng/mL)	AUC_{inf} (h·ng/mL)	CL (L/h)
15	3	12.2 (65.4)	1.0 (0.5, 2.0)	-	192[*2]	-	-
20	36	23.6 (57.4)	1.0 (0.5, 4.5)	12.4 (36.6)[*3]	144 (55.3)	209 (56.5)[*3]	134 (59.7)[*3]
30	31[*8]	34.0 (56.3)	1.0 (0.5, 8.0)	13.4 (35.6)[*4]	212 (49.3)[*5]	264 (56.8)[*4]	136 (44.3)[*4]
45	17	48.6 (79.0)	1.0 (0.5, 4.0)	15.2 (18.1)[*6]	283 (43.9)	372 (32.6)[*6]	131 (27.7)[*6]
60	4	55.4 (39.6)	2.0 (1.0, 3.0)	16.8 (13.2)[*7]	317 (26.7)	454 (34.9)[*7]	142 (29.8)[*7]

Arithmetic mean (CV%), - Not calculated. Data at 10 mg (n = 1) are not included because PK parameter values were unavailable. [*1] Median (range), [*2] Individual values, [*3] n = 22, [*4] n = 16, [*5] n = 29, [*6] n = 9, [*7] n = 3, [*8] 2 patients without PK parameter data were excluded.

4.(ii).A.(3).4) Foreign phase I/II study (5.3.3.2.6, Study B2102 [March 2006 to [redacted] 2009])

An open-label study was conducted to investigate the PK, etc. of panobinostat in 176 patients with advanced hematological malignancy (140 patients included in the PK analysis). In each 28-day

treatment cycle, (a) panobinostat (20, 30, 40, 60, 80 mg) was administered orally once daily 3 times a week, or (b) panobinostat (30, 45, 60, 80 mg) was administered orally once daily 3 times a week every other week, to measure plasma panobinostat concentration. PK parameters of panobinostat following a single-dose administration are shown in the following table. C_{max} and AUC_{inf} of panobinostat were generally dose-proportional within the dose range investigated. However, the applicant explained that, with the increase in the dose of panobinostat, the absorption of panobinostat from the lower digestive tract may have decreased because of the relatively high pH in that region [see "4.(i).B.(2) Effect of gastrointestinal pH on PK of panobinostat"].

PK parameters of panobinostat following single-dose administration

Dose (mg)	n	C_{max} (ng/mL)	T_{max}[*1] (h)	$T_{1/2}$ (h)	AUC_{0-24h} (h·ng/mL)	AUC_{inf} (h·ng/mL)	CL/F (L/h)
20	9	19.5 (60.8)	2.1 (0.5, 3.1)	13.8 (48.2)[*2]	113 (57.5)[*2]	145 (58.8)[*2]	180 (48.8)[*2]
30	18[*13]	39.8 (69.1)	1.0 (0.5, 28.0)	18.2 (30.1)[*3]	211 (67.7)[*4]	272 (52.2)[*5]	158 (72.2)[*5]
40	24[*13]	58.0 (59.0)	0.8 (0.5, 3.1)	13.6 (24.0)[*6]	268 (72.5)	329 (76.8)[*7]	201 (77.3)[*7]
45	15[*14]	54.0 (52.6)	1.0 (0.5, 1.1)	19.7 (59.3)[*8]	244 (64.4)[*9]	290 (41.3)[*5]	179 (37.7)[*5]
60	53	66.9 (69.6)	1.0 (0.5, 45.7)	15.4 (26.9)[*10]	278 (61.5)[*11]	356 (63.6)[*10]	240 (58.1)[*10]
80	18	63.5 (57.7)	1.0 (0.5, 6.0)	14.6 (17.9)[*3]	295 (54.5)[*12]	397 (48.6)[*3]	246 (50.2)[*3]

Arithmetic mean (CV%,; [*1] Median (range), [*2] n = 7, [*3] n = 12, [*4] n = 17, [*5] n = 9, [*6] n = 23, [*7] n = 22, [*8] n = 10, [*9] n = 14, [*10] n = 44, [*11] n = 51, [*12] n = 16, [*13] One patient without PK parameter data was excluded. [*14] One patient who received 60 mg by mistake was excluded.

4.(ii).A.(3).5) Foreign phase I study (5.3.3.2.7, Study B2108 [[redacted] 20[redacted] to June 20[redacted]])

An open-label study was conducted to investigate the mass balance of panobinostat in 4 patients with advanced cancer. ^{14}C-labeled panobinostat (20 mg) was administered orally in a single dose under fasting conditions, to measure radioactivity in the whole blood and plasma and plasma concentrations of unchanged panobinostat and the metabolite M37.8 (reduced form of hydroxamic acid side chain). The PK parameters of radioactivity in plasma and blood are shown in the following table. T_{max} and $T_{1/2}$ of radioactivity in plasma were similar to those in blood, whereas C_{max} and AUC of radioactivity in blood were lower than those in plasma. Based on these results, the applicant explained that the distribution rate of panobinostat in blood cells is small.

PK parameters of radioactivity

Sample	C_{max} (ngEq/mL)	T_{max}[*] (h)	AUC_{0-168h} (h·ngEq/mL)	AUC_{inf} (h·ngEq/mL)	$T_{1/2}$ (h)
Blood	103 (34.0)	2.5 (1.5, 3.0)	5090 (33.6)	5850 (34.9)	54.5 (8.8)
Plasma	156 (25.7)	2.0 (1.50, 3.0)	7120 (17.8)	9030 (14.1)	68.6 (18.2)

n = 4, arithmetic mean (CV%), [*] Median (range)

The PK parameters of unchanged panobinostat and metabolite M37.8 (reduced form of hydroxamic acid side chain) are shown in the following table. The percentage of C_{max} and AUC of the unchanged panobinostat-derived radioactivity relative to the plasma radioactivity was 15.6% and 1.2%, respectively. The percentage of AUC of M37.8-derived radioactivity relative to that of the unchanged panobinostat-derived radioactivity was approximately 60%, when calculated on a molar basis. Urinary and fecal excretion rates of radioactivity (% of the administered radioactivity) up to 7 days after administration were 40.6% and 54.3%, respectively, whereas the urinary and fecal excretion rates of unchanged panobinostat were very low (1.9% and 0.82%, respectively). Based on the results, the applicant explained that panobinostat is eliminated mainly by metabolism and renal excretion contributes only minimally to the elimination of unchanged panobinostat.

PK parameters of panobinostat and metabolite M37.8

Analyte	C_{max} (ng/mL)	T_{max}[*] (h)	AUC_{last} (h·ng/mL)	AUC_{inf} (h·ng/mL)	$T_{1/2}$ (h)
Panobinostat	24.3 (49.4)	0.8 (0.5, 1.0)	107 (40.7)	112 (38.4)	30.6 (7.8)
M37.8	1.18 (93.2)	3.0 (1.0, 24)	58 (108.6)	-	-

n = 4, arithmetic mean (CV%), - Not calculated, [*] Median (range)

4.(ii).A.(3).6) Foreign phase I study (5.3.5.2.2, Study B2207 [October 2007 – ongoing (data cut-off, [redacted], 20[redacted])])

An open-label study was conducted to investigate the safety, etc. of panobinostat with concomitant BTZ (dose escalation cohort) and panobinostat with concomitant BTZ and DEX (expansion cohort) in 47 patients with relapsed or refractory MM (40 patients included in the PK analysis).

In the dose escalation cohort, panobinostat (10, 20, 25, 30 mg) was administered orally once daily 3 times a week and BTZ (1.0, 1.3 mg/m^2) intravenously once daily on Days 1, 4, 8, and 11, in each 21-day treatment cycle. In the expansion cohort, panobinostat (20 mg) was administered orally once daily 3 times a week for 2 weeks, followed by a 1-week washout period, and BTZ (1.3 mg/m^2) was administered once daily according to the schedule used in the dose escalation cohort, in each 21-day treatment cycle. Starting from Cycle 2, 20 mg DEX was administered orally once daily on Days 1, 2, 4, 5, 8, 9, 11, and 12.

The PK parameters of panobinostat and BTZ in the dose escalation cohort are shown in the following table. C_{max} and AUC of panobinostat increased with the increase of the dose of panobinostat. In the panobinostat 20 mg group, the difference in BTZ dose (1.0 or 1.3 mg/m^2) had no clear effect on the PK of panobinostat. According to the applicant, the PK parameters of BTZ significantly varied among individuals, and no consistent trend was observed in the values between BTZ 1.0 mg/m^2 and BTZ 1.3 mg/m^2; this suggests that the difference in panobinostat dose had no clear effect on the PK of BTZ.

PK parameters of panobinostat in dose escalation cohort

Dose of each drug		Day of measurement	n	C_{max} (ng/mL)	T_{max}[*1] (h)	AUC_{0-24h} (h·ng/mL)	AUC_{inf} (h·ng/mL)	$T_{1/2}$ (h)
Panobinostat (mg)	BTZ (mg/m^2)							
10	1.0	8	4	3.5 (10.8)	2.0 (1.0, 2.0)	24.1 (33.0)	27.9 (55.3)	7.4 (90.0)
		15	4	4.8 (68.8)	1.0 (0.5, 2.8)	22.9 (34.3)	23.9 (54.7)	6.2 (68.1)
20	1.0	8	6	10.8 (125.5)	2.4 (1.0, 3.0)	87.5 (100.2)	132.8 (108.5)[*2]	13.8 (3.3)[*2]
		15	4[*3]	7.6 (50.6)	2.0 (1.0, 3.9)	59.4 (32.4)	104.2 (74.5)	14.4 (56.7)
	1.3	8	15[*3]	15.8 (63.2)	1.0 (0.1, 6.0)	89.1 (58.8)	119.7 (71.8)	13.2 (65.6)
		15	14[*3]	12.2 (103.3)	1.8 (0.5, 3.0)	75.9 (83.6)	103.5 (103.7)	14.1 (62.3)
25	1.3	8	7[*3]	18.0 (47.6)	2.0 (0.5, 3.0)	106.4 (31.6)	150.3 (40.6)	15.1 (26.4)
		15	7[*3]	12.0 (105.4)	2.0 (0.9, 6.0)	83.7 (103.8)	101.8 (166.0)	10.8 (60.5)
30	1.3	8	5[*3]	14.5 (74.8)	1.0 (1.0, 3.0)	102.8 (45.0)	163.1 (34.2)	18.7 (41.4)
		15	4[*3]	19.8 (109.6)	1.8 (0.5, 3.5)	136.3 (88.5)	192.1 (81.1)	14.9 (23.4)

Geometric mean (CV%); BTZ, Bortezomib; [*1] Median (range); [*2] n = 5; [*3] Patients without PK parameter data were excluded.

PK parameters of BTZ in dose escalation cohort on Day 8

Dose	n[*1]	C_{max} (ng/mL)	T_{max}[*2] (h)	AUC_{0-24h} (h·ng/mL)
Panobinostat 10 mg + BTZ 1.0 mg/m^2	4	72.7 (49.5)	0.1 (0.1, 0.2)	55.9 (29.3)
Panobinostat 20 mg + BTZ 1.0 mg/m^2	7	179.5 (223.3)	0.1 (0, 0.1)	95.9 (74.1)
Panobinostat 20 mg + BTZ 1.3 mg/m^2	14	157.9 (65.5)	0.1 (0, 1.3)	117.2 (58.8)
Panobinostat 25 mg + BTZ 1.3 mg/m^2	4	101.9 (26.5)	0.1 (0.1, 0.1)	88.6 (38.9)
Panobinostat 30 mg + BTZ 1.3 mg/m^2	5	76.8 (43.1)	0.1 (0.1, 0.1)	77.1 (16.4)

Geometric mean (CV%); BTZ, Bortezomib; [*1] 34 subjects with at least 1 evaluable PK parameter value during the study period were subjected to analysis. [*2] Median (range)

In the expansion cohort, the PK parameters of panobinostat and BTZ were as shown in the following table. AUC_{0-24h} of panobinostat with concomitant DEX (Day 8 in Cycle 2) was approximately 20% lower than that without DEX (Day 8 in Cycle 1). The applicant explained that, given panobinostat is metabolized mainly by CYP3A4 [see "3.(ii).A.(3).1) *In vitro* metabolism"], the metabolism of panobinostat may have been enhanced by the CYP3A-inducing effect of DEX.

PK parameters of panobinostat and BTZ (expansion cohort)

DEX	Dose	Analyte	n	C_{max} (ng/mL)	T_{max}* (h)	AUC_{0-24h} (h·ng/mL)	$T_{1/2}$ (h)
Not used	Panobinostat 20 mg /BTZ 1.3 mg/m^2	Panobinostat	15	9.5 (60.4)	2.0 (0.5, 3.0)	61.8 (60.9)	13.3 (34.7)
		BTZ		107.9 (114.6)	1.0 (0.1, 0.5)	91.7 (87.5)	-
Used	Panobinostat 20 mg /BTZ 1.3 mg/m^2 /DEX 20 mg	Panobinostat	12	8.1 (90.3)	1.0 (0.5, 6.3)	47.5 (76.8)	15.9 (29.2)
		BTZ		81.4 (87.7)	0.1 (0.1, 1.0)	94.7 (40.0)	-

Geometric mean (CV%); - not calculated; DEX, dexamethasone; BTZ, bortezomib; * median (range)

4.(ii).A.(4) Drug-drug interactions

4.(ii).A.(4).1) Study on drug-drug interactions with dextromethorphan hydrobromide hydrate (DM) (5.3.3.4.1, Study B2109 [November 2007 to January 2009])

An open-label study was conducted to investigate the effect of panobinostat on the PK of DM (a substrate for CYP2D6) in 17 patients with advanced or metastatic solid cancer.

Panobinostat (20 mg) was administered orally once daily on Days 3, 5, and 8, and DM (60 mg) orally once daily on Days 1 and 8. Drug-drug interactions were investigated in patients for whom CYP2D6 genotype was determined as intermediate metabolizer, extensive metabolizer, or ultra metabolizer and patients in whom the ratio of AUC_{0-48h} of plasma dextrorphan (*O*-demethylated form of DM) to that of plasma DM was <0.3.

The geometric mean ratios [90% CI] for C_{max} and AUC_{inf} of DM in the combination with panobinostat versus DM alone were 1.83 [1.44, 2.34] and 1.64 [1.17, 2.31], respectively. In contrast, concomitant use of panobinostat did not affect T_{max} or $T_{1/2}$ of DM. Based on the result that concomitant use of panobinostat increased the exposure to a CYP2D6 substrate, the applicant explained that caution should be given on the use of panobinostat in combination with a CYP2D6 substrate with a narrow therapeutic range.

4.(ii).A.(4).2) Study on drug-drug interactions with KCZ (5.3.3.4.2, Study B2110 [September 2007 to April 2010])

An open-label study was conducted to investigate the effect of KCZ (a potent CYP3A inhibitor) on the PK of panobinostat in 14 patients with advanced solid cancer.

Panobinostat (20 mg) was administered orally once daily on Days 1 and 8, and KCZ (400 mg) orally once daily from Day 5 to Day 9.

The geometric mean ratios [90% CI] for C_{max} and AUC_{inf} of panobinostat in combination with KCZ versus panobinostat alone were 1.62 [1.21, 2.17] and 1.78 [1.45, 2.18], respectively. CYP3A-induced metabolism was thus estimated to account for 43.8% of total oral clearance. In contrast, concomitant KCZ did not affect T_{max} or $T_{1/2}$ of panobinostat. The applicant explained that since concomitant use of a potent CYP3A inhibitor was shown to increase panobinostat exposure, caution should be given on the combination therapy.

The effect of CYP3A4 and CYP3A5 genotypes on the PK of panobinostat was also investigated in this study. The CYP3A5 genotypes identified were a homozygote of *CYP3A5*3* (**3/*3*, inactive type) in 11 of 14 patients and a heterozygote of *CYP3A5*3* and *CYP3A5*1* (**1/*3*, wild type) in 3 of 14 patients. There was no clear difference either in C_{max} or in AUC following panobinostat monotherapy between patients with **3/*3* and **1/*3* genotypes. On the other hand, the CYP3A4 genotype identified in all of the 14 patients was a homozygote of *CYP3A4*1A* (wild type). Therefore the effect of different CYP3A4 genotypes on the PK of panobinostat could not be investigated.

4.(ii).A.(5) Foreign phase I study in patients with hepatic impairment (5.3.3.3.1, Study X2101 [March 2010 to November 2012])

An open-label study was conducted to investigate the effect of hepatic impairment on the PK of panobinostat following a single oral doses of panobinostat 30 mg in fed state in 10 patients with

advanced solid cancer having normal hepatic function and 15 patients with advanced solid cancer having mild, moderate, or severe hepatic impairment (8, 6, and 1 patient, respectively).

As compared with in patients with normal hepatic function, panobinostat C_{max} in patients with mild, moderate, and severe hepatic impairment was higher by 57%, 83%, and 69%, respectively, and AUC_{inf} higher by 43%, 105%, and 81%, respectively (the table below). Plasma concentration of M37.8, a metabolite of panobinostat, was investigated in patients with normal hepatic function or with mild, moderate, or severe hepatic impairment. The AUC ratios for M37.8 versus unchanged panobinostat were 1.2, 0.62, 1.0, and 0.70, respectively, showing no clear difference among the patient groups.

PK parameters of panobinostat in patients with hepatic impairment

Severity of hepatic impairment[*1]	n	C_{max} (ng/mL)	T_{max}[*2] (h)	$T_{1/2}$ (h)	AUC_{inf} (h·ng/mL)	$AUC_{0\text{-}48h}$ (h·ng/mL)
Normal	10	18.5 (81.2)	2.0 (0.5, 7.0)	28.8 (27.3)	150 (72)	125 (70)
Mild	7	29.1 (57.3)	2.0 (0.5, 4.0)	26.3 (27.6)	215 (56)	184 (54)
Moderate	6	33.9 (50.9)	2.0 (1.0, 4.0)	34.6 (31.5)	308 (44)	250 (43)
Severe	1	31.2	2	19.9	272	235

Geometrical mean (CV%); [*1] Normal, total bilirubin (TBI) ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) ≤ ULN; mild, ULN < TBI ≤ 1.5 × ULN, or TBI ≤ ULN and AST > ULN; moderate, 1.5 × ULN < TBI ≤ 3 × ULN; severe, 3 × ULN < TBI ≤ 10 × ULN; [*2] Median (range)

4.(ii).A.(6) Foreign phase I study in patients with renal impairment (5.3.3.3.2, Study X2105 [March 2010 – ongoing (data cut-off, [redacted], 20[redacted])])

An open-label study was conducted to investigate the effect of renal impairment on the PK of panobinostat following a single oral doses of panobinostat 30 mg in fed state in 11 patients with advanced solid cancer patients having normal renal function and 26 patients with advanced solid cancer having mild, moderate, or severe renal impairment (10, 10 and 6 patients, respectively).

C_{max} and AUC_{inf} of panobinostat did not tend to be higher in patients with renal impairment than in patients with normal renal function. $T_{1/2}$ values were similar regardless of the severity of the renal impairment (the table below). Plasma concentrations of M37.8 were investigated in patients with normal renal function or mild, moderate, or severe renal impairment. The AUC ratios for M37.8 versus unchanged panobinostat were 0.64, 0.81, 1.13, and 1.20, respectively, showing no clear difference among patient groups.

PK parameters of panobinostat in patients with renal impairment

Severity of renal impairment[*1]	n	C_{max} (ng/mL)	T_{max}[*2] (h)	$T_{1/2}$ (h)	AUC_{inf} (h·ng/mL)	$AUC_{0\text{-}48h}$ (h·ng/mL)
Normal	11	31.0 (117)	1.02 (0.5, 4.0)	29.3 (56.9)	225 (99)	189 (88)
Mild	10	18.2 (68.6)	1.0 (0.5, 4.3)	33.1 (26.0)	144 (62)	118 (67)
Moderate	10	29.6 (92.5)	1.0 (0.5, 2.0)	33.0 (21.5)	223 (77)	177 (77)
Severe	6	14.0 (82.2)	0.75 (0.5, 4.0)	27.5 (23.8)	132 (50)	111 (49)

Geometric mean (CV%); [*1] Severe, creatinine clearance (CLcr) <30 mL/min; moderate, ≥30 mL/min and <50 mL/min; mild, ≥50 mL/min and <80 mL/min; normal, ≥80 mL/min; [*2] Median (range)

4.(ii).A.(7) Study on the relationship between exposure and QT/QTc interval

In the foreign phase I/II study (Study A2102), the incidence of prolonged QTc interval tended to increase with dose. Based on the results of 12 clinical studies in which panobinostat was administered orally (Studies B1101, B2101, B2102, B2201, B2202, B2203, B2211, B2109, B2110, B2111, X2101, and X2105), the relationship between plasma panobinostat concentrations and changes from baseline in QT interval corrected for heart rate by Fridericia method (QTcF) was analyzed using a linear mixed effect model. No clear relationship was observed between panobinostat concentrations and QTcF when panobinostat was administered 3 times a week. On the other hand, QTcF tended to be prolonged with dose when panobinostat was administered 3 times a week every other week, twice a week every week, or in a single dose. It was predicted that when the maximum plasma panobinostat concentration (C_{max}) was 20, 50, or 65 ng/mL, which would be achieved following the oral doses of 20, 40, and 60 mg panobinostat, respectively [see "4.(ii).A.(3).3) Foreign phase I study" and "4.(ii).A.(3).4) Foreign phase

I/II study"], QTcF would be 1.07 to 5.96, 3.14 to 12.87, and 4.18 to 16.33 msec, respectively. Based on the findings, the applicant explained that panobinostat may prolong QT intervals.

4.(ii).A.(8) Population pharmacokinetic (PPK) analysis

Based on the PK data (7834 time points in 581 patients) obtained from Japanese and foreign phase I and II studies (Studies A2101, A2102, B1101, B1201, B2101, B2102, B2201, B2202, B2203, B2211, B2109, B2110, B2111, and E2214), a population pharmacokinetic (PPK) analysis was performed using a non-linear mixed effect model (software, NONMEM extended version VI). The PK of panobinostat was described using a 3-compartment model with the first-order absorption process.

In this analysis, the following were investigated: (a) the effects of sex, age, body surface area, race (Caucasian, Black, Asian, other), cancer type (solid cancer, hematological malignancy), and baseline laboratory values (hepatic function [TBI, AST], renal function [CLcr]) on CL and distribution volume of the central compartment (V2), (b) the effects of the drug preparation on Ka and F, and (c) the effects of concomitant medications (drugs with QT-prolonging effect, CYP2D6 substrates, CYP3A4/5 substrates, potent CYP3A4/5 inhibitors or inducers, 5-hydroxytryptamine 3 receptor [5-HT_3] blockers) on CL. As a result, age, body surface area, and race were selected as significant covariates for CL and V2. The effect of covariates on CL and V2 were as shown below. However, the applicant explained that given the extent of the inter-individual variability of CL and V2 estimated by the final model (coefficient of variation (CV), 65.3% and 57.8%, respectively), the effects of age, body surface area, and race on CL and V2 are clinically insignificant.

- CL and V2 of panobinostat were estimated to be 21% and 27% lower, respectively, in patients with a 1.5 m^2 body surface area than in typical patients (body surface area, 1.9 m^2), and to be 12% and 25% lower, respectively, in 30-year-old patients than in typical patients (61 years old).

- Assuming the body surface area to be 1.9 m^2, CL of panobinostat was estimated to be 17% higher in Asians, 1% higher in Blacks, and 28% lower in other races than in Caucasians. V2 of panobinostat was estimated to be higher by 37%, 24%, and 13%, respectively. When the body surface area of Caucasians and Asians was assumed to be 1.9 and 1.7 m^2, respectively, CL and V2 of panobinostat were estimated to be 4.7% and 17.7% higher, respectively, in Asians than in Caucasians.

4.(ii).A.(9) Relationship between exposure versus efficacy and safety

4.(ii).A.(9).1) Relationship between exposure and efficacy

The relationship between panobinostat exposure and efficacy was investigated based on the results of Study B2207. When panobinostat (10, 20 mg) was administered orally once daily 3 times a week in combination with BTZ (1.0 mg/m^2), $AUC_{0\text{-}24h}$ (geometric means) of panobinostat on Day 15 in Cycle 1 was 22.9 h·ng/mL (10 mg dose) and 59.4 h·ng/mL (20 mg dose). The response rates according to the criteria of the International Myeloma Working Group (IMWG) were 14.3% (1 of 7 patients, 10 mg dose) and 28.6% (2 of 7 patients, 20 mg dose), tending to increase with increasing $AUC_{0\text{-}24h}$ of panobinostat. When panobinostat (20, 25, 30 mg) was administered orally once daily 3 times a week in combination with BTZ (1.3 mg/m^2), $AUC_{0\text{-}24h}$ (geometric means) of panobinostat on Day 15 in Cycle 1 was 75.9 h·ng/mL (20 mg dose), 83.7 h·ng/mL (25 mg dose), and 136.3 h·ng/mL (30 mg dose). The response rates were 52.9% (9 of 17 patients, 20 mg dose), 55.6% (5 of 9 patients, 25 mg dose), and 57.1% (4 of 7 patients, 30 mg dose), showing no increase with increasing $AUC_{0\text{-}24h}$ of panobinostat.

No clear relationship was observed between C_{max} following the first dose in 13 Japanese patients included in the PK analysis in the global phase III study (Study D2308) and the response rates assessed by the investigator based on the modified criteria established by the European Society for Blood and Marrow Transplantation (EBMT) [see "4.(iii).A. *Evaluation data* (2) Global study"].

4.(ii).A.(9).2) Relationship between exposure and safety

The most frequently reported Grade ≥3 adverse event was thrombocytopenia in Study D2308. Therefore, a relationship between plasma panobinostat concentration and decreased platelet count was investigated based on the results of 14 Japanese and foreign clinical studies in patients with cancer (Studies A2101, A2102, B1101, B1201, B2101, B2102, B2109, B2110, B2111, B2201, B2202, B2203, B2211, and E2214) using a PPK model and an indirect response model, which is a pharmacodynamic model that

assumes that panobinostat inhibits platelet formation. Assuming the baseline platelet counts to be 266 × 10^9/L, platelet counts following the 4-week treatment with 30, 40, and 60 mg panobinostat 3 times every week or every other week were simulated. According to the estimation, the lowest platelet counts following treatment 3 times every week were 134 × 10^9/L (30 mg dose), 116 × 10^9/L (40 mg dose), and 85 × 10^9/L (30 mg dose), and those following treatment 3 times every other week were 178 × 10^9/L (30 mg dose), 162 × 10^9/L (40 mg dose), and 140 × 10^9/L (60 mg dose).

The applicant explained that these results suggest that platelet count decreases with increasing plasma panobinostat concentration.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Difference in the PK of panobinostat between Japanese and non-Japanese patients

The applicant explained the difference in the PK of panobinostat between Japanese and non-Japanese patients as follows:

The difference in the PK of panobinostat between Japanese and non-Japanese patients was investigated based on the PK data of panobinostat obtained from Japanese clinical studies (Studies B1101 and B1201) and foreign clinical studies (Studies B2101, B2102, B2201, B2202, B2203, B2211, B2109, B2110, B2111, X2101, and X2105) (the table below). In studies with limited sampling points, the mean $AUC_{0\text{-}24h}$ was similar for Japanese and non-Japanese patients, whereas in studies with dense sampling points, the mean $AUC_{0\text{-}24h}$ was lower in Japanese patients than in non-Japanese patients. Furthermore, difference in the PK of panobinostat in combination with BTZ and DEX between Japanese and non-Japanese patients was investigated based on the PK data of panobinostat obtained in Studies D2308 and B2207 [see "4.(ii).A.(2) Global study" and "4.(ii).A.(3).6) Foreign phase I study"]. The mean C_{max} and $AUC_{0\text{-}24h}$ of panobinostat in Japanese patients were higher by 55% and 70%, respectively, as compared with non-Japanese patients.

As explained, the investigations failed to provide consistency in the difference between Japanese and non-Japanese patients in the mean C_{max} or AUC of panobinostat. The inconsistency may be due to the significantly large inter-individual variability in the PK of panobinostat both in Japanese and non-Japanese patients. The distribution patterns of the individual values (range) of C_{max} and AUC of panobinostat were similar for Japanese patients (7.7-34.5 ng/mL and 55.0-138 h·ng/mL, respectively) and non-Japanese patients (2.7-35.5 ng/mL and 12.7-134 h·ng/mL, respectively). The applicant considered that there is no clear difference in the PK of panobinostat between Japanese and non-Japanese patients.

$AUC_{0\text{-}24h}$ following the oral administration of panobinostat (20 mg) in Japanese and non-Japanese patients

Method of blood sampling*	Race	n	$AUC_{0\text{-}24h}$ (h·ng/mL)	
			Arithmetic mean (CV%)	Median (range)
Dense sampling	Japanese	6	67 (43.2)	64 (36, 108)
	Non-Japanese	79	126 (59.1)	115 (29, 423)
Limited sampling	Japanese	4	115 (28.7)	109 (87.1, 155)
	Non-Japanese	160	105 (53.7)	94 (8, 286)

* Sampling at 5 time points within 24 hours after administration was handled as "limited sampling" and sampling at >5 time points as "dense sampling."

PMDA considers as follows:

Although the submitted data do not suggest a clear difference in the PK of panobinostat between Japanese and non-Japanese patients, information on the possible difference in the PK of panobinostat between Japanese and non-Japanese patients should be further collected through various sources including published articles.

4.(ii).B.(2) Pharmacokinetic interactions

The study on drug-drug interactions with KCZ showed that panobinostat exposure increased when panobinostat was administered in combination with a potent CYP3A inhibitor [see "4.(ii).A.(4).2) Study on drug-drug interactions with KCZ"]. Therefore, PMDA asked the applicant to explain the necessity to conduct a clinical study to investigate the pharmacokinetic interactions of panobinostat mediated by CYP3A induction.

The applicant responded as follows:
From the reasons described below, it is clear that panobinostat exposure decreases when a potent CYP3A inducer is administered concomitantly. Additional clinical studies are therefore considered unnecessary for the investigation of the pharmacokinetic interactions of panobinostat mediated by CYP3A induction.

- Panobinostat is metabolized mostly by CYP3A. CYP3A-mediated metabolism is considered to account for approximately 44% of oral clearance of panobinostat [see "4.(ii).A.(4).2) Study on drug-drug interactions with KCZ"].

- In Study B2207, concomitant DEX, a CYP3A-inducing agent, decreased AUC of panobinostat approximately by 20% [see "4.(ii).A.(3).6) Foreign phase I study"].

PMDA asked the applicant to explain the effect of a concomitant potent CYP3A inducer on the PK and efficacy of panobinostat.

The applicant responded as follows:
The effect of a potent CYP3A inducer rifampicin on the PK of panobinostat was investigated. The analysis was based on the physiological pharmacokinetic model used in the study on the effect of panobinostat on the PK of midazolam [see "3.(ii).A.(5).1) Enzyme inhibition"]. The results predicted that concomitant rifampicin would decrease AUC of panobinostat by approximately 70%, which suggested that panobinostat exposure decreases when panobinostat is administered in combination with a potent CYP3A inducer. The AUC ratios for panobinostat following dual combination (panobinostat + rifampicin) or triple combination (panobinostat + rifampicin + DEX) versus panobinostat monotherapy was estimated based on the above-mentioned model. The ratios were estimated to be 0.42 both in the dual and triple combination, suggesting that concomitant DEX does not clearly affect panobinostat exposure in the presence of a potent CYP3A inducer.

The use of the above-mentioned model was considered appropriate, based on the results of the following studies.

- Panobinostat exposure following the panobinostat (20 mg) combination therapy with KCZ (400 mg) was investigated under the same dosing conditions as in the foreign phase I study (Study B2110). The AUC ratio of panobinostat following the combination therapy with KCZ relative to that following the panobinostat monotherapy was predicted to be 1.78, which was generally consistent with the AUC ratio actually observed in Study B2110 (geometric mean ratio, 1.78) [see "4.(ii).A.(4).2) Study on drug-drug interactions with KCZ"].

- Based on the physiological pharmacokinetic model mentioned earlier, panobinostat exposure following the panobinostat (20 mg) combination therapy with DEX* (20 mg) was investigated under the same dosing conditions as in Study B2207. The AUC ratio of panobinostat in combination with DEX versus panobinostat alone was predicted to be 0.85, which was generally consistent with the AUC ratio actually observed in Study B2207 (geometric mean ratio, 0.77) [see "4.(ii).A.(3).6) Foreign phase I study"].

  * A physiological pharmacokinetic model was constructed taking account of the PK and CYP3A-inducing effect of DEX, by referring to the results of the clinical study on interactions between triazolam and DEX (*Pharmacol Toxicol.* 1998;83:135-8).

The effect of a potent CYP3A inducer on the PK and efficacy of panobinostat was investigated in Study D2308. The median progression-free survival (PFS) was shorter in the patient cohort receiving a concomitant potent CYP3A inducer (5.65 months in the panobinostat group [9 patients] and 4.86 months in the placebo group [11 patients]) than in the patient cohort not receiving the concomitant CYP3A inducer (12.25 months in the panobinostat group [378 patients] and 8.31 months in the placebo group [371 patients]). These results suggest that the efficacy of panobinostat may be attenuated by a concomitant potent CYP3A inducer.

PMDA considers as follows:
A concomitant potent CYP3A inducer is expected to decrease plasma panobinostat concentration, and available data suggest that the efficacy of panobinostat is attenuated when it is used in combination with a potent CYP3A inducer. Therefore, the dose of panobinostat may need to be increased when used with a potent CYP3A inducer. However, since no study data are currently available on the dose adjustment of panobinostat in combination with a potent CYP3A inducer, the combination of panobinostat and a potent CYP3A inducer should be avoided as much as possible.

The above information should be appropriately provided to healthcare professionals through the package insert, etc.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The efficacy and safety evaluation data were as follows: the results from 2 Japanese phase I studies, 1 global phase III study, 9 foreign phase I studies, 1 foreign phase I/II study, and 1 foreign phase II study. The reference data were as follows: the results from 1 Japanese phase II study, 1 foreign phase I study, 1 foreign phase I/II study, and 5 foreign phase II studies.

List of clinical studies on efficacy and safety

Data category	Region	Study identifier	Phase	Population	No. of enrollment	Dosage regimen	Primary endpoints
Evaluation	Japan	A1101	I	Patients with advanced solid cancer	14	Panobinostat (10, 15, 20 mg/m^2) was administered intravenously once daily on Days 1 and 8 in each 21-day treatment cycle.	Safety PK
		B1101	I	Patients with advanced solid cancer or CTCL	14	Panobinostat (10, 15, 20 mg) was administered orally once daily 3 times a week.	Safety PK
	Global	D2308	III	Patients with relapsed or refractory MM	768 (a) 387 (b) 381	Treatment Phase 1 (Cycle 1-8): In each 21-day treatment cycle, panobinostat (20 mg) (a) or placebo (b) was administered orally once daily on Days 1, 3, 5, 8, 10, and 12, in combination with intravenous BTZ (1.3 mg/m^2) once daily on Days 1, 4, 8, and 11, and with oral DEX (20 mg) once daily on Days 1, 2, 4, 5, 8, 9, 11, and 12. Treatment Phase 2 (Cycle 9-16): In each 21-day treatment cycle, panobinostat (20 mg) (a) or placebo (b) was administered orally once daily on Days 1, 3, 5, 8, 10, and 12, in combination with intravenous BTZ (1.3 mg/m^2) once daily on Days 1 and 8, and with oral DEX (20 mg) once daily on Days 1, 2, 8, and 9.	Efficacy Safety PK
	Foreign	A2101	I	Patients with advanced solid cancer or malignant lymphoma	86	21-day treatment cycle Group 1: Panobinostat (1.2, 2.4, 4.8, 7.2, 9 mg/m^2) was administered intravenously once daily from Day 1 to Day 3 and from Day 8 to Day 10. Group 4: Panobinostat (20, 25 mg/m^2) was administered intravenously once daily on Days 1 and 8. 28-day treatment cycle Group 2: Panobinostat (2.4, 4.8, 9.6, 15, 20 mg/m^2) was administered intravenously once daily from Day 1 to Day 3 and from Day 15 to Day 17. Group 3: Panobinostat (10, 15, 20 mg/m^2) was administered intravenously once daily on Days 1, 8, and 15.	Safety PK
		A2102	I/II	Patients with advanced hematological malignancy	15	In each 21-day treatment cycle, panobinostat (4.8, 7.2, 9.0, 11.5, 14.0 mg/m^2) was administered intravenously once daily from Day 1 to Day 7.	Safety PK
		B2101	I	Patients with advanced solid cancer or non-Hodgkin's lymphoma	95	Group 1: Panobinostat (10, 15, 20, 30 mg) was administered orally once daily 3 times a week. Group 3: Panobinostat (30, 45 mg) was administered orally once daily 3 times every other week. Group 4a: Panobinostat (20 mg) was administered orally once daily 3 times a week. Group 5: Panobinostat (30, 45, 60 mg) was administered orally once daily twice a week. Group 6: Panobinostat (20 mg) was administered orally once daily 3 times a week. The dosage regimen for Groups 2 and 4b had been planned to be determined based on the MTD, etc., in Group 1 and Group 5, respectively, but as a result, patient enrollment in these groups were cancelled.	Safety PK
		B2108	I	Patients with advanced cancer	4	^{14}C-labeled panobinostat (20 mg) was administered orally in a single dose, followed by oral panobinostat (20 mg) once daily 3 times a week.	Safety PK
		B2109	I	Patients with advanced or metastatic solid cancer	17	Panobinostat (20 mg) was administered orally once daily on Days 3, 5, and 8. Dextromethorphan (60 mg) was administered orally once daily on Days 1 and 8. Then, panobinostat (20 mg) was administered orally once daily 3 times a week.	Safety PK
		B2110	I	Patients with advanced solid cancer	14	Panobinostat (20 mg) was administered orally once daily on Days 1 and 8. Ketoconazole (400 mg) was administered orally once daily from Day 5 to Day 9. Then, panobinostat (20 mg) was administered orally once daily 3 times a week.	Safety PK
		B2111	I	Patients with advanced solid cancer	36	Panobinostat (20 mg) was administered orally once daily twice a week. Then, panobinostat (45 mg) was administered orally once daily twice a week.	Safety PK

List of clinical studies on efficacy and safety

Data category	Region	Study identifier	Phase	Population	No. of enrollment	Dosage regimen	Primary endpoints
		B2207	I	Patients with relapsed or refractory MM	62 (a) 47 (b) 15	(a) Dose escalation cohort: In each 21-day treatment cycle, panobinostat (10, 20, 25, 30 mg) was administered orally once daily 3 times a week in combination with intravenous BTZ (1.0, 1.3 mg/m^2) once daily on Days 1, 4, 8, and 11. (b) Expansion cohort: In each 21-day treatment cycle, panobinostat (20 mg) was administered orally once daily on Days 1, 3, 5, 8, 10, and 12 in combination with intravenous BTZ (1.3 mg/m^2) once daily on Days 1, 4, 8, and 11. From Cycle 2, DEX (20 mg) was administered orally once daily on Days 1, 2, 4, 5, 8, 9, 11, and 12.	Safety PK
		X2101	I	Advanced solid cancer patients with hepatic impairment	25	Single-dose Phase: Panobinostat (30 mg) was administered orally in a single dose. Extension Phase: Panobinostat (30 mg) was administered orally once daily 3 times a week.	Safety PK
		X2105	I	Advanced solid cancer patients with renal impairment	37	Single-dose Phase: Panobinostat (30 mg) was administered orally in a single dose. Extension Phase: Panobinostat (30 mg) was administered orally once daily 3 times a week.	Safety PK
		DUS71	II	Patients with BTZ-refractory MM	55	Treatment Phase 1 (Cycle 1-8): In each 21-day treatment cycle, panobinostat (20 mg) was administered orally once daily on Days 1, 3, 5, 8, 10, and 12 in combination with intravenous BTZ (1.3 mg/m^2) once daily on Days 1, 4, 8, and 11, and with oral DEX (20 mg) once daily on Days 1, 2, 4, 5, 8, 9, 11, and 12. Treatment Phase 2 (Cycle 9-16): In each 21-day treatment cycle, panobinostat (20 mg) was administered orally once daily on Days 1, 3, 5, 8, 10, and 12 in combination with intravenous BTZ (1.3 mg/m^2) once daily on Days 1 and 8, and with oral DEX (20 mg) once daily on Days 1, 2, 8, and 9.	Efficacy Safety
Reference	Japan	B1201	II	Patients with CTCL and ATL	4	Panobinostat (20 mg) was administered orally once daily 3 times a week.	Safety PK
	Foreign	B2102	I/II	Patients with advanced hematological malignancy	176	Group 1: Panobinostat (20, 30, 40, 60, 80 mg) was administered orally once daily 3 times a week. Group 2: Panobinostat (30, 45, 60, 80 mg) was administered orally once daily 3 times every other week.	Safety PK
		B2206	I	Patients with relapsed MM	46	In each 28-day treatment cycle, panobinostat (5, 10, 20, 25 mg) was administered orally once daily 3 times a week in combination with oral Lenalidomide (25 mg) once daily from Day 1 to Day 21, and with oral DEX (40 mg) once daily from Day 1 to Day 4, from Day 9 to Day 12, and from Day 17 to Day 20 (from Day 1 to Day 4 in Cycle 5 and succeeding cycles).	Safety
		B2201	II	Patients with CTCL	139	Panobinostat (20 mg) was administered orally once daily 3 times a week.	Safety PK
		B2202	II	Patients with CML	29	Panobinostat (20 mg) was administered orally once daily 3 times a week.	Safety PK
		B2203	II	Patients with refractory MM	38	Panobinostat (20 mg) was administered orally once daily 3 times a week.	Safety PK
		B2211	II	Patients with CML	27	Panobinostat (20 mg) was administered orally once daily 3 times a week.	Safety PK
		E2214	II	Patients with Hodgkin's lymphoma	129	Panobinostat (40 mg) was administered orally once daily 3 times a week.	Safety PK

MM, multiple myeloma; BTZ, Bortezomib; DEX, Dexamethasone; Lenalidomide, Lenalidomide hydrate; CTCL, cutaneous T-cell lymphoma; ATL, adult T cell leukemia; CML, chronic myeloid leukemia; MTD, maximum tolerated dose

The outline of each clinical study is described below.

Major adverse events other than death reported in each clinical study are described in “4.(iv) Adverse events, etc. observed in clinical studies,” and PK study data in “4.(i) Summary of biopharmaceutic studies and associated analytical methods” and in “4.(ii) Summary of clinical pharmacology studies.”

Evaluation data

(1) Japanese clinical studies

1) Japanese phase I study (5.3.3.2.1, Study A1101 [July 2008 to ■ 2009])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced solid cancer (target sample size, 9-18) in 3 medical institutions in Japan.

In each 21-day treatment cycle, panobinostat (10, 15, 20 mg/m^2) was administered intravenously once daily on Days 1 and 8.

All 14 patients enrolled in the study received panobinostat and were included in the safety analysis set.

Dose-limiting toxicity (DLT) was evaluated in Cycle 1; Grade 3 γ-glutamyl transferase increased reported by 1 patient in the 20 mg/m^2 group was identified as DLT.

No death occurred during the treatment period or within 28 days after the last dose.

2) Japanese phase I study (5.3.3.2.4, Study B1101 [November 2006 to May 2008])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced solid cancer or CTCL (target sample size, 9-18) in 3 medical institutions in Japan.

In each 28-day treatment cycle, panobinostat (10, 15, 20 mg) was administered orally once daily 3 times a week.

Of 14 patients enrolled in the study, 13 patients received panobinostat and were included in the safety analysis set. DLT was evaluated in Cycle 1. No DLT was observed in any groups, with all doses not reaching the maximum tolerated dose (MTD).

No death occurred during the treatment period or within 28 days after the last dose.

(2) Global study

Global phase III study (5.3.5.1.1, Study D2308 [January 2010 – ongoing (data cut-off, September 10, 2013)])

A double-blind, placebo-controlled, randomized, comparative study was conducted to investigate the efficacy, safety, and PK of panobinostat in combination with BTZ and DEX in patients with relapsed or refractory MM (target sample size, 762) in 194 medical institutions in 34 countries or regions including Japan.

The study consisted of Treatment Phases 1 and 2. Patients who were rated as no change (NC) or better based on the modified EBMT criteria* in Cycle 8 of Treatment Phase 1 proceeded to Treatment Phase 2. Treatment Phase 1 consisted of eight 21-day cycles. Panobinostat (20 mg) or placebo was administered orally once daily on Days 1, 3, 5, 8, 10, and 12, in combination with intravenous BTZ (1.3 mg/m^2) once daily on Days 1, 4, 8, and 11, and with oral DEX (20 mg) once daily on Days 1, 2, 4, 5, 8, 9, 11, and 12. Treatment Phase 2 also consisted of eight 21-day cycles. Panobinostat (20 mg) or placebo was administered orally once daily on Days 1, 3, 5, 8, 10, and 12, in combination with intravenous BTZ (1.3 mg/m^2) once daily on Days 1 and 8, and with oral DEX (20 mg) once daily on Days 1, 2, 8, and 9.

* The modified EBMT criteria (*Br J Haematol.* 1998;102:1115-23) includes a new efficacy classification of "near CR (nCR)" that requires all criteria of complete response (CR) except "absence of serum and urine monoclonal immunoglobulin (M protein) cannot be confirmed by immunofixation."

All of the 768 patients who were enrolled in the study and randomized (387 patients in the panobinostat + BTZ + DEX group [panobinostat group], 381 patients in the placebo + BTZ + DEX group [placebo group]) were included in the full analysis set (FAS) and subjected to the efficacy analysis. Of these, 758 patients who received at least 1 dose of the study drug (panobinostat, placebo, BTZ, or DEX) (381 patients in the panobinostat group, 377 patients in the placebo group) were included in the safety analysis set.

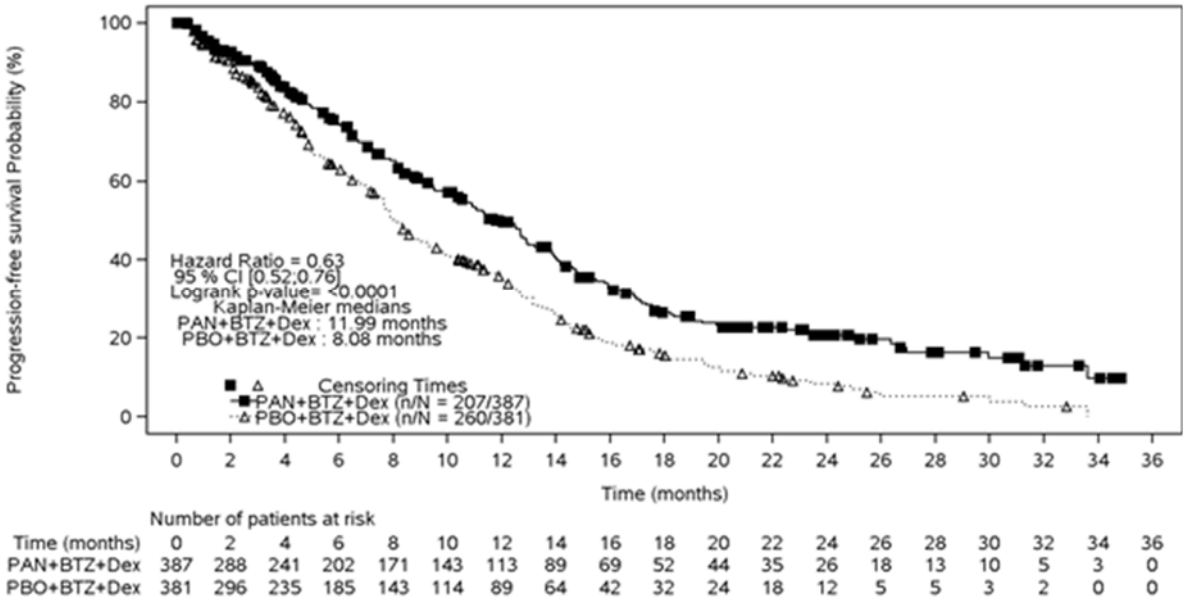
The primary efficacy endpoint was progression-free survival (PFS) assessed by the investigator based on the modified EBMT. In this study, 2 interim analyses were planned. The first interim analysis aimed to evaluate the non-usefulness of the therapy when 33% of the target number of 460 events occurred, and the second to evaluate the efficacy when 80% of the target number of 460 events occurred. Based on the first interim analysis, the independent data monitoring committee (IDMC) recommended to continue the study. The study was continued without the planned second interim analysis because it could have overlap with the final analysis. The probability of the type 1 error associated with the conduct of the interim analysis was adjusted using α-spending function of O'Brien-Fleming type based on Lan-DeMets method.

The final PFS analysis results are shown in the following table and figure, showing the superiority of panobinostat to placebo.

Final PFS analysis results (assessed by investigator, FAS, data cut-off, September 10, 2013)

	Panobinostat	Placebo
Number of patients	387	381
Number of death or aggravation (%)	207 (53.5%)	260 (68.2%)
Median [95% CI] (months)	11.99 [10.32, 12.94]	8.08 [7.56, 9.23]
Hazard ratio[*1] [95% CI]	0.63 [0.52, 0.76]	
P value (two-sided)[*2, *3]	<0.0001	

[*1] Cox proportional hazard model adjusted for stratification factors (number of prior treatment regimens, presence/absence of prior BTZ therapy), [*2] Stratified log-rank test (stratified by the number of prior treatment regimens and presence/absence of prior BTZ therapy),
[*3] Two-sided significance level of 0.0458 (cancelled second interim analysis taken into consideration)



Kaplan-Meier curves of PFS (assessed by investigator, FAS, data cut-off, September 10, 2013)

The safety analysis revealed that 30 of 381 patients (7.9%) in the panobinostat group and 18 of 377 patients (4.8%) in the placebo group died during the treatment period or within 28 days after the last dose. The causes of death were, in the panobinostat group, disease progression (4 patients), septic shock (3 patients), myocardial infarction, renal failure acute, and respiratory failure (2 patients each), cardiac arrest, myocardial ischaemia, gastrointestinal haemorrhage, intestinal ischaemia, death, bronchopneumonia, lung infection, pneumonia, pulmonary tuberculosis, toxicity to various agents, cerebral haemorrhage, cerebrovascular accident, acute respiratory failure, lung disorder, pulmonary haemorrhage, pulmonary oedema, and shock haemorrhagic (1 patient each); and, in the placebo group, disease progression (6 patients), pneumonia (3 patients), cardiac arrest, cardio-respiratory arrest, cardiopulmonary failure, necrotising fasciitis, neutropenic sepsis, brain injury, haemorrhage intracranial, acute respiratory failure, and pulmonary embolism (1 patient each). A causal relationship to the study drug could not be ruled out for myocardial infarction, lung infection, pneumonia, pulmonary

tuberculosis, acute respiratory failure, pulmonary haemorrhage, and shock haemorrhagic (1 patient each) in the panobinostat group, and haemorrhage intracranial and pneumonia (1 patient each) in the placebo group.

(3) Foreign clinical studies

1) Foreign phase I study (5.3.3.2.2, Study A2101 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced solid cancer or malignant lymphoma (target sample size; approximately 68-104 patients each in Groups 1 and 2, approximately 38-44 patients in Group 3, 20 patients in Group 4) in 4 medical institutions overseas.

In Group 1, panobinostat (1.2, 2.4, 4.8, 7.2, 9.0 mg/m^2) was administered intravenously once daily on Day 1 to Day 3 and Day 8 to Day 10 of each 21-day treatment cycle. In Group 2, panobinostat (2.4, 4.8, 9.6, 15.0, 20.0 mg/m^2) was administered intravenously once daily on Day 1 to Day 3 and Day 15 to Day 17 of each 28-day treatment cycle. In Group 3, panobinostat (10.0, 15.0, 20.0 mg/m^2) was administered intravenously once daily on Days 1, 8, and 15 of each 28-day treatment cycle. In Group 4, panobinostat (20.0, 25.0 mg/m^2) was administered intravenously once daily on Days 1 and 8 of each 21-day treatment cycle.

A total of 86 patients (23 in Group 1, 7 in Group 2, 47 in Group 3, 9 in Group 4) were enrolled in the study. All patients treated with panobinostat were included in the safety analysis set.

DLT was evaluated in Cycle 1. In Group 1, DLT was observed in 1 of 7 patients receiving 7.2 mg/m^2 (Grade 2 thrombocytopenia [1 patient]) and in 5 of 8 patients receiving 9.0 mg/m^2 (Grade 4 thrombocytopenia [3 patients], Grade 3 neutropenia, Grade 4 neutropenia, Grade 3 hyperbilirubinaemia [1 patient each, a single patient may have had more than one events]). Based on this, MTD was determined to be 7.2 mg/m^2. In Group 2, DLT was observed in 1 of 1 patient receiving 20 mg/m^2 (Grade 4 torsade de pointes, Grade 3 sinus bradycardia, Grade 3 vomiting, Grade 3 dehydration, Grade 4 febrile neutropenia). Based on this, 20.0 mg/m^2 was judged to exceed MTD, and MTD was not determined. In Group 3, DLT was observed in 1 of 8 patients receiving 20.0 mg/m^2 (Grade 4 thrombocytopenia). Based on this, MTD was determined to be 20.0 mg/m^2. In Group 4, DLT was observed in 1 of 3 patients receiving 25.0 mg/m^2 (Grade 3 fatigue) and in 1 of 6 patients receiving 20.0 mg/m^2 (Grade 3 fatigue, Grade 3 QT prolonged), but MTD was not determined in this group.

The safety analysis revealed that 8 of 86 patients (9.3%) died during the treatment period or within 28 days after the last dose. The fatal cases occurred in 1 of 23 patients (4.3%) in Group 1, 1 of 7 patients (14.3%) in Group 2, 6 of 47 patients (12.8%) in Group 3, and none in Group 4. The causes of the deaths were disease progression (1 patient) in Group 1, disease progression (1 patient) in Group 2, disease progression (4 patients) in Group 3, and pneumonia and sepsis (1 patient each) in Group 4. A causal relationship to panobinostat was ruled out for all causes of the deaths.

2) Foreign phase I/II study (5.3.3.2.3, Study A2102 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced haematological malignancy (target sample size, 99-141) in 3 medical institutions overseas.

In each 21-day treatment cycle, panobinostat (4.8, 7.2, 9.0, 11.5, 14.0 mg/m^2) was administered intravenously once daily on Day 1 to Day 7.

All 15 patients enrolled in the study were included in the safety analysis set.

DLT was evaluated in Cycle 1. DLT was observed in 1 of 3 patients receiving 11.5 mg/m^2 (Grade 3 QT prolonged) and in 5 of 5 patients receiving 14.0 mg/m^2 (Grade 3 QT prolonged [3 patients], Grade 3 bilateral pleural effusion, and staphylococcal sepsis [1 patient each]). This study was discontinued before MTD was determined.

The safety analysis revealed that 1 of 15 patients (6.7%) died during the treatment period or within 28 days after the last dose. The death was caused by staphylococcal sepsis, and a causal relationship to panobinostat could not be ruled out.

3) Foreign phase I study (5.3.3.2.5, Study B2101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced solid cancer or non-Hodgkin's lymphoma (target sample size: Dose Escalation Phase, maximum 15 patients in Group 1, 2, 3, and 5 each; expansion cohort, 35 patients in Group 1, 20 patients in Group 2, 20 patients in Group 3, 20-40 patients in Group 4a/b, 30-40 patients in Group 5, 20-40 patients in Group 6) in 5 medical institutions overseas.

One treatment cycle consisted of 28 days. In Group 1, panobinostat (10, 15, 20, 30 mg) was administered orally once daily 3 times a week. In Group 2, panobinostat was administered orally once every day at the dose determined based on the DLT, MTD, and PK profiles in Group 1. In Group 3, panobinostat (30, 45 mg) was administered orally once daily 3 times every other week. In Group 4a, panobinostat was administered orally at MTD determined in Group 1 at the same dosing schedule as in Group 1. In Group 4b, panobinostat was administered orally at MTD and dosage regimen in Group 5. In Group 5, panobinostat (30, 45, 60 mg) was administered orally once daily twice a week. In Group 6, panobinostat was administered orally at MTD in Group 1 at the same dosing schedule as in Group 1.

A total of 95 patients (47 in Group 1, 23 in Group 3, 2 in Group 4a, 22 in Group 5, 1 in Group 6) were enrolled in the dose escalation phase and in the expansion cohort of the study. In Group 1, 1 patient was enrolled in the study twice and received the treatment twice. Therefore, the data of the second treatment in this patient were excluded from the analysis. Taking account of QTc prolonged observed in Study A2101 and the incidence of decreased platelet count in Study B2101, patient enrollment in Group 2 or Group 4b was cancelled.

DLT was evaluated in Cycle 1. In Group 1, DLT was observed in 2 of 10 patients receiving 30 mg (Grade 3 diarrhoea, Grade 4 thrombocytopenia [1 patient each]). Based on this, MTD was determined to be 20 mg. In Group 3, DLT was observed in 2 of 2 patients receiving 45 mg (Grade 4 thrombocytopenia [2 patients]). Based on this, MTD was determined to be 30 mg. In Group 5, DLT was observed in 2 of 6 patients receiving 45 mg (Grade 3 fatigue, Grade 3 QT prolonged [1 patient each]) and in 1 of 4 patients receiving 60 mg (Grade 4 thrombocytopenia). Based on this, MTD was determined to be 45 mg.

The safety analysis revealed that 12 of 94 patients (12.8%) died during the treatment period or within 28 days after the last dose. The breakdown by dosage regimen was as follows: 5 of 49 patients (10.2%) treated 3 times a week (Groups 1, 4a, 6); 2 of 23 patients (8.7%) treated 3 times every other week (Group 3); and 5 of 22 patients (22.7%) treated twice a week (Group 5). The causes of the deaths were mycosis fungoides (2 patients), prostate cancer, renal cell carcinoma, and leiomyosarcoma (1 patient each) in Groups 1, 4a, and 6; metastatic breast cancer and mesothelioma (1 patient each) in Group 3; and adenocarcinoma pancreas, non-Hodgkin's lymphoma, metastatic breast cancer, metastatic oesophageal carcinoma, and metastatic neoplasm (1 patient each) in Group 5. A causal relationship to panobinostat was ruled out for all causes of the deaths.

4) Foreign phase I study (5.3.3.2.7, Study B2108 [[redacted] 20[redacted]to June 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced caner (target sample size, 4-6) in 2 medical institutions overseas.

^{14}C-labeled panobinostat (20 mg) was administered orally in a single dose. Then, unlabeled panobinostat (20 mg) was administered orally once daily 3 times a week in each 28-day treatment cycle.

No death occurred during the treatment period or within 28 days after the last dose.

5) Foreign phase I study (5.3.3.4.1, Study B2109 [November 2007 to January 2009])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced or metastatic solid cancer (target sample size, 24) in 5 medical institutions overseas.

Panobinostat (20 mg) was administered orally once daily on Days 3, 5, and 8, and DM (60 mg) orally once daily on Days 1 and 8, followed by oral panobinostat (20 mg) once daily 3 times a week.

The safety analysis revealed that 3 of 16 patients (18.8%) died during the treatment period or within 28 days after the last dose. The causes of the deaths were cerebral haemorrhage, respiratory failure, and ovarian cancer (1 patient each). A causal relationship to the study drug was ruled out for all causes of the deaths.

6) Foreign phase I study (5.3.3.4.2, Study B2110 [September 2007 to April 2010])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced solid cancer (target sample size, 24) in 2 medical institutions overseas.

Panobinostat (20 mg) was administered orally once daily on Days 1 and 8, and KCZ (400 mg) orally once daily from Day 5 to Day 9, followed by oral panobinostat (20 mg) once daily 3 times a week.

The safety analysis revealed that 1 of 13 patients (7.7%) died during the treatment period or within 28 days after the last dose. The death was caused by myocardial infarction. A causal relationship to the study drug was ruled out.

7) Foreign phase I study (5.3.1.1.1, Study B2111 [[redacted] 2007 to February 2011])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced solid cancer (target sample size, 36) in 9 medical institutions overseas.

Panobinostat (20 mg) was administered orally once daily twice a week during the PK evaluation period and, if the treatment was well tolerated during the PK evaluation period, panobinostat was continued at 45 mg once daily twice a week.

The safety analysis revealed that 2 of 36 patients (5.6%) died during the treatment period or within 28 days after the last dose. The deaths were caused by disease progression (2 patients), and a causal relationship to the study drug was ruled out for both patients.

8) Foreign phase I study (5.3.5.2.2, Study B2207 [October 2007 – ongoing (data cut-off, [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in combination with BTZ in patients with relapsed or refractory MM (target sample size; 47 patients in the dose escalation cohort, 12-15 patients in the expansion cohort) in 14 medical institutions overseas.

In the dose escalation cohort, panobinostat (10, 20, 25, 30 mg) was administered orally once daily 3 times every week, and BTZ (1.0, 1.3 mg/m^2) intravenously once daily on Days 1, 4, 8, and 11, in each 21-day treatment cycle. Treatment in the expansion cohort was as follows: In Cycle 1 (21days), panobinostat (20 mg) was administered orally once daily 3 times a week for 2 weeks, followed by a 1-week washout period, and BTZ (1.3 mg/m^2) was administered intravenously once daily on Days 1, 4, 8, and 11. From Cycle 2 onward, DEX (20 mg) was administered orally once daily on Days 1, 2, 4, 5, 8, 9, 11, and 12, in addition to panobinostat and BTZ.

All 47 patients enrolled in the dose escalation cohort and all 15 patients enrolled in the expansion cohort received panobinostat and were included in the safety analysis set.

In the dose escalation cohort, DLT was observed in 3 of 15 patients receiving panobinostat 20 mg and BTZ 1.3 mg/m^2 (Grade 4 thrombocytopenia, Grade 3 vomiting, Grade 3 orthostatic hypotension [1 patient each]), in 2 of 6 patients receiving panobinostat 25 mg and BTZ 1.3 mg/m^2 (Grade 2 tumour lysis syndrome, Grade 4 thrombocytopenia [1 patient each]), and in 4 of 6 patients receiving panobinostat 30 mg and BTZ 1.3 mg/m^2 (Grade 4 thrombocytopenia [2 patients], Grade 3 fatigue, Grade 3 weakness, Grade 2 anorexia, Grade 2 asthenia, Grade 2 fatigue [1 patient each]). Based on this, MTD was determined to be 20 mg for panobinostat and 1.3 mg/m^2 for BTZ.

The safety analysis revealed that 2 of 47 patients (4.3%) in the dose escalation cohort and in 2 of 15 patients (13.3%) in the expansion cohort died during the treatment period or within 28 days after the last dose. The deaths were due to the primary disease (2 patients) in the dose escalation cohort and ischaemic stroke and injury (1 patient each) in the expansion cohort. A causal relationship to the study drug was ruled out for all events.

9) Foreign phase I study (5.3.3.3.1, Study X2101 [March 2010 to November 2012])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced solid cancer, including patients with hepatic impairment (target sample size, 22-28) in 6 medical institutions overseas.

In the single-dose phase, panobinostat (30 mg) was administered orally in a single dose. In the extension phase, panobinostat (30 mg) was administered orally once daily 3 times a week in each 28-day treatment cycle.

All of the 25 patients enrolled in the study received panobinostat and were included in the safety analysis set. A total of 10 patients were free from hepatic impairment. Among the others, hepatic impairment was mild in 8 patients, moderate in 6 patients, and severe in 1 patient.

The safety analysis revealed that 5 of 25 patients (20.0%) died during the treatment period or within 28 days after the last dose. The causes of the deaths were disease progression (3 patients), and pulmonary oedema and metastatic prostate cancer (1 patient each). A causal relationship to panobinostat was ruled out for all causes of the deaths.

10) Foreign phase I study (5.3.3.3.2, Study X2105 [March 2010 – ongoing (data cut-off, [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced solid cancer, including patients with renal impairment (target sample size, 36) in 5 medical institutions overseas.

In the Single-dose Phase, panobinostat (30 mg) was administered orally in a single dose. In the Extension Phase, panobinostat (30 mg) was administered orally once daily 3 times a week in each 28-day treatment cycle.

All of the 37 patients enrolled in the study received panobinostat and were included in the safety analysis set. A total of 11 patients were free from renal impairment. Among the others, renal impairment was mild in 10 patients, moderate in 10 patients, and severe in 6 patients.

The safety analysis revealed that 3 of 37 patients (8.1%) died during the treatment period or within 28 days after the last dose. The causes of the deaths were choroid melanoma, arteriosclerosis, and disease progression (1 patient each). A causal relationship to panobinostat was ruled out for all causes of the deaths.

11) Foreign phase II study (5.3.5.2.1, Study DUS71 [June 2010 – ongoing (data cut-off, [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of panobinostat in combination with BTZ and DEX in patients with BTZ-refractory* MM (target sample size; ≥24 patients in Stage 1, 23 patients in Stage 2) in 12 medical institutions overseas.

* Patients with disease progression found during or within 60 days after the last dose of the most recent therapy including BTZ

The study consisted of Stage 1 and Stage 2. If ≥4 of the first 24 patients in Stage 1 responded to the treatment, the study was to proceed to Stage 2. Treatment Phase 1 consisted of eight 21-day treatment cycles: panobinostat (20 mg) was administered orally once daily on Days 1, 3, 5, 8, 10, and 12 of each treatment cycle, BTZ (1.3 mg/m^2) intravenously once daily on Days 1, 4, 8, and 11, and DEX (20 mg) orally once daily on Days 1, 2, 4, 5, 8, 9, 11, and 12. Treatment Phase 2 consisted of eight 21-day

treatment cycles: panobinostat (20 mg) was administered orally once daily on Days 1, 3, 5, 8, 10, and 12 of each treatment cycle, BTZ (1.3 mg/m^2) intravenously once daily on Days 1 and 8, and DEX (20 mg) orally once daily on Days 1, 2, 8, and 9.

All 55 patients enrolled in the study received at least 1 dose of the study drug (panobinostat, BTZ, or DEX) and were included in the FAS and the safety analysis set.

According to the modified EBMT criteria, the primary efficacy endpoint of the response rate [95% CI] at the end of Cycle 8 was 34.5% [22.2%, 46.7%]. The tumor regression effect was as shown in the following table.

Tumor regression effect* (assessed by investigator, FAS, N = 55)

	Number of patients (%)
Best overall response	
CR	0
nCR	1 (1.8)
Partial response (PR)	18 (32.7)
Minor Response (MR)	10 (18.2)
No change (NC)	20 (36.4)
Relapse after CR	0
Progressive disease (PD)	3 (5.5)
Unknown	3 (5.5)
Response (CR, nCR, or PR) (response rate [%])	19 (34.5)

* Modified EBMT criteria [see "4.(iii).A. *Evaluation data* (2) Global study"]

The safety analysis revealed that 4 of 55 patients (7.3%) died during the treatment period or within 28 days after the last dose. The causes of the deaths were plasma cell myeloma (3 patients) and multi-organ failure (1 patient). A causal relationship to the study drug was ruled out for all causes of death.

Reference data

(1) Japanese clinical study

Japanese phase II study (5.3.5.4.1, Study B1201 [[redacted] 2008 to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the efficacy, safety, and PK of panobinostat in patients with CTCL or ATL (target sample size; ≥14 patients with CTCL, ≥21 patients with ATL) in 8 medical institutions in Japan.

In each 28-day treatment cycle, panobinostat (20 mg) was administered orally once daily 3 times a week.

All 4 patients enrolled in the study received panobinostat and were included in the safety analysis set.

No death occurred during the treatment period or within 28 days after the last dose. This study was terminated prematurely because of skin ulcer reported by 3 of 4 patients [see "4.(iii).B.(3).13) Skin ulcer"].

(2) Foreign clinical studies

1) Foreign phase I/II study (5.3.3.2.6, Study B2102 [March 2006 to [redacted] 2009])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with advanced haematological malignancy (maximum target sample size, 308 patients) in 7 medical institutions overseas.

In each 28-day treatment cycle, panobinostat (20, 30, 40, 60, 80 mg) was administered orally once daily 3 times a week in Group 1, and panobinostat (30, 45, 60, 80 mg) orally once daily 3 times every other week in Group 2.

A total of 176 patients enrolled in the study (120 in Group 1, 56 in Group 2) received panobinostat and were included in the safety analysis set.

The safety analysis revealed that 42 of 176 patients (23.9%) died during the treatment period or within 28 days after the last dose. The causes of the deaths were disease progression (31 patients), pneumonia,

sepsis, and multi-organ failure (2 patients each), and septic shock, pulmonary haemorrhage, respiratory failure, cerebrovascular accident, and renal failure (1 patient each). A causal relationship to the study drug could not be ruled out for pulmonary haemorrhage and multi-organ failure (1 patient each).

2) Foreign phase I study (5.3.5.4.5, Study B2206 [April 2008 to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the safety and PK of panobinostat in patients with relapsed MM (target sample size, ≥12) in 10 medical institutions overseas.

In each 28-day treatment cycle, panobinostat (5, 10, 20, 25 mg) was administered orally once daily on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26, and lenalidomide (25 mg) orally once daily from Day 1 to Day 21, followed by washout from Day 22 to Day 28. DEX (40 mg) was concomitantly administered orally once daily from Day 1 to Day 4, from Day 9 to Day 12, and from Day 17 to Day 20 in Cycle 1 to Cycle 4, and from Day 1 to Day 4 from Cycle 5 onward.

All 46 patients enrolled in the study were included in the safety analysis set.

The safety analysis revealed that 7 of 46 patients (15.2%) died during the treatment period or within 28 days after the last dose. The causes of the deaths were respiratory failure (3 patients), myocardial infarction, bronchial disorder, multi-organ failure, and intestinal perforation (1 patient each). A causal relationship to the study drug could not be ruled out for respiratory failure and multi-organ failure (1 patient each).

3) Foreign phase II study (5.3.5.4.2, Study B2201 [January 2007 – ongoing (data cut-off, [redacted] [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the efficacy, safety, and PK of panobinostat in patients with CTCL (target sample size, 118) in 41 medical institutions overseas.

Panobinostat (20 mg) was administered orally once daily 3 times a week.

All 139 patients enrolled in the study were included in the safety analysis set.

The safety analysis revealed that 6 of 139 patients (4.3%) died during the treatment period or within 28 days after the last dose. The causes of the deaths were infection, death, sudden cardiac death, septic shock, sepsis, and cardiac arrest (1 patient each). A causal relationship with the study drug could not be ruled out for cardiac arrest.

4) Foreign phase II study (5.3.5.4.3: Study B2202 [[redacted] 2007 through September 2008])

An open-label, uncontrolled study was conducted to investigate the efficacy, safety, and PK of panobinostat in patients with chronic myeloid leukemia (CML) (target sample size, 120) in 19 medical institutions overseas.

In each 28-day treatment cycle, panobinostat (20 mg) was administered orally once daily 3 times a week.

All 29 patients enrolled in the study were included in the safety analysis set.

No death occurred during the treatment period or within 28 days after the last dose.

5) Foreign phase II study (5.3.5.4.4, Study B2203 [April 2007 to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the efficacy, safety, and PK of panobinostat in patients with refractory MM (target sample size; 36 patients in Stage 1, 36 patients in Stage 2) in 16 medical institutions overseas. A total of 36 patients were enrolled in Stage 1 and, if ≥4 patients responded to the treatment, 36 patients were to be enrolled in Stage 2.

In each 21-day treatment cycle, panobinostat (20 mg) was administered orally once daily 3 times a week.

All 38 patients enrolled in the study were included in the safety analysis set.

The safety analysis revealed that 3 of 38 patients (7.9%) died during the treatment period or within 28 days after the last dose. The cause of the deaths was disease progression in all fatal cases and a causal relationship to the study drug was ruled out.

6) Foreign phase II study (5.3.5.4.6, Study B2211 [February 2007 to August 2008])
An open-label, uncontrolled study was conducted to investigate the efficacy, safety, and PK of panobinostat in patients with CML (target sample size, 71) in 20 medical institutions overseas.

In each 28-day treatment cycle, panobinostat (20 mg) was administered orally once daily 3 times a week.

All 27 patients enrolled in the study were included in the safety analysis set.

The safety analysis revealed that 6 of 27 patients (22.2%) died during the treatment period or within 28 days after the last dose. The causes of the deaths were disease progression (3 patients), multi-organ failure, respiratory failure, and haemorrhagic cerebral infarction (1 patient each). A causal relationship to the study drug was ruled out for all events.

7) Foreign phase II study (5.3.5.4.7, Study E2214 [September 2008 to [redacted] 20[redacted]])
An open-label, uncontrolled study was conducted to investigate the efficacy, safety, and PK of panobinostat in patients with Hodgkin's lymphoma (target sample size, 102) in 45 medical institutions overseas.

In each 21-day treatment cycle, panobinostat (40 mg) was administered orally once daily 3 times a week.

All of the 129 patients enrolled in the study were included in the safety analysis set.

The safety analysis revealed that 3 of 129 patients (2.3%) died during the treatment period or within 28 days after the last dose. The causes of the deaths were disease progression (2 patients) and septic shock (1 patient). A causal relationship to the study drug was ruled out for all events.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Data for review

PMDA decided that the global phase III study (Study D2308) in patients with relapsed or refractory MM was most important for evaluating the efficacy and safety of panobinostat. The agency therefore focused on Study D2308 in the review of panobinostat.

4.(iii).B.(2) Efficacy

Based on the following review, PMDA has concluded that panobinostat is effective in patients with relapsed or refractory MM.

4.(iii).B.(2).1) Control group

The applicant explained the rationale for the use of placebo + BTZ + DEX as control in Study D2308 as follows:
At the time when Study D2308 was planned, monotherapy with BTZ, lenalidomide, or thalidomide, etc. and the combination therapy with BTZ and DEX were recommended as therapeutic options for patients with relapsed or refractory MM in foreign countries (*Haematologica.* 2006;91:929-34, *Haematologica.* 2007;92:1149-50, *Eur J Haematol.* 2009;83:449-54) (the US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma [NCCN Guidelines] [version 2, 2009]). In Japan, BTZ was approved with indications for patients with relapsed or refractory MM. Also, the Japanese guidelines recommended the combination therapy with BTZ and DEX as a therapeutic option, as it was in foreign countries (the Clinical Practice Guidelines for Multiple Myeloma, second edition, edited by Japanese Society of Myeloma [Bunkodo Co., Ltd., 2008]).

The applicant considered that the use of BTZ + DEX as the control was appropriate in Study D2308 in patients with relapsed or refractory MM.

PMDA accepted the explanation of the applicant.

4.(iii).B.(2).2) Primary endpoint

The applicant explained the appropriateness of the primary endpoint (PFS assessed by the investigator) used in Study D2308, as follows:

MM is a relapsing disease that is refractory to existing therapies. The response duration has been reported to decrease with each successive regimen (*Mayo Clin Proc.* 2004;79:867-74). Prolonged PFS can delay a subsequent regimen against disease progression and is expected to contribute to prolonged overall survival (OS). Also, PFS is recognized as a surrogate for OS in Japan and other countries (*Leukemia.* 2008;22:231-9, General Rules for the Clinical and Pathological Studies on Tumors of Hematopoietic and Lymphoid Tissues, first edition, edited by the Japanese Society of Hematology and the Japanese Society for Lymphoreticular Tissue Research [Kanehara & Co., Ltd., 2010]). Based on these findings, the applicant considered that PFS was a clinically significant endpoint and therefore used PFS as the primary endpoint for Study D2308 in patients with relapsed or refractory MM.

PMDA considered that the explanation of the applicant was reasonable. However, due to the absence of a standard therapy, OS is also an important parameter in the evaluation of the therapeutic effect on relapsed or refractory MM. PMDA therefore decided to evaluate the efficacy of panobinostat based primarily on PFS, with reference to the OS results.

4.(iii).B.(2).3) Efficacy

Panobinostat was shown to be superior to placebo in PFS assessed by the investigator based on the modified EBMT criteria, the primary endpoint of Study D2308 [see "4.(iii).A. *Evaluation data* (2) Global study"].

The results of the interim OS analysis,[*1] a secondary endpoint, are shown in the following table, and the Kaplan-Meier curves of OS in the figure just below the table. An additional OS analysis[*2] revealed that OS events occurred in 169 of 387 patients (43.7%) in the panobinostat group and 190 of 381 patients (49.9%) in the placebo group. The median OS [95% CI] was 38.24 [34.63, 45.37] months in the panobinostat group and was 35.38 [29.37, 39.92] months in the placebo group, failing to show significant statistical difference (stratified log-rank test, $P = 0.1783$, two-sided significance level of 1×10^{-7}, data cut-off, [redacted], 20[redacted]).

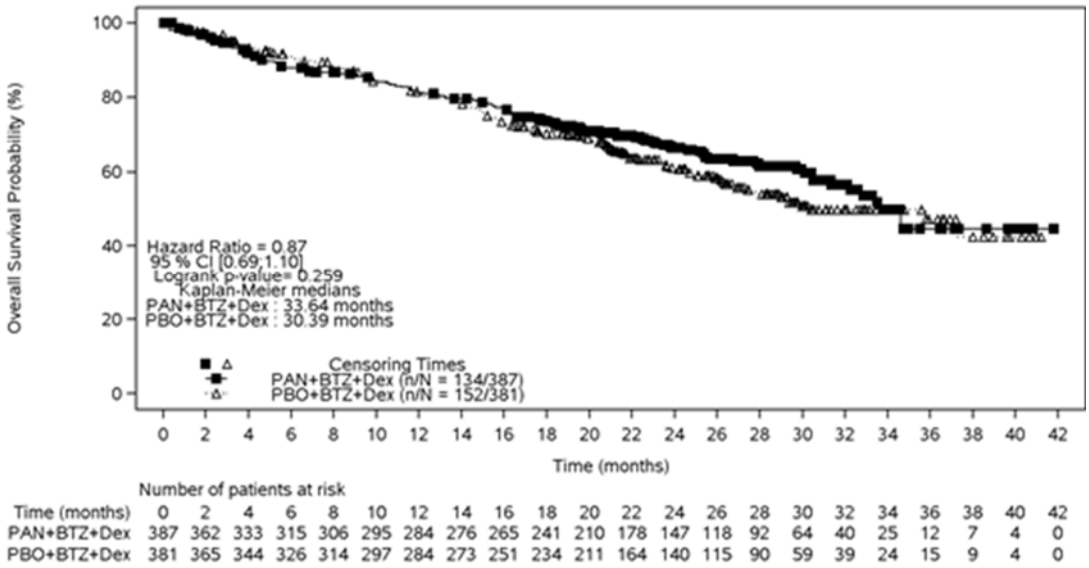
[*1] The interim OS analysis was planned to be conducted at the time point of the final PFS analysis. The two-sided significance level of OS in the interim analysis was 0.0131.

[*2] In the protocol revised on [redacted], 20[redacted] another OS analysis was planned to be conducted at the time point when the number of OS events reached approximately 90% of the number of events required for the final analysis (415 events). Pursuant to the revision, the α-spending functions for the interim and final analyses were adjusted to control the probability of type 1 error in the entire study.

Interim OS analysis results (FAS, data cut-off, September 10, 2013)

	Panobinostat	Placebo
Number of patients	387	381
Number of death	134 (34.6%)	152 (39.9%)
Median [95% CI] (months)	33.64 [31.34, NE]	30.39 [26.87, NE]
Hazard ratio[*1] [95% CI]	0.87 [0.69, 1.10]	
P value (two-sided)[*2,*3]	0.2586	

NE, Non-estimable; [*1] Cox proportional hazard model adjusted for stratification factors (number of prior treatment regimen [1, 2 or 3], presence or absence of prior BTZ therapy); [*2] Stratified log-rank test; [*3] Two-sided significance level of 0.0131



Kaplan-Meier curves of OS (FAS, data cut-off, September 10, 2013)

The applicant explained that, in Study D2308, protocol deviation was found in the measurement of M protein, a PFS parameter. PMDA asked the applicant to explain the reason for the deviation and how the difference in the M protein measuring methods could affect the results of the measurement.

The applicant responded as follows:
The protocol of Study D2308 required the quantification of serum and urine M protein by protein electrophoresis (PEP), according to the modified EBMT criteria. The applicant initially interpreted the M protein, the target protein to be quantified, as the spikes of M protein (M-spikes) observed in globulin fractions (α1, α2, β, and γ fractions). Assuming that M-spike exactly represents M protein, the applicant did not include a clear definition of M-spike in the protocol.

No reports have been found on the equivalence between PEP globulin fraction assay and PEP M-spike fraction assay. However, the difference in measured values between the two assays is expected to be small when M-spikes are clearly seen, but to be large when M-spikes are small and unclear. According to a report, the equivalence between PEP M-spike fraction assay and immunoglobulin assay was assessed based on the correlation between measurements of IgA, IgM, and IgG by both methods. The assessment revealed a certain level of correlation within the concentration range of 11 to 67 g/L (IgA), 8.5 to 25.1 g/L (IgM), and 19.2 to 56 g/L (IgG) (*Clin Chem.* 2009;55:1523-9). Even so, the immunoglobulin assay shows protein levels including normal immunoglobulin as well as M protein. Each M protein assay has different features, making it difficult to obtain identical results from 2 or more different assays. Each subject should be monitored for M protein by a single assay over time (e.g., *Leukemia.* 2006;20:1467-73). Therefore, the revised protocol of Study 2308 stipulates that the M protein assay used for each subject should not be changed after the revision of the protocol so that consistency in the interpretation of assay results is ensured.

PMDA asked the applicant to explain PFS results by M protein assay in Study D2308.

The applicant responded as follows:
The following table shows PFS results obtained by the protocol-specified PEP M-spike assay and by non-protocol-specified assays, i.e., the immunoglobulin assay or PEP globulin fraction assay.

PFS classified by M protein assay in Study D2308 (assessed by investigator)

	Protocol-specified (PEP M-spike assay)		Non-protocol-specified (immunoglobulin assay or PEP globulin fraction assay)	
	Panobinostat	Placebo[*1]	Panobinostat	Placebo[*1]
Number of patients	292	282	95	98
Number of death or aggravation	154	196	53	64
(%)	(52.7)	(69.5)	(55.8)	(65.3)
Median [95% CI] (months)	12.68 [10.61, 14.06]	8.08 [7.06, 9.72]	9.53 [7.89, 12.48]	7.95 [7.03, 9.23]
Hazard ratio [95% CI] [*2]	0.64 [0.52, 0.79]		0.67 [046, 0.98]	

[*1] Excluding 1 patient with unknown M protein assay. [*2] Cox proportional hazard model adjusted for stratification factors (number of prior treatment regimens, presence or absence of prior BTZ therapy)

A total of 193 patients underwent M protein monitoring by non-protocol-specified assays. Of these, 13 patients (7 patients in the panobinostat group, 6 patients in the placebo group) were monitored by the immunoglobulin assay alone and 67 patients (27 patients in the panobinostat group, 40 patients in the placebo group) by PEP globulin fraction assay alone. Thus, throughout Study D2308, M protein monitoring was performed by a single method in 326 of 387 patients (84.2%) in the panobinostat group and in 328 of 381 patients (86.1%) in the placebo group. The median PFS [95% CI] was 12.48 [10.25, 13.93] months in the panobinostat group and 8.08 [7.20, 9.69] months in the placebo group (hazard ratio [95% CI], 0.66 [0.54, 0.81]).

PMDA considers as follows:
Study D2308 had a group of patients with PFS evaluated based on M protein measured by more than 1 method. The use of different methods may have affected the evaluation of the efficacy of panobinostat. Nevertheless, the study demonstrated the superiority of panobinostat to placebo in the primary endpoint of PFS assessed by the investigator. Taking account of this observation and the following findings, PMDA concluded that panobinostat is effective for relapsed or refractory MM.

- In patients who were monitored for M protein by a single assay throughout Study D2308, PFS was improved in the panobinostat group as compared with the placebo group.

- The results of the two interim OS analyses did not show inferiority of panobinostat to placebo.

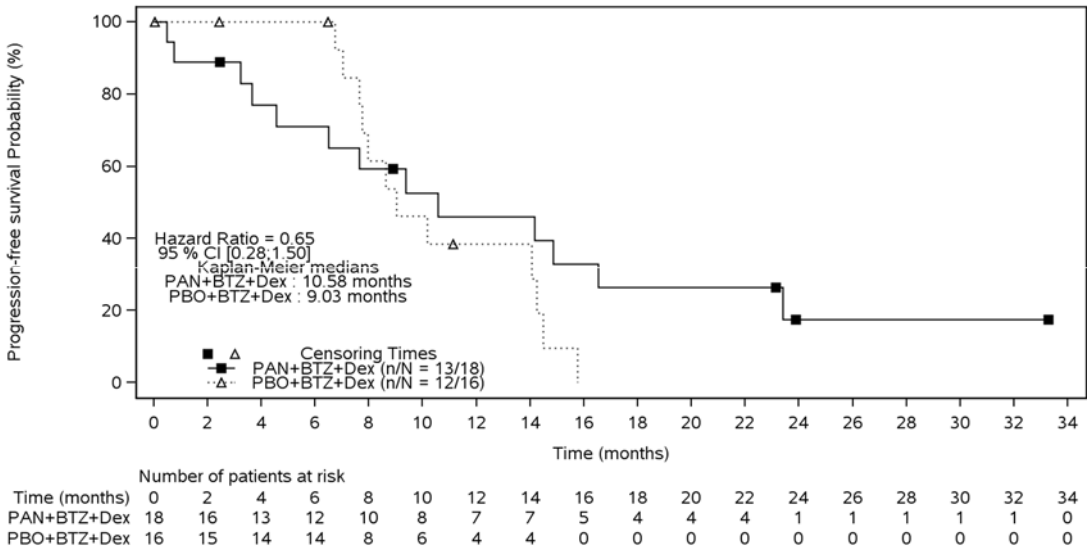
4.(iii).B.(2).4) Efficacy in Japanese patients

The applicant explained the efficacy of panobinostat in Japanese patients as follows:
In Study D2308, the results of PFS are shown in the following table and Kaplan-Meier curves in Japanese patients in the following figure.

PFS results in Japanese patients in Study D2308 (assessed by investigator, FAS, data cut-off, September 10, 2013)

	Panobinostat	Placebo
Number of patients	18	16
Number of censored patients	5 (27.8%)	4 (25.0%)
Number of events	13 (72.2%)	12 (75.0%)
Median [95% CI] (months)	10.58 [3.65, 16.53]	9.03 [7.66, 14.26]
Hazard ratio[*] [95% CI]	0.65 [0.28, 1.50]	

[*] Cox proportional hazard model



Kaplan-Meier curves of PFS in Japanese patients in Study D2308 (assessed by investigator, FAS, data cut-off, September 10, 2013)

The crossing PFS Kaplan-Meier curves of the panobinostat and placebo groups precluded the accurate interpretation of the efficacy of panobinostat in the Japanese population. It is difficult to evaluate the efficacy of panobinostat in Japanese patients based on the above results. PMDA therefore asked the applicant to explain the efficacy of panobinostat in Japanese patients with relapsed or refractory MM.

The applicant responded as follows:
The following is the rationale for the expected efficacy of panobinostat in Japanese patients with relapsed or refractory MM as seen in non-Japanese patients.

- In Study D2308, the hazard ratios [95% CI] of PFS were similar for the Japanese subpopulation (0.65 [0.28, 1.50]) and the entire study population (0.63 [0.52, 0.76]).

- It is reported that achieving CR or nCR is an important indicator for improved PFS, etc. in patients with relapsed or refractory MM (*J Clin Oncol.* 2010;28:2612-24, *Leukemia.* 2014;28:258-68). Therefore, based on the results of the response rate, a secondary endpoint in Study D2308, the percentage of patients with CR or nCR was compared between the entire study population and the Japanese subpopulation. The results in the Japanese subpopulation were more favorable in the panobinostat group than in the placebo group as were in the entire study population (the table below).

Tumor regression effect* in Study D2308 (assessed by investigator, FAS)

	Entire study population		Japanese subpopulation	
	Panobinostat	Placebo	Panobinostat	Placebo
Number of patients	387	381	18	16
Response (CR, nCR, or PR)	235	208	11	12
Response rate [95% CI] (%)	60.7 [55.7, 65.6]	54.6 [49.4, 59.7]	61.1 [35.7, 82.7]	75.0 [47.6, 92.7]
Complete response (CR or nCR)	107	60	6	2
Complete response rate [95% CI] (%)	27.6 [23.3, 32.4]	15.7 [12.2, 19.8]	33.3 [13.3, 59.0]	12.5 [1.6, 38.3]

* Modified EBMT criteria [see "4.(iii).A. *Evaluation data* (2) Global study"]

An open-label, uncontrolled study (Study D1201) is ongoing in Japanese patients with relapsed or refractory MM to evaluate the percentage of patients who achieve CR or nCR after 8 cycles of treatment with panobinostat using the same dosage regimen as used in Study D2308. The study will be completed in [redacted] 20[redacted].

PMDA considers as follows:
The applicant explained that panobinostat would be effective in Japanese patients as well. This explanation is reasonable to a certain extent, because, in Study D2308, the percentage of Japanese patients who achieved CR or nCR was similar to that in the entire study population. However, the results of the ongoing Study D1201 should be provided to healthcare professionals as soon as made available.

4.(iii).B.(3) Safety [for adverse events, see "4.(iv) Adverse events, etc. observed in clinical studies"]

As a result of the reviews described in the following sections 1) to 13), PMDA has learned that panobinostat should be administered with careful attention to the following adverse events: QT prolongation, bone marrow depression, haemorrhage, infection, hepatic dysfunction, renal dysfunction, diarrhoea/nausea/vomiting/dehydration, cardiac disorders (cardiac failure, ischaemic heart disease, tachyarrhythmia), colitis ischaemic, and venous thromboembolism.

However, PMDA has concluded that the use of panobinostat should be allowed provided that the patient is monitored and controlled or other appropriate actions are taken for adverse events by a physician with expertise in hematopoietic malignancy. Because of limited experiences in the use of panobinostat in Japanese patients, further safety information should be collected after the market launch.

4.(iii).B.(3).1) Safety profile of panobinostat

The outline of the safety profile in Studies D2308, DUS71, and B2207 (expanded cohort) is shown in the following table. (Studies DUS71 and B2207 investigated the safety of panobinostat + BTZ + DEX.)

Outline of safety profile

	Number of patients (%)			
	Study D2308		Study DUS71	Study B2207 (expanded cohort)
	Panobinostat N = 381	Placebo N = 377	N = 55	N = 15
Adverse events	380 (99.7)	376 (99.7)	54 (98.2)	15 (100)
Grade ≥3 adverse events	364 (95.5)	310 (82.2)	49 (89.1)	13 (86.7)
Adverse events resulting in death	26 (6.8)	12 (3.3)	1 (1.8)	2 (13.3)
Serious adverse events	228 (59.8)	157 (41.6)	39 (70.9)	6 (40.0)
Adverse events leading to treatment discontinuation	138 (36.2)	77 (20.4)	10 (18.2)	5 (33.3)
Adverse events leading to treatment interruption or dose reduction	338 (88.7)	285 (75.6)	48 (87.3)	11 (73.3)

In Study D2308, adverse events with a ≥10% higher incidence in the panobinostat group than in the placebo group were thrombocytopenia (64.6% [246 of 381 patients] in the panobinostat group, 40.8% [154 of 377 patients] in the placebo group), neutropenia (29.9% [114 of 381 patients], 10.6% [40 of 377 patients]), diarrhoea (68.2% [260 of 381 patients], 41.6% [157 of 377 patients]), nausea (36.2% [138 of 381 patients], 20.7% [78 of 377 patients]), vomiting (25.7% [98 of 381 patients], 13.0% [49 of 377 patients]), fatigue (41.2% [157 of 381 patients], 29.2% [110 of 377 patients]), pyrexia (26.0% [99 of 381 patients], 14.9% [56 of 377 patients]), decreased appetite (28.1% [107 of 381 patients], 12.5% [47 of 377 patients]), and hypokalaemia (27.3% [104 of 381 patients], 14.1% [53 of 377 patients]). Grade ≥3 adverse events with a ≥10% higher incidence in the panobinostat group than in the placebo group were thrombocytopenia (57.0% [217 of 381 patients], 24.9% [94 of 377 patients]), neutropenia (24.1% [92 of 381 patients], 8.0% [30 of 377 patients]), diarrhoea (25.5% [97 of 381 patients], 8.0% [30 of 377 patients]), and hypokalaemia (19.2% [73 of 381 patients], 6.4% [24 of 377 patients]). Serious adverse events with a ≥3% higher incidence in the panobinostat group than in the placebo group were pneumonia (14.7% [56 of 381 patients], 10.6% [40 of 377 patients]), diarrhoea (11.3% [43 of 381 patients], 2.4% [9 of 377 patients]), and thrombocytopenia (7.3% [28 of 381 patients], 2.1% [8 of 377 patients]).

Adverse events leading to study drug discontinuation with a ≥1% higher incidence in the panobinostat group than in the placebo group were diarrhoea (4.5% [17 of 381 patients], 1.6% [6 of 377 patients]), neuropathy peripheral (3.7% [14 of 381 patients], 1.9% [7 of 377 patients]), asthenia (2.9% [11 of 381 patients], 0%), and thrombocytopenia (1.6% [6 of 381 patients], 0.5% [2 of 377 patients]). Adverse events leading to interruption or dose reduction of the study drug that occurred at a ≥5% higher incidence

in the panobinostat group than in the placebo group were thrombocytopenia (31.0% [118 of 381 patients], 10.9% [41 of 377 patients]), diarrhoea (26.0% [99 of 381 patients], 9.0% [34 of 377 patients]), fatigue (16.3% [62 of 381 patients], 7.2% [27 of 377 patients]), neutropenia (10.2% [39 of 381 patients], 2.4% [9 of 377 patients]), and pyrexia (7.9% [30 of 381 patients], 2.9% [11 of 377 patients]).

PMDA considers as follows:
Pneumonia, diarrhoea, and thrombocytopenia, etc. occurred more frequently in the panobinostat group than in the placebo group in Study D2308. These adverse events should be regarded as panobinostat-induced events and therefore require attention. Information on these events should be appropriately provided to medical professionals.

4.(iii).B.(3).2) Safety of panobinostat in Japanese patients
The differences in the safety profile of panobinostat between Japanese and non-Japanese patients are summarized in the following table.

Summary of the differences in the safety profile of panobinostat between Japanese and non-Japanese patients (Study D2308)

	Number of patients (%)			
	Panobinostat		Placebo	
	Japanese N = 18	Non-Japanese N = 363	Japanese N = 16	Non-Japanese N = 361
All adverse events	18 (100)	362 (99.7)	16 (100)	360 (99.7)
Grade ≥3 adverse events	17 (94.4)	347 (95.6)	14 (87.5)	296 (82.0)
Adverse events resulting in death	1 (5.6)	25 (6.9)	0	12 (3.3)
Serious adverse events	13 (72.2)	215 (59.2)	8 (50.0)	149 (41.3)
Adverse events leading to treatment discontinuation	9 (50.0)	129 (35.5)	4 (25.0)	73 (20.2)
Adverse events leading to treatment interruption or dose reduction	17 (94.4)	321 (88.4)	14 (87.5)	271 (75.1)

Among adverse events with a ≥20% higher incidence in Japanese patients than in non-Japanese patients in Study D2308, those with a ≥20% higher incidence in the panobinostat group than in the placebo group were hypoalbuminaemia (44.4% [8 of 18 patients] in Japanese patients, 3.6% [13 of 363 patients] in non-Japanese patients), decreased appetite (55.6% [10 of 18 patients], 26.7% [97 of 363 patients]), rash (55.6% [10 of 18 patients], 6.3% [23 of 363 patients]), hypophosphataemia (61.1% [11 of 18 patients], 8.8% [32 of 363 patients]), leukopenia (50.0% [9 of 18 patients], 14.6% [53 of 363 patients]), nausea (61.1% [11 of 18 patients], 35.0% [127 of 363 patients]), dehydration (27.8% [5 of 18 patients], 6.3% [23 of 363 patients]), peripheral sensory neuropathy (44.4% [8 of 18 patients], 9.4% [34 of 363 patients]), neutropenia (50.0% [9 of 18 patients], 28.9% [105 of 363 patients]), and insomnia (38.9% [7 of 18 patients], 18.2% [66 of 363 patients]). In the panobinostat group of Study D2308, only asthenia occurred at a ≥20% higher incidence in non-Japanese patients than in Japanese patients (23.1% [84 of 363 patients] vs. 0%). In the panobinostat group of Study D2308, adverse events reported by ≥2 Japanese patients only were hypoparathyroidism and amylase increased (2 patients each).

Among serious adverse events with a ≥10% higher incidence in Japanese patients than in non-Japanese patients in the panobinostat group of Study D2308, those that occurred with a ≥10% higher incidence in the panobinostat group than in the placebo group were pneumonia (27.8% [5 of 18 patients], 14.0% [51 of 363 patients]), ileus (22.2% [4 of 18 patients], 0.3% [1 of 363 patients]), and pharyngitis (11.1% [2 of 18 patients], 0%).

Among adverse events with a ≥20% higher incidence in Japanese patients than in non-Japanese patients in the panobinostat group of Study D2308, those leading to the discontinuation of study drug were ileus (11.1% [2 of 18 patients], 0%), taste disturbance (5.6% [1 of 18 patients], 0%), and peripheral sensory neuropathy (5.6% [1 of 18 patients], 0.6% [2 of 363 patients]), and adverse events leading to treatment interruption or dose reduction of the study drug were neutropenia (16.7% [3 of 18 patients], 9.9% [36 of 363 patients]), hypophosphataemia (16.7% [3 of 18 patients], 0.6% [2 of 363 patients]), peripheral sensory neuropathy (16.7% [3 of 18 patients], 5.0% [18 of 363 patients]), ileus (11.1% [2 of 18 patients], 0.6% [2 of 363 patients]), leukopenia (5.6% [1 of 18 patients], 1.7% [6 of 363 patients]), decreased

appetite (5.6% [1 of 18 patients], 1.4% [5 of 363 patients]), dysgeusia (5.6% [1 of 18 patients], 0.3% [1 of 363 patients]), and dehydration (5.6% [1 of 18 patients], 1.4% [5 of 363 patients]).

PMDA considers as follows:
Although the incidence of some events differed between Japanese and non-Japanese patients, it is impossible to rigorously compare the differences because of the limited number of Japanese patients studied. However, among the adverse events with a ≥20% higher incidence in Japanese patients than in non-Japanese patients, those that occurred more frequently in the panobinostat group than in the placebo group and those that resulted in dose adjustment including temporary interruption of panobinostat, etc. should be notified to healthcare professionals, highlighting the difference in the incidence rates between Japanese and non-Japanese patients.

In the following sections, PMDA reviews the safety data obtained mainly from Studies D2308, DUS71, and B2207 (expanded cohort), focusing on adverse events resulting in death and those requiring the dose adjustment of panobinostat.

4.(iii).B.(3).3) QT prolongation

The applicant explained QT prolongation and tachyarrhythmia caused by panobinostat as follows:
Adverse events in preferred terms (PT) corresponding to "Torsade de pointes/QT prolongation" in the Standardised MedDRA Queries (SMQ) (MedDRA/J ver.16.0) were investigated as adverse events related to QT prolongation (the table below).

Incidences of QT-prolongation-related adverse events (Study D2308)

Event (MedDRA/J ver.16.0)	Number of patients (%)			
	Panobinostat N = 381		Placebo N = 377	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Syncope	23 (6.0)	14 (3.7)	9 (2.4)	6 (1.6)
Electrocardiogram QT prolonged	7 (1.8)	0	7 (1.9)	1 (0.3)
Loss of consciousness	5 (1.3)	3 (0.8)	3 (0.8)	1 (0.3)
Cardiac arrest	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Ventricular tachycardia	2 (0.5)	1 (0.3)	0	0
Electrocardiogram repolarisation abnormality	1 (0.3)	0	0	0
Sudden death*	1 (0.3)	0	1 (0.3)	0
Ventricular arrhythmia	1 (0.3)	0	0	0
Cardio-respiratory arrest	0	0	1 (0.3)	1 (0.3)

* Counted as an all Grade event but not as Grade ≥3 events because no grade classification had been made. The cause of sudden death was "death" in the patient receiving panobinostat and "disease progression" in the patient receiving placebo.

In the panobinostat and placebo groups of Study D2308, QT prolongation was observed in 40 patients (10.5%) and in 23 patients (6.1%), respectively. Grade ≥3 QT prolongation was observed in 20 patients (5.2%) and in 11 patients (2.9%), respectively. In Studies DUS71 and B2207 (expanded cohort), QT prolongation was observed in 5 patients (9.1%) and in 1 patient (6.7%), respectively, and all events were Grade ≥3.

QT prolongation resulted in death in 1 patient (0.3%) in the panobinostat group and in 2 patients (0.5%) in the placebo group in Study D2308. The deaths were caused by cardiac arrest (1 patient [0.3%]) in the panobinostat group and by cardiac arrest and cardio-respiratory arrest (1 patient each [0.3%]) in the placebo group. A causal relationship to the study drug was ruled out for all events. No QT-prolongation-induced death occurred in Study DUS71 or B2207 (expanded cohort). Serious QT prolongation was observed in 14 patients (3.7%) in the panobinostat group and in 7 patients (1.9%) in the placebo group in Study D2308. A causal relationship to panobinostat could not be ruled out for 8 patients (2.1%) in the panobinostat group. Serious QT prolongation was also observed in 1 patient (6.7%) in Study B2207 (expanded cohort), but a causal relationship to panobinostat was ruled out in this patient. In Study DUS71, no serious QT prolongation was observed. QT prolongation leading to the discontinuation of study drug was reported by 7 patients (1.8%) in the panobinostat group and 4 patients (1.1%) in the placebo group in Study D2308, whereas it was not reported in Study DUS71 or B2207 (expanded cohort). QT prolongation leading to the interruption or dose reduction of the study drug was reported by 14 patients (3.7%) in the panobinostat group and 5 patients (1.3%) in the placebo group in Study D2308, and 2 patients (3.6%) and 1 patient (6.7%), respectively, in Studies DUS71 and B2207 (expanded cohort).

In Study D2308, QTcF prolongation of >60 ms from baseline was observed in 3 patients (0.8%) in the panobinostat group and in 4 patients (1.1%) in the placebo group. QTcF of >500 ms was not observed in the panobinostat group but observed in 2 patients (0.5%) in the placebo group. In Studies DUS71 and B2207 (expanded cohort), there were no patients who showed QTcF prolongation of >60 ms from baseline or QTcF of >500 ms.

PMDA considers as follows:
Since panobinostat caused QT prolongation, resulting in death in some patients, caution should be exercised against QT prolongation associated with panobinostat. Patients should be carefully monitored through periodic electrocardiography and electrolyte tests before and during treatment with panobinostat. Healthcare professionals should be appropriately informed, through the package insert, etc., of the following criteria used in clinical studies of panobinostat: the criteria for the start of treatment with panobinostat pertaining to QTc intervals and blood electrolytes; and the criteria for treatment interruption, dose reduction, and treatment discontinuation in case of QT prolongation, etc. These measures aim to ensure that panobinostat-induced QT prolongation is treated appropriately [see "4.(iii).B.(5) Dosage and administration"].

4.(iii).B.(3).4) Bone marrow depression
The applicant explained bone marrow depression caused by panobinostat as follows:
Preferred Terms (PTs) of adverse events equivalent to "Haematopoietic cytopenias affecting more than one type of blood cell," "Haematopoietic erythropenia," "Haematopoietic leukopenia," and "Haematopoietic thrombocytopenia" in SMQ (MedDRA/J ver.16.0) were investigated as adverse events related to bone marrow depression (the table below).

Incidence of bone marrow depression (Study D2308, events reported by ≥2 patients in either group)

Event (MedDRA/J ver.16.0)	Number of patients (%)			
	Panobinostat N = 381		Placebo N = 377	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Cytopenia[*1]				
Pancytopenia	5 (1.3)	3 (0.8)	2 (0.5)	2 (0.5)
Anaemia[*2]				
Anaemia	158 (41.5)	63 (16.5)	126 (33.4)	60 (15.9)
Haemoglobin decreased	18 (4.7)	12 (3.1)	13 (3.4)	10 (2.7)
Red blood cell count decreased	3 (0.8)	0	2 (0.5)	0
Leukopenia[*3]				
Neutropenia	114 (29.9)	92 (24.1)	40 (10.6)	30 (8.0)
Leukopenia	62 (16.3)	35 (9.2)	31 (8.2)	12 (3.2)
Lymphopenia	52 (13.6)	47 (12.3)	35 (9.3)	28 (7.4)
Neutrophil count decreased	13 (3.4)	10 (2.6)	3 (0.8)	3 (0.8)
White blood cell count decreased	13 (3.4)	11 (2.9)	2 (0.5)	1 (0.3)
Lymphocyte count decreased	8 (2.1)	8 (2.1)	3 (0.8)	3 (0.8)
Febrile neutropenia	4 (1.0)	4 (1.0)	2 (0.5)	2 (0.5)
Monocyte count decreased	2 (0.5)	0	0	0
Neutropenic sepsis	2 (0.5)	2 (0.5)	1 (0.3)	1 (0.3)
Thrombocytopenia[*4]				
Thrombocytopenia	246 (64.6)	217 (57.0)	154 (40.8)	94 (24.9)
Platelet count decreased	43 (11.3)	35 (9.2)	17 (4.5)	13 (3.4)

[*1] SMQ "Haematopoietic cytopenias affecting more than one type of blood cell," [*2] SMQ "Haematopoietic erythropenia," [*3] SMQ "Haematopoietic leukopenia," [*4] "Haematopoietic thrombocytopenia"

In Study D2308, bone marrow depression was observed in 321 patients (84.3%) in the panobinostat group and in 229 patients (60.7%) in the placebo group. Grade ≥3 events were observed in 282 patients (74.0%) and 170 patients (45.1%), respectively. In Studies DUS71 and B2207 (expanded cohort), bone marrow depression was observed in 45 patients (81.8%) and 11 patients (73.3%), respectively. Grade ≥3 events were observed in 37 patients (67.3%) and 11 patients (73.3%), respectively.

In Study D2308, bone marrow depression with fatal outcome was not reported in the panobinostat group, but 1 patient (0.3%) in the placebo group died due to neutropenic sepsis. A causal relationship to the

study drug was ruled out. In Studies DUS71 and B2207 (expanded cohort), there was no bone marrow depression with fatal outcome. In Study D2308, serious bone marrow depression was observed in 47 patients (12.3%) in the panobinostat group and in 14 patients (3.7%) in the placebo group, and a causal relationship to the study drug could not be ruled out in 34 patients (8.9%) and 6 patients (1.6%), respectively. In Studies DUS71 and B2207 (expanded cohort), serious bone marrow depression was observed in 19 patients (34.5%) and 4 patients (26.7%), respectively, and a causal relationship to the study drug could not be ruled out in 16 patients (29.1%) and 4 patients (26.7%), respectively. In Study D2308, bone marrow depression leading to the discontinuation of study drug was reported by 9 patients (2.4%) in the panobinostat group and 3 patients (0.8%) in the placebo group. In Studies DUS71 and B2207 (expanded cohort), bone marrow depression leading to the discontinuation of study drug was not reported. In Study D2308, bone marrow depression leading to the interruption or dose reduction of the study drug was reported by 170 patients (44.6%) in the panobinostat group and 60 patients (15.9%) in the placebo group. In Studies DUS71 and B2207 (expanded cohort), bone marrow depression leading to the interruption or dose reduction of the study drug was reported by 30 patients (54.5%) and 5 patients (33.3%), respectively.

PMDA considers as follows:
There were cases of serious bone marrow depression for which a causal relationship to panobinostat could not be ruled out. Healthcare professionals should therefore be advised through the package insert, etc. to perform hematology testing regularly during treatment with panobinostat to allow infection control, blood transfusion, etc. Healthcare professionals should also be appropriately informed, through the package insert, etc., of the following criteria used in the clinical studies of panobinostat: the criteria for the start of treatment with panobinostat pertaining to platelet count and neutrophil count; and the criteria for the interruption, dose reduction, and discontinuation of panobinostat in case of decreased platelet count, decreased neutrophil count, etc. These measures aim to ensure that appropriate measures are taken in case of panobinostat-induced bone marrow depression [see "4.(iii).B.(5) Dosage and administration"].

4.(iii).B.(3).5) Hemorrhage
The applicant explained hemorrhage caused by panobinostat as follows:
Adverse events in PTs corresponding to "Haemorrhage terms (excluding laboratory terms)" in SMQ (MedDRA/J ver.16.0) were investigated as hemorrhage-related adverse events.

In Study D2308, hemorrhage was observed in 79 patients (20.7%) in the panobinostat group and in 44 patients (11.7%) in the placebo group. Grade ≥3 hemorrhage-related events were observed in 16 patients (4.2%) and 9 patients (2.4%), respectively. In Studies DUS71 and B2207 (expanded cohort), hemorrhage was observed in 14 patients (25.5%) and 2 patients (13.3%), respectively, and Grade ≥3 hemorrhage was observed in 1 patient (1.8%) and 1 patient (6.7%), respectively.

In Study D2308, hemorrhage resulted in death in 5 patients (1.3%) in the panobinostat group and in 1 patient (0.3%) in the placebo group. The death was caused by gastrointestinal hemorrhage, cerebral hemorrhage, pulmonary hemorrhage, hemorrhagic shock, and acute respiratory failure presumably caused by pulmonary hemorrhage (1 patient each [0.3%]) in the panobinostat group, and hemorrhage intracranial (1 patient [0.3%]) in the placebo group. A causal relationship to the study drug could not be ruled out for pulmonary hemorrhage, shock hemorrhagic, and acute respiratory failure in the panobinostat group and for hemorrhage intracranial in the placebo group. In Studies DUS71 and B2207 (expanded cohort), there was no hemorrhage-induced death. In Study D2308, serious hemorrhage was observed in 17 patients (4.5%) in the panobinostat group and in 8 patients (2.1%) in the placebo group, and a causal relationship to the study drug could not be ruled out in 9 patients (2.4%) and 2 patients (0.5%), respectively. In Study B2207 (expanded cohort), serious hemorrhage was observed in 1 patient (6.7%), but a causal relationship to the study drug was ruled out. In Study DUS71, there was no serious hemorrhage. In Study D2308, hemorrhage leading to the discontinuation of study drug was reported by 3 patients (0.8%) in the panobinostat group and 1 patient (0.3%) in the placebo group. In Studies DUS71 and B2207 (expanded cohort), hemorrhage leading to the discontinuation of study drug was not reported. Hemorrhage leading to the interruption or dose reduction of the study drug was reported by 12 patients (3.1%) in the panobinostat group and 4 patients (1.1%) in the placebo group of Study D2308 and 2 patients (3.6%) in Study DUS71, but none in Study B2207 (expanded cohort).

Of 95 patients* who had hemorrhage in Study D2308 (panobinostat group), Study DUS71, or Study B2207 (expanded cohort), 89 patients (93.7%) had thrombocytopenia within 30 days before hemorrhage, and 59 patients (62.1%) of these had Grade ≥3 thrombocytopenia. All of the 18 patients with Grade ≥3 hemorrhage had thrombocytopenia within 30 days before hemorrhage, and 14 patients (77.8%) of these had Grade ≥3 thrombocytopenia. These results suggest that thrombocytopenia is a risk factor for hemorrhage.

* Include 1 patient who had hemorrhage after the start of a new antineoplastic therapy following discontinuation of panobinostat.

PMDA considers as follows:
There were hemorrhage-induced deaths for which a causal relationship to panobinostat could not be ruled out. Healthcare professionals should therefore be advised through the package insert, etc. to exercise caution against hemorrhage, to monitor the patient's condition during the treatment with panobinostat, and to take appropriate measures including the interruption of panobinostat in case of any abnormality. Also, since decreased platelet count is a possible risk factor of hemorrhage, hematology test should be performed regularly during the treatment with panobinostat. In case of any abnormality, panobinostat should be discontinued and appropriate measures should be taken. Healthcare professionals should also be appropriately informed, through the package insert, etc., of the following criteria used in clinical studies of panobinostat: the criteria for the initiation of treatment with panobinostat pertaining to platelet count; and the criteria for the interruption, dose reduction, and discontinuation of panobinostat in case of decreased platelet count [see "4.(iii).B.(5) Dosage and administration"]. The results of the investigation on the relationship between thrombocytopenia and hemorrhage in clinical studies of panobinostat should be provided appropriately to healthcare professionals through written materials, etc.

4.(iii).B.(3).6) Infection
The applicant explained infection caused by panobinostat as follows:
PTs of infection-related adverse events under the system organ class of "Infections and infestations" (MedDRA/J ver.16.0) were summarized in the table below.

Incidence of infections (Study D2308, events reported by ≥1% of patients in either group)

Event (MedDRA/J ver.16.0)	Number of patients (%)			
	Panobinostat N = 381		Placebo N = 377	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Upper respiratory tract infection	68 (17.8)	9 (2.4)	55 (14.6)	6 (1.6)
Pneumonia	65 (17.1)	48 (12.6)	48 (12.7)	39 (10.3)
Nasopharyngitis	49 (12.9)	0	47 (12.5)	2 (0.5)
Urinary tract infection	28 (7.3)	9 (2.4)	19 (5.0)	6 (1.6)
Bronchitis	22 (5.8)	1 (0.3)	26 (6.9)	2 (0.5)
Respiratory tract infection	19 (5.0)	5 (1.3)	21 (5.6)	5 (1.3)
Herpes zoster	18 (4.7)	4 (1.0)	40 (10.6)	7 (1.9)
Influenza	14 (3.7)	1 (0.3)	12 (3.2)	1 (0.3)
Rhinitis	11 (2.9)	0	11 (2.9)	0
Sepsis	11 (2.9)	11 (2.9)	7 (1.9)	6 (1.6)
Sinusitis	11 (2.9)	0	12 (3.2)	2 (0.5)
Oral candidiasis	10 (2.6)	0	6 (1.6)	1 (0.3)
Pharyngitis	13 (3.4)	2 (0.5)	11 (2.9)	1 (0.3)
Septic shock	11 (2.9)	11 (2.9)	3 (0.8)	3 (0.8)
Gastroenteritis	12 (3.1)	6 (1.6)	8 (2.1)	2 (0.5)
Lower respiratory tract infection	12 (3.1)	3 (0.8)	8 (2.1)	3 (0.8)
Cellulitis	8 (2.1)	2 (0.5)	4 (1.1)	1 (0.3)
Oral herpes	9 (2.4)	0	4 (1.1)	0
Hordeolum	7 (1.8)	0	11 (2.9)	0
Infection	8 (2.1)	6 (1.6)	7 (1.9)	3 (0.8)
Candidiasis	4 (1.0)	0	1 (0.3)	1 (0.3)
Cystitis	8 (2.1)	0	6 (1.6)	0
Clostridium difficile colitis	4 (1.0)	2 (0.5)	0	0
Viral infection	6 (1.6)	1 (0.3)	1 (0.3)	0
Lung infection	6 (1.6)	4 (1.0)	7 (1.9)	2 (0.5)
Herpes simplex	4 (1.0)	0	3 (0.8)	0
Otitis media	4 (1.0)	1 (0.3)	0	0
Periodontitis	4 (1.0)	0	1 (0.3)	0
Fungal skin infection	2 (0.5)	0	5 (1.3)	0
Herpes virus infection	1 (0.3)	0	4 (1.1)	0

In Study D2308, infection was observed in 262 patients (68.8%) in the panobinostat group and in 252 patients (66.8%) in the placebo group. Grade ≥3 infection was observed in 119 patients (31.2%) and 90 patients (23.9%), respectively. In Studies DUS71 and B2207 (expanded cohort), infection was observed in 41 patients (74.5%) and 12 patients (80.0%), respectively, and Grade ≥3 infection was observed in 18 patients (32.7%) and 4 patients (26.7%), respectively.

In Study D2308, infection resulted in death in 10 patients (2.6%) in the panobinostat group and in 5 patients (1.3%) in the placebo group. The causes of the deaths were septic shock (3 patients [0.8%]), respiratory failure (2 patients [0.5%]), bronchopneumonia, pneumonia, lung infection, pulmonary tuberculosis, and lung disorder associated with lung infection (1 patient each [0.3%]) in the panobinostat group; and pneumonia (3 patients [0.8%]), and necrotising fasciitis and neutropenic sepsis (1 patient each [0.3%]) in the placebo group. A causal relationship to the study drug could not be ruled out for lung infection, pneumonia, and pulmonary tuberculosis (1 patient each [0.3%]) in the panobinostat group and pneumonia (1 patient [0.3%]) in the placebo group. In Studies DUS71 and B2207 (expanded cohort), there was no fatal infection. In Study D2308, serious infection was observed in 120 patients (31.5%) in the panobinostat group and in 75 patients (19.9%) in the placebo group. A causal relationship to the study drug could not be ruled out in 51 patients (13.4%) and 22 patients (5.8%), respectively. In Studies DUS71 and B2207 (expanded cohort), serious infection was observed in 16 patients (29.1%) and 2 patients (13.3%), respectively, and a causal relationship to the study drug could not be ruled out in 5 patients (9.1%) in Study DUS71. Infection leading to the discontinuation of study drug was reported by 19 patients (5.0%) in the panobinostat group and 14 patients (3.7%) in the placebo group in Study D2308, 2 patients (3.6%) in Study DUS71, and none in Study B2207 (expanded cohort). Infection leading to the interruption or dose reduction of the study drug was reported by 133 patients (34.9%) in the panobinostat group and 121 patients (32.1%) in the placebo group in Study D2308, 13 patients (23.6%) in Study DUS71, and 5 patients (33.3%) in Study B2207 (expanded cohort).

According to the applicant, hepatitis B reactivation is another clinically important adverse event associated with panobinostat in addition to infection. Therefore, PMDA asked the applicant to explain the occurrences of hepatitis B reactivation following the administration of panobinostat.

The applicant responded as follows:
In Study D2308, hepatitis B was observed in 3 patients (0.8%) in the panobinostat group and in 1 patient (0.3%) in the placebo group. All the events observed in the panobinostat group were serious, and a causal relationship to the study drug could not be ruled out. The event observed in 1 patient in the placebo group was also serious but a causal relationship to the study drug was ruled out. The 3 patients in the panobinostat group had no prior or concurrent hepatitis B before or at enrollment in the study. The 3 patients had been tested for HBs antigen, anti-HBs antibody, or anti-HBc antibody before enrollment in the study. Of these, 1 patient tested positive for both anti-HBs and anti-HBc antibodies approximately 3 years before the enrollment, and another patient tested positive for HBs antibody alone; this suggested the 2 patients may have experienced the recurrence of hepatitis B after the administration of panobinostat. The remaining patient tested negative for HBs antigen but the test results for anti-HBs and anti-HBc antibodies and whether or not the patient had a history of hepatitis B were unknown. In Studies DUS71 and B2207 (expanded cohort), no hepatitis B was observed. In Study B2206 in which panobinostat was to be concomitantly administered with lenalidomide and DEX, a serious adverse event of aggravated hepatitis B was observed in 1 patient (2.2%), but a causal relationship to panobinostat was ruled out.

PMDA considers as follows:
There were cases of fatal infection for which a causal relationship to panobinostat could not be ruled out. Healthcare professionals should therefore be appropriately advised, through the package insert, etc., to monitor the patient by regular blood tests, etc. during treatment with panobinostat, and to take appropriate measures including treatment interruption of panobinostat in case of any abnormalities. Also, since there were cases of serious hepatitis B reactivation for which a causal relationship to panobinostat could not be ruled out, healthcare professionals should be appropriately informed of the occurrence of hepatitis B after administration of panobinostat so that they can exercise caution against infection.

4.(iii).B.(3).7) Hepatic dysfunction
The applicant explained hepatic dysfunction caused by panobinostat as follows:
The PTs of adverse events related to hepatic dysfunction classified into the SMQs of "Cholestasis and jaundice of hepatic origin," "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions," "Hepatitis, non-infectious," and "Liver-related investigations, signs and symptoms" (MedDRA/J ver.16.0) were summarized.

In Study D2308, hepatic dysfunction was observed in 63 patients (16.5%) in the panobinostat group and in 46 patients (12.2%) in the placebo group. Grade ≥3 events were observed in 16 patients (4.2%) and 13 patients (3.4%), respectively. In the panobinostat group, events with an incidence of ≥5% were alanine aminotransferase (ALT) increased (23 patients [6.0%]) and hypoalbuminaemia (21 patients [5.5%]). In Studies DUS71 and B2207 (expanded cohort), hepatic dysfunction was observed in 5 patients (9.1%) and 6 patients (40.0%), respectively, and Grade ≥3 events were observed in 2 patients (3.6%) in Study DUS71.

Hepatic dysfunction resulting in death was not reported in either Study D2308, DUS71, or B2207 (expanded cohort). In Study D2308, serious hepatic dysfunction was observed in 3 patients each (0.8%) in the panobinostat and placebo groups, and a causal relationship to the study drug could not be ruled out in 2 patients each (0.5%) in both groups. In Study DUS71, serious hepatic dysfunction was observed in 1 patient (1.8%), but a causal relationship to the study drug was ruled out. In Study B2207 (expanded cohort), there were no cases of serious hepatic dysfunction. In Study D2308, hepatic dysfunction leading to the discontinuation of study drug was reported by 1 patient each (0.3%) both in the panobinostat group and in the placebo group. In Studies DUS71 and B2207 (expanded cohort), hepatic dysfunction leading to the discontinuation of study drug was not reported. Hepatic dysfunction leading to the interruption or dose reduction of the study drug was reported by 10 patients (2.6%) in the panobinostat group and 3 patients (0.8%) in the placebo group in Study D2308, 2 patients (3.6%) in Study DUS71, and none in Study B2207 (expanded cohort).

PMDA considers as follows:
There were cases of serious hepatic dysfunction for which a causal relationship to panobinostat could not be ruled out. Healthcare professionals should therefore be appropriately advised through the package insert, etc. to perform regular liver function tests before and during treatment with panobinostat, and to take appropriate measures, including the interruption of treatment, in case of abnormality.

4.(iii).B.(3).8) Renal dysfunction
The applicant explained renal dysfunction caused by panobinostat as follows:
The PTs of adverse events related to renal dysfunction categorized into the SMQ of "Acute renal failure" (MedDRA/J ver.16.0) were summarized.

In Study D2308, renal dysfunction was observed in 72 patients (18.9%) in the panobinostat group and in 41 patients (10.9%) in the placebo group. Grade ≥3 renal dysfunction was observed in 19 patients (5.0%) and 17 patients (4.5%), respectively. In Studies DUS71 and B2207 (expanded cohort), renal dysfunction was observed in 10 patients (18.2%) and 3 patients (20.0%), respectively, and Grade ≥3 renal dysfunction was observed in 1 patient (1.8%) in Study DUS71.

In Study D2308, 2 patients (0.5%) in the panobinostat group died due to renal dysfunction, but none in the placebo group. The cause of the deaths was renal failure acute (2 patients [0.5%]), but a causal relationship to the study drug was ruled out for both events. In Studies DUS71 and B2207 (expanded cohort), there was no death caused by renal dysfunction. In Study D2308, serious renal dysfunction was observed in 14 patients (3.7%) in the panobinostat group and in 15 patients (4.0%) in the placebo group, and a causal relationship to the study drug could not be ruled out in 4 patients (1.0%) and 3 patients (0.8%), respectively. In Study DUS71, serious renal dysfunction was observed in 5 patients (9.1%), and a causal relationship to the study drug could not be ruled out in 1 patient (1.8%). The breakdown of serious renal dysfunction in Study D2308 was, in the panobinostat group, renal failure acute (7 patients [1.8%]), renal failure (4 patients [1.0%]), oliguria, blood creatinine increased, and renal dysfunction (1 patient each [0.3%]), and a causal relationship to the study drug could not be ruled out for renal failure (3 patients [0.8%]) and blood creatinine increased (1 patient [0.3%]). In the placebo group, the breakdown of serious renal dysfunction was renal failure acute (9 patients [2.4%]), renal failure (4 patients [1.1%]), blood creatinine increased (2 patients [0.5%]), and renal dysfunction, anuria, and azotaemia (1 patient each [0.3%]), and a causal relationship to the study drug could not be ruled out for blood creatinine increased, renal failure, and anuria (1 patient each [0.3%]) (a single patient may have had more than one events). In Study DUS71, the breakdown of serious renal dysfunction was renal failure acute (4 patients) and renal dysfunction (2 patients), and a causal relationship to the study drug could not be ruled out for renal failure acute occurring in1 patient (1.8%) (a single patient may have had more than one events). In Study B2207 (expanded cohort), no serious renal dysfunction was observed. Renal dysfunction leading to the interruption or dose reduction of the study drug was reported by 14 patients (3.7%) in the panobinostat group and 6 patients (1.6%) in the placebo group in Study D2308, but none in Study DUS71 or B2207 (expanded cohort).

PMDA considers as follows:
There were cases of serious renal dysfunction for which a causal relationship to panobinostat could not be ruled out. Healthcare professionals should therefore be appropriately informed, through the package insert, etc. of the occurrence, etc. of renal dysfunction following treatment with panobinostat.

4.(iii).B.(3).9) Diarrhea, nausea, vomiting, and dehydration
The applicant explained diarrhea, nausea, vomiting, and dehydration caused by panobinostat, as follows:
The PTs (MedDRA/J ver.16.0) of diarrhea-related adverse events "diarrhoea," "diarrhoea haemorrhagic," and "frequent bowel movements" were tabulated.

In Study D2308, diarrhea was observed in 260 patients (68.2%) in the panobinostat group and in 157 patients (41.6%) in the placebo group. Grade ≥3 diarrhea was observed in 97 patients (25.5%) and 31 patients (8.2%), respectively. In Studies DUS71 and B2207 (expanded cohort), diarrhea was observed in 39 patients (70.9%) and 13 patients (86.7%), respectively, and Grade ≥3 diarrhea was observed in 11 patients (20.0%) and 3 patients (20.0%), respectively.

There was no death caused by diarrhea in either Study D2308, DUS71, or B2207 (expanded cohort). Serious diarrhea was observed in 43 patients (11.3%) in the panobinostat group and in 9 patients (2.4%) in the placebo group in Study D2308 and in 3 patients (5.5%) in Study DUS71, and a causal relationship to the study drug could not be ruled out in 30 patients (7.9%), 6 patients (1.6%), and 3 patients (5.5%), respectively. No serious diarrhea was observed in Study B2207 (expanded cohort). Diarrhea leading to the discontinuation of study drug was reported by 17 patients (4.5%) in the panobinostat group and 6 patients (1.6%) in the placebo group in Study D2308, and 2 patients (3.6%) in Study DUS71, but none in Study B2207 (expanded cohort). Diarrhea leading to the interruption or dose reduction of the study drug was reported by 99 patients (26.0%) in the panobinostat group and 34 patients (9.0%) in the placebo group in Study D2308, 11 patients (20.0%) in Study DUS71, and 1 patient (6.7%) in Study B2207 (expanded cohort).

The PTs (MedDRA/J ver.16.0) of adverse events related to nausea or vomiting "nausea" and "vomiting" were tabulated.

In Study D2308, nausea was observed in 138 patients (36.2%) in the panobinostat group and in 78 patients (20.7%) in the placebo group. Grade ≥3 nausea was observed in 21 patients (5.5%) and 2 patients (0.5%), respectively. In Studies DUS71 and B2207 (expanded cohort), nausea was observed in 33 patients (60.0%) and 10 patients (66.7%), respectively, and Grade ≥3 nausea was observed in 3 patients (5.5%) in Study DUS71. In Study D2308, vomiting was observed in 98 patients (25.7%) in the panobinostat group and in 49 patients (13.0%) in the placebo group. Grade ≥3 vomiting was observed in 28 patients (7.3%) and 5 patients (1.3%), respectively. In Studies DUS71 and B2207 (expanded cohort), vomiting was observed in 16 patients (29.1%) and 7 patients (46.7%), respectively, and Grade ≥3 vomiting was observed in 1 patient (1.8%) in Study DUS71.

There was no death caused by nausea or vomiting in either Study D2308, DUS71, or B2207 (expanded cohort). In Study D2308, serious nausea was observed in 7 patients (1.8%) in the panobinostat group and none in the placebo group. A causal relationship to the study drug could not be ruled out in 6 patients (1.6%). In Studies DUS71 and B2207 (expanded cohort), serious nausea was observed in 1 patient (1.8%) and 1 patient (6.7%), respectively, and a causal relationship to the study drug could not be ruled out in either case. In Study D2308, serious vomiting was observed in 12 patients (3.1%) in the panobinostat group and in 3 patients (0.8%) in the placebo group, and a causal relationship to the study drug could not be ruled out in 11 patients (2.9%) and 3 patients (0.8%), respectively. No serious vomiting occurred in either Study DUS71 or B2207 (expanded cohort). Nausea leading to the discontinuation of study drug was reported by 2 patients (0.5%) in the panobinostat group and none in the placebo group in Study D2308, and there were no such cases in either Study DUS71 or B2207 (expanded cohort). Vomiting leading to the discontinuation of study drug was reported by 2 patients (0.5%) in the panobinostat group and none in the placebo group in Study D2308. There were no such cases in either Study DUS71 or B2207 (expanded cohort). Nausea leading to the interruption or dose reduction of the study drug was reported by 17 patients (4.5%) in the panobinostat group and 8 patients (2.1%) in the placebo group in Study D2308, and 4 patients (7.3%) in Study DUS71, but none in Study B2207 (expanded cohort). Vomiting leading the interruption or dose reduction of the study drug was reported by 23 patients (6.0%) in the panobinostat group and 6 patients (1.6%) in the placebo group of Study D2308, and 6 patients (10.9%) in Study DUS71, but none in Study B2207 (expanded cohort).

The PT (MedDRA/J ver.16.0) of dehydration-related adverse event "dehydration" was tabulated.

In Study D2308, dehydration was observed in 28 patients (7.3%) in the panobinostat group and in 11 patients (2.9%) in the placebo group. Grade ≥3 dehydration was observed in 10 patients (2.6%) and 6 patients (1.6%), respectively. In Studies DUS71 and B2207 (expanded cohort), dehydration was observed in 9 patients (16.4%) and 4 patients (26.7%), respectively, and Grade ≥3 dehydration was observed in 3 patients (5.5%) and 1 patient (6.7%), respectively.

There was no death caused by dehydration in either Study D2308, DUS71, or B2207 (expanded cohort). In Study D2308, serious dehydration was observed in 11 patients (2.9%) in the panobinostat group and in 5 patients (1.3%) in the placebo group, and a causal relationship to the study drug could not be ruled out in 4 patients (1.0%) and 2 patients (0.5%), respectively. In Studies DUS71 and B2207 (expanded

cohort), serious dehydration was observed in 3 patients (5.5%) and 2 patients (13.3%), respectively, and a causal relationship to the study drug could not be ruled out in 1 patient in Study DUS71. There were no cases of the discontinuation of study drug due to dehydration in either Study D2308, DUS71, or B2207 (expanded cohort). Dehydration leading to the interruption or dose reduction of the study drug was reported by 6 patients (1.6%) in the panobinostat group and 2 patients (0.5%) in the placebo group in Study D2308, 1 patient (1.8%) in Study DUS71, and 1 patient (6.7%) in Study B2207 (expanded cohort).

PMDA considers as follows:
There were cases of serious diarrhea, nausea, and vomiting for which a causal relationship to panobinostat could not be ruled out. Healthcare professionals should therefore be appropriately informed, through the package insert, etc., of the protocol-defined criteria for the interruption, dose reduction, and discontinuation of panobinostat in case of diarrhea, nausea, and vomiting, to ensure that appropriate measures are taken for panobinostat-induced diarrhea, nausea, and vomiting [see "4.(iii).B.(5) Dosage and administration"]. Also, serious dehydration for which a causal relationship to panobinostat could not be ruled out have been reported. Attention should be paid to the occurrence of dehydration during treatment with panobinostat through adequate monitoring of patients' conditions including signs and symptoms of dehydration.

4.(iii).B.(3).10) Cardiac disorders (cardiac failure, ischaemic heart disease, tachyarrhythmia)
The applicant explained cardiac disorders (cardiac failure, ischaemic heart disease, tachyarrhythmia) caused by panobinostat as follows:
The PTs of adverse events related to cardiac disorders (cardiac failure, ischaemic heart disease, tachyarrhythmia) categorized into the SMQs (MedDRA/J ver.16.0) of "Cardiac failure," "Myocardial infarction," "Other ischaemic heart disease," "Supraventricular tachyarrhythmias," "Tachyarrhythmia terms, nonspecific," and "Ventricular tachyarrhythmias" were summarized in the table below.

Incidences of cardiac disorders (Study D2308; events reported by ≥2 patients in either group)

Event (MedDRA/J ver.16.0)	Number of patients (%)			
	Panobinostat N = 381		Placebo N = 377	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac failure[*1]				
Cardiac failure	3 (0.8)	1 (0.3)	4 (1.1)	1 (0.3)
Pulmonary oedema	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)
Cardiac failure congestive	0	0	2 (0.5)	2 (0.5)
Ischaemic heart disease[*2]				
Angina pectoris	6 (1.6)	1 (0.3)	5 (1.3)	1 (0.3)
Myocardial ischaemia	3 (0.8)	3 (0.8)	0	0
Myocardial infarction	3 (0.8)	3 (0.8)	0	0
Acute coronary syndrome	2 (0.5)	1 (0.3)	0	0
Tachyarrhythmia[*3]				
Atrial fibrillation	11 (2.9)	3 (0.8)	5 (1.3)	1 (0.3)
Tachycardia	11 (2.9)	1 (0.3)	4 (1.1)	2 (0.5)
Palpitations	10 (2.6)	0	5 (1.3)	0
Sinus tachycardia	9 (2.4)	1 (0.3)	1 (0.3)	0
Heart rate increased	3 (0.8)	0	0	0
Supraventricular extrasystoles	2 (0.5)	0	3 (0.8)	0
Ventricular tachycardia	2 (0.5)	1 (0.3)	0	0

[*1] SMQ "Cardiac failure" [*2] SMQ "Myocardial infarction" and "Other ischaemic heart disease" [*3] SMQ "Supraventricular tachyarrhythmias," "Tachyarrhythmia terms, nonspecific," and "Ventricular tachyarrhythmias"

In Study D2308, cardiac failure was observed in 8 patients each (2.1%) in both the panobinostat group and the placebo group. Grade ≥3 cardiac failure was observed in 3 patients (0.8%) and 5 patients (1.3%), respectively. In Study B2207 (expanded cohort), cardiac failure was observed in 1 patient (6.7%), and it was Grade 1 in severity. In Study DUS71, no cardiac failure occurred.

In Study D2308, cardiac failure resulted in death in 1 patient (0.3%) in the panobinostat group and in 1 patient (0.3%) in the placebo group. The causes of the deaths were pulmonary oedema (1 patient [0.3%]) in the panobinostat group and cardiopulmonary failure (1 patient [0.3%]) in the placebo group, and a

causal relationship to the study drug was ruled out for both deaths. There was no death caused by cardiac failure in Study B2207 (expanded cohort). In Study D2308, serious cardiac failure was observed in 3 patients (0.8%) in the panobinostat group and in 4 patients (1.1%) in the placebo group, and a causal relationship to the study drug could not be ruled out in 1 patient (0.3%) in the placebo group. No serious cardiac failure occurred in Study B2207 (expanded cohort). Cardiac failure leading to the discontinuation of study drug was reported by 1 patient (0.3%) in the panobinostat group and 2 patients (0.5%) in the placebo group in Study D2308, but none in Study B2207 (expanded cohort). Cardiac failure leading to the interruption or dose reduction of the study drug was not reported in either Study D2308 or B2207 (expanded cohort).

Based on these results, the applicant considered that treatment with panobinostat is unlikely to increase the risk of cardiac failure.

In Study D2308, ischaemic heart disease was observed in 15 patients (3.9%) in the panobinostat group and in 5 patients (1.3%) in the placebo group. Grade ≥3 ischaemic heart disease was observed in 9 patients (2.4%) and 1 patient (0.3%), respectively. In Study B2207 (expanded cohort), ischaemic heart disease was observed in 1 patient (6.7%), and it was Grade 4 in severity. In Study DUS71, no ischaemic heart disease occurred.

Ischaemic heart disease resulted in death in 3 patients (0.8%) in the panobinostat group but none in the placebo group in Study D2308, and none in both Studies DUS71 and B2207 (expanded cohort). The causes of the deaths were myocardial infarction (2 patients [0.5%]) and myocardial ischaemia (1 patient [0.3%]). A causal relationship to the study drug could not be ruled out for myocardial infarction (1 patient [0.3%]). In Study D2308, serious ischaemic heart disease was observed in 8 patients (2.1%) in the panobinostat group and in 2 patients (0.5%) in the placebo group, and a causal relationship to the study drug could not be ruled out in 2 patients (0.5%) in the panobinostat group. In Study B2207 (expanded cohort), serious ischaemic heart disease was observed in 1 patient (6.7%), but a causal relationship to the study drug was ruled out. In Study DUS71, there were no cases of serious ischaemic heart disease. Ischaemic heart disease leading to the discontinuation of study drug was reported by 1 patient (0.3%) in the panobinostat group but none in the placebo group in Study D2308, 1 patient (6.7%) in Study B2207 (expanded cohort), and none in Study DUS71. Ischaemic heart disease leading to the interruption or dose reduction of the study drug was reported by 6 patients (1.6%) in the panobinostat group and 2 patients (0.5%) in the placebo group in Study D2308, but none in either Study DUS71 or B2207 (expanded cohort).

Most of subjects who experienced ischaemic heart disease were found to have a prior or concurrent cardiovascular event or diabetes mellitus. Based on these results, the applicant considered that there was no significant difference in the incidence or severity of ischaemic heart disease between the panobinostat and placebo groups in Study D2308. Given the findings from the analysis of characteristics of subjects, treatment with panobinostat is unlikely to increase the risk of ischaemic heart disease.

In Study D2308, tachyarrhythmia was observed in 46 patients (12.1%) in the panobinostat group and in 18 patients (4.8%) in the placebo group. Grade ≥3 tachyarrhythmia was observed in 7 patients (1.8%) and 4 patients (1.1%), respectively. In Studies DUS71 and B2207 (expanded cohort), tachyarrhythmia was observed in 7 patients (12.7%) and 1 patient (6.7%), respectively, but there were no Grade ≥3 events.

There was no death caused by tachyarrhythmia in either Study D2308, DUS71, or B2207 (expanded cohort). In Study D2308, serious tachyarrhythmia was observed in 8 patients (2.1%) in the panobinostat group and in 3 patients (0.8%) in the placebo group, and a causal relationship to the study drug could not be ruled out in 4 patients (1.0%) and 1 patient (0.3%), respectively. In Study DUS71, serious tachyarrhythmia was observed in 1 patient (1.8%), but a causal relationship to the study drug was ruled out. In Study B2207 (expanded cohort), no serious tachyarrhythmia occurred. Tachyarrhythmia leading to the discontinuation of study drug was reported by 2 patients (0.5%) in the panobinostat group in Study D2308, but none in the placebo group, or in either Study DUS71 or B2207 (expanded cohort). Tachyarrhythmia leading to the interruption or dose reduction of the study drug was reported by 4 patients (1.0%) in the panobinostat group and 3 patients (0.8%) in the placebo group in Study D2308, 1 patient (1.8%) in Study DUS71, but none in Study B2207 (expanded cohort).

Accordingly, the applicant considered that treatment with panobinostat is unlikely to increase the risk of tachyarrhythmia.

PMDA considers as follows:
There were deaths due to cardiac disorders for which a causal relationship to panobinostat could not be ruled out. Healthcare professionals should therefore be appropriately informed, through the package insert, etc., of the occurrence, etc. of cardiac disorders following treatment with panobinostat.

4.(iii).B.(3).11) Ischaemic colitis
The applicant explained ischaemic colitis caused by panobinostat as follows:
PTs of ischaemic colitis-related adverse events categorized into the SMQ (MedDRA/J ver.16.0) of "Ischaemic colitis" were summarized.

In Study D2308, ischaemic colitis was observed in 17 patients (4.5%) in the panobinostat group and in 6 patients (1.6%) in the placebo group. Grade ≥3 ischaemic colitis was observed in 7 patients (1.8%) and 4 patients (1.1%), respectively. The breakdown of the events in the panobinostat group included gastrointestinal haemorrhage (5 patients [1.3%]), haematochezia (4 patients [1.0%]), colitis (3 patients [0.8%]), rectal haemorrhage (2 patients [0.5%]), anal haemorrhage, enterocolitis, intestinal ischaemia, and large intestine perforation (1 patient each [0.3%]) (a single patient may have had more than one events). Grade ≥3 ischaemic colitis were gastrointestinal haemorrhage (3 patients [0.8%]), haematochezia, rectal haemorrhage, intestinal ischaemia, and large intestinal perforation (1 patient each [0.3%]). In Study DUS71, ischaemic colitis was observed in 3 patients (5.5%), and a Grade ≥3 event was observed in 1 patient (1.8%). In Study B2207 (expanded cohort), there were no cases of ischaemic colitis.

In Study D2308, ischaemic colitis resulted in death in 2 patients (0.5%) in the panobinostat group (ischaemia and gastrointestinal haemorrhage in 1 patient each), and a causal relationship to the study drug was ruled out for both events. There were no cases of death due to ischaemic colitis in the placebo group of Study D2308, or in either Study DUS71 or B2207 (expanded cohort). In Study D2308, serious ischaemic colitis was observed in 10 patients (2.6%) in the panobinostat group and in 3 patients (0.8%) in the placebo group, and a causal relationship to the study drug could not be ruled out in 4 patients (1.0%) and 1 patient (0.3%), respectively. In Studies DUS71 and B2207 (expanded cohort), there were no cases of serious ischaemic colitis. Ischaemic colitis leading to the discontinuation of study drug was reported by 1 patient (0.3%) in the panobinostat group in Study D2308, but none in the placebo group, or in either Study DUS71 or B2207 (expanded cohort). Ischaemic colitis leading to the interruption or dose reduction of the study drug was reported by 6 patients (1.6%) in the panobinostat group and 3 patients (0.8%) in the placebo group in Study D2308, 1 patient (1.8%) in Study DUS71, but none in Study B2207 (expanded cohort).

PMDA considers as follows:
There were cases of serious ischemic colitis for which a causal relationship to panobinostat could not be ruled out. Healthcare professionals should therefore be appropriately informed, through the package insert, etc., of the occurrence, etc. of ischemic colitis following treatment with panobinostat.

4.(iii).B.(3).12) Venous thromboembolism
The applicant explained venous thromboembolism caused by panobinostat as follows:
The PT of venous thromboembolism-related adverse event categorized into the SMQ (MedDRA/J ver.16.0) of "Embolic and thrombotic events, venous" was summarized.

In Study D2308, venous thromboembolism was observed in 20 patients (5.2%) in the panobinostat group and in 15 patients (4.0%) in the placebo group. Grade ≥3 venous thromboembolism was observed in 9 patients (2.4%) and 6 patients (1.6%), respectively. In Studies DUS71 and B2207 (expanded cohort), venous thromboembolism was observed in 4 patients (7.3%) and 1 patient (6.7%), respectively, and Grade ≥3 events were observed in 2 patients (3.6%) and 1 patient (6.7%), respectively.

Venous thromboembolism resulted in death in 1 patient (0.3%) in the placebo group in Study D2308. The event was pulmonary embolism, and a causal relationship to the study drug was ruled out. There were no cases of death due to venous thromboembolism in the panobinostat group in Study D2308, or in either Study DUS71 or B2207 (expanded cohort). Serious venous thromboembolism was observed in 6 patients (1.6%) in the panobinostat group and in 8 patients (2.1%) in the placebo group in Study D2308, and a causal relationship to the study drug could not be ruled out in 3 patients (0.8%) and 2 patients (0.5%), respectively. In Study DUS71, serious venous thromboembolism was observed in 1 patient (1.8%), and a causal relationship to the study drug could not be ruled out. In Study B2207 (expanded cohort), there were no cases of serious venous thromboembolism. Venous thromboembolism leading to the discontinuation of study drug was reported by 2 patients (0.5%) in the panobinostat group of Study D2308, none in the placebo group of Study D2308, and none in either Study DUS71 or B2207 (expanded cohort). Venous thromboembolism leading to the interruption or dose reduction of the study drug was reported by 4 patients (1.0%) in the panobinostat group and 4 patients (1.1%) in the placebo group in Study D2308, 2 patients (3.6%) in Study DUS71, but none in Study B2207 (expanded cohort).

Based on these results, the applicant considered that treatment with panobinostat was unlikely to increase the risk of venous thromboembolism.

PMDA considers as follows:
There were cases of serious venous thromboembolism for which a causal relationship to panobinostat could not be ruled out. Healthcare professionals should therefore be appropriately informed, through the package insert, etc. of the occurrence, etc. of venous thromboembolism following treatment with panobinostat.

4.(iii).B.(3).13) Skin ulcer
Since the Japanese phase II study (Study B1201) was terminated prematurely because of the occurrence of skin ulcer [see "4.(iii).A *Reference data* (1) Japanese clinical study"], PMDA asked the applicant to explain the occurrence of skin ulcer.

The applicant responded as follows:
In Study B1201 in patients with cutaneous T-cell lymphoma (CTCL) or adult T-cell leukemia (ATL), skin ulcer was observed in 3 of 4 patients. The breakdown of the events included neoplasm malignant (aggravated primary disease localized to the left third finger, aggravated ATL with skin ulcer) in 2 patients and skin ulcer (systemic skin ulceration) in 1 patient. A causal relationship to the study drug was ruled out for the progression of malignant neoplasm in 2 patients. The patient with skin ulcer died because of sepsis caused by infection associated with aggravated ulcer, and a causal relationship of the skin ulcer to the study drug could not be ruled out.

In Study D2308, skin ulcer was observed in 3 patients (0.8%) in the panobinostat group and in 1 patient (0.3%) in the placebo group. There were no Grade ≥3 events. In Study DUS71, skin ulcer was observed in 1 patient (1.8%), and it was Grade 2 in severity. In Study B2207 (expanded cohort), there were no cases of skin ulcer.

Accordingly, the applicant considered that these skin ulcer-related events were unique to CTCL and ATL that are characterized by skin lesions, and are therefore unlikely to develop in patients with relapsed or refractory MM.

PMDA accepted the explanation of the applicant.

4.(iii).B.(4) Clinical positioning and indication
The proposed indication for panobinostat was "relapsed or refractory multiple myeloma." The applicant explained that the following precautionary statements would be included in the "Precautions for Indication" section in the package insert: (a) panobinostat should be administered to patients who are non-responsive to at least one of the standard regimens or who had a relapse after such regimen, and (b) eligibility of the patient for the therapy should be determined based on a good understanding of clinical study results and of the efficacy and safety of panobinostat.

Based on the results of the review in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety," and the reviews described in the sections 1) and 2) below, PMDA has concluded that the indication for panobinostat should be "relapsed or refractory multiple myeloma" as proposed by the applicant, and the following precautionary statements should be included in the "Precautions for Indications" section of the package insert.

- Panobinostat should be administered to patients who are non-responsive to at least one of the standard regimens or who had a relapse after such regimen.

- Eligibility of the patient for the therapy should be determined based on a good understanding of the study results in the "Clinical Studies" section of the package insert, including prior regimens of patients enrolled in the clinical studies, and of the efficacy and safety of panobinostat.

4.(iii).B.(4).1) Clinical positioning of panobinostat

PMDA confirmed that typical clinical oncology textbooks in and outside Japan describe the position of panobinostat in the treatment of relapsed or refractory MM, as shown below. Of note, panobinostat is not mentioned in the National Cancer Institute Physician Data Query (NCI-PDQ) (June 24, 2014), the Clinical Practice Guidelines for Hematopoietic Tumor, 2013 Edition (Kanehara & Co., Ltd., 2013), or the Clinical Practice Guidelines for Multiple Myeloma, Third Edition (Bunkodo Co., Ltd., 2012).

Clinical practice guidelines

- The NCCN Guidelines (version 4, 2015): The combination of panobinostat with BTZ and DEX is recommended for patients with MM who have received at least two prior regimens including BTZ and an immunomodulatory agent (thalidomide or lenalidomide).

Textbooks

- DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 10th edition (Lippincott Williams & Wilkins, 2014, USA): Since both clinical and nonclinical studies suggested the effectiveness of panobinostat in combination with BTZ, a randomized comparative study (Study D2308) was conducted to compare the efficacy, etc. between the BTZ monotherapy and the combination therapy with panobinostat and BTZ.

- Wintrobe's Clinical Hematology, Thirteenth Edition (Lippincott Williams & Wilkins, 2013, USA): In an open-label, uncontrolled study of panobinostat in combination with BTZ, 14 of 28 patients (50%) responded to the treatment, with 4 of the 14 achieving CR (ASH Annual Meeting Abstract 2009;114:3852). A randomized, comparative study of panobinostat in combination with BTZ (Study D2308) is ongoing.

PMDA considers as follows:

Based on prolonged PFS and acceptable safety profiles demonstrated in Study D2308 in patients with relapsed or refractory MM, the use of panobinostat in combination with BTZ and DEX may be regarded as a therapeutic option for patients with relapsed or refractory MM.

4.(iii).B.(4).2) Prior regimens

In Study D2308, patients with MM who had received 1 to 3 prior regimens were enrolled if they met either of the following criteria: (a) patients with relapsed MM who achieved minor response (MR) or better following the last treatment and had no disease progression during or within 60 days after the treatment, or (b) patients with refractory MM who experienced relapse following 1 or more regimens and did not achieve MR following prior regimens except with BTZ or had disease progression during or within 60 days after the treatment.

Patients with BTZ-refractory MM were excluded from Study D2308. PMDA asked the applicant to explain whether or not the use of panobinostat to these patients is appropriate.

The applicant responded as follows:

In Study DUS71 in patients with BTZ-refractory MM who had received 2 or more prior regimens including thalidomide or lenalidomide, the response rate in patients who received panobinostat in

combination with BTZ and DEX was 34.5% [see "4.(iii).A *Evaluation data* (3).11) Foreign phase II study"]. In a clinical study of pomalidomide and another clinical study of carfilzomib (unapproved in Japan) patients with BTZ-refractory MM with prior regimens, the response rates were reported to be 23.7% to 31% (*Lancet Oncol.* 2013;14:1055-66, *Blood.* 2012;120:2817-25). These results suggest that panobinostat is more effective than pomalidomide and carfilzomib in patients with BTZ-refractory MM. In addition, the results of Studies DUS71 and D2308 did not show clear difference in the safety profile of panobinostat between patients with BTZ-refractory MM and patients with BTZ-sensitive MM. The applicant considers that panobinostat is recommendable for patients with BTZ-refractory MM.

PMDA considers as follows:
The discussion of the applicant on the efficacy of panobinostat in patients with BTZ-refractory MM is based solely on the comparison with the external controls, precluding the adequate evaluation of the efficacy of panobinostat in these patients. Therefore, panobinostat is not recommendable for patients with BTZ-refractory MM. Nevertheless, panobinostat is usually used by physicians with expertise in hematopoietic malignancy; the product therefore can be used properly by healthcare professionals as long as they are informed, through the package insert, of prior regimens, etc. of the patients with relapsed or refractory MM in Study D2308. Therefore, the indication for panobinostat should be "relapsed or refractory multiple myeloma."

4.(iii).B.(5) Dosage and administration
The proposed dosage and administration of panobinostat was "in combination with other antineoplastic drugs, the usual adult dosage is 20 mg of panobinostat administered orally once daily 3 times a week for 2 weeks (Days 1, 3, 5, 8, 10, and 12), followed by a 9-day rest period (Days 13-21). The 3-week treatment cycle is repeated. The dose may be adjusted according to the condition of the patient."

PMDA conducted reviews as described in the later sections 1) to 4) and concluded that the dosage and administration of panobinostat should be defined as "in combination with bortezomib and dexamethasone, the usual adult dosage is 20 mg of panobinostat administered orally once daily 3 times a week for 2 weeks (Days 1, 3, 5, 8, 10, and 12), followed by a 9-day rest period (Days 13-21). The 3-week treatment cycle is repeated. The dose may be adjusted according to the condition of the patient." Also, the following precautionary statements should be provided in the "Precautions for Dosage and Administration" section of the package insert.

- The efficacy and safety of panobinostat monotherapy have not been established.
- Concomitant BTZ and DEX should be administered by physicians with a good understanding of the "Clinical Studies" section. The package inserts of the concomitant drugs should be read carefully.
- The efficacy and safety of panobinostat in combination with antineoplastic drugs other than BTZ and DEX have not been established.
- The efficacy and safety of panobinostat administered for >16 cycles (48 weeks) have not been established.
- Increased blood panobinostat concentration was reported in patients with hepatic impairment. In these patients, dose reduction should be considered and the condition of the patients should be closely monitored for possible adverse events.
- Before starting treatment with panobinostat, the following criteria should be read.

Criteria for the start of treatment

Platelet count	≥100,000/μL
Neutrophil count	≥1500/μL
QTc interval	<450 msec (panobinostat should not be administered if the mean QTc is prolonged to ≥450 msec on ECG performed after electrolyte abnormality is corrected.)
Blood electrolytes[*1]	If patients had electrolyte abnormality, the electrolyte level should be corrected as needed.

[*1] Blood potassium, magnesium, and phosphate

- The interruption, dose reduction, or discontinuation of panobinostat due to adverse drug reactions should be decided based on the following criteria according to the symptoms, grade,[*2] etc. of the adverse drug reactions. The 3-week treatment cycles should be maintained even after dose reduction. The dose may be reduced according to the patient's condition, by 5 mg/ but not to <10 mg/day.

[*2] NCI-CTCAE v.4.0

Criteria for the interruption, reduction, and discontinuation of panobinostat due to adverse drug reactions

	Criteria for interruption and dose reduction	Dose adjustment
Platelet count	<25,000/μL or <50,000/μL with haemorrhage	Interrupt treatment until platelet count increases to ≥50,000/μL. Reduce the current dosing level by 5 mg/dose when resuming treatment. If frequent platelet transfusion is required, consider discontinuing treatment. Reduce the dose again by 5 mg/dose (to 10 mg/dose) when decreased platelet count recurs during resumed treatment. Discontinue treatment if decreased platelet count recurs at 10 mg/dose.
Neutrophil count	≥500/μL and <1000/μL	Interrupt treatment until neutrophil count increases to ≥1000/μL. Resume treatment at the starting dose.
	<500/μL	Interrupt treatment until neutrophil count increases to ≥1000/μL. Reduce the current dosing level by 5 mg/dose when resuming treatment. Reduce the dose again by 5 mg/dose (to 10 mg/dose) when decreased neutrophil count recurs during resumed treatment. Discontinue treatment if decreased neutrophil count recurs at 10 mg/dose.
	Febrile neutropenia (<1000/μL with pyrexia of ≥38.5°C)	Interrupt treatment until pyrexia resolves and neutrophil count increases to ≥1000/μL. Reduce the current dosing level by 5 mg/dose when resuming treatment. Reduce the dose again by 5 mg/dose (to 10 mg/dose) when febrile neutropenia recurs during resumed treatment. Discontinue treatment if febrile neutropenia recurs at 10 mg/dose.
Diarrhea that persists despite the use of antidiarrheal drugs	Grade 2	Interrupt treatment until diarrhea improves to Grade ≤1. Resume treatment at the starting dose.
	Grade 3	Interrupt treatment until diarrhea improves to Grade ≤1. Reduce the current dosing level by 5 mg/dose when resuming treatment. Reduce the dose again by 5 mg/dose (to 10 mg/dose) when diarrhea recurs during resumed treatment. Discontinue treatment if diarrhea recurs at 10 mg/dose.
	Grade 4	Discontinue treatment.
Nausea or vomiting that persists despite the use of antiemetics	Grade ≥3	Interrupt treatment until nausea or vomiting improves to Grade ≤1. Reduce the current dosing level by 5 mg/dose when resuming treatment. Reduce the dose again by 5 mg (to 10 mg/dose) when nausea or vomiting recurs during resumed treatment. Discontinue treatment if the adverse drug reaction recurs at 10 mg/dose.
QTc interval	Prolongation to 480-500 msec or Prolongation of >60 msec from baseline	Interrupt treatment. Discontinue treatment if prolonged QTc interval does not resolve within 7 days. Resume treatment at the starting dose when prolonged QTc interval resolves within 7 days. If prolonged QTc interval recurs during resumed treatment but resolves within 7 days, reduce the dose by 5 mg/dose. If prolonged QTc interval recurs thereafter, reduce the dose again by 5 mg/dose (to 10 mg/dose). Discontinue treatment if prolonged QTc interval recurs at 10 mg/dose.
	Prolongation to more than 500 msec	Discontinue treatment.

	Criteria for interruption and dose reduction	Dose adjustment
Other adverse drug reactions	Grade ≥3 adverse drug reactions or relapse of Grade 2 adverse drug reactions	Interrupt treatment until symptom improves to Grade ≤1. Reduce the current dosing level by 5 mg/dose when resuming the treatment. Reduce the dose again by 5 mg/dose (to 10 mg/dose) when an adverse drug reaction recurs during resumed treatment. Discontinue treatment if the adverse drug reaction recurs at 10 mg/dose.

4.(iii).B.(5).1) Dose and dosing interval

The applicant explained the rationale for the determined dose and dosing interval of panobinostat, as follows:

In Studies A2101 and A2102, panobinostat was administered intravenously daily. The studies revealed a possible risk of QT prolongation due to the increased exposure to panobinostat. Therefore, in Study B2101, which was ongoing at that time, the enrollment of patients in the Group 2 for daily oral administration was cancelled [see "4.(iii).A *Evaluation data* (3).3) Foreign phase I study"]. Instead, intermittent dosing was investigated in Study B2101, and the MTD of oral panobinostat in once daily 3 times a week was determined to be 20 mg. In Study B2203 in patients with refractory MM, safety, etc. of oral panobinostat 20 mg once daily 3 times a week was investigated. The study yielded a favorable safety profile but failed to demonstrate the efficacy of panobinostat monotherapy.

The results of nonclinical studies [see "3.(i).A.(1).5) Inhibition of the growth of malignant tumor-derived cell strains"] showed that panobinostat strongly inhibits tumor growth when used in combination with BTZ as compared with panobinostat monotherapy. Therefore, in Study B2207 in patients with relapsed or refractory MM, the MTD, etc. of panobinostat in combination with BTZ was investigated. In the dose escalation cohort of Study B2207, panobinostat was administered once daily 3 times every week and BTZ was administered once daily twice a week for 2 weeks followed by a 1-week washout period. As a result, the MTD was determined to be 20 mg for panobinostat and 1.3 mg/m^2 for BTZ. In the expanded cohort of Study B2207, the incidence and severity of thrombocytopenia decreased in the regimen of 2-week treatment followed by 1-week washout as compared with every-week treatment. Therefore, the dosage regimen for panobinostat was changed from every-week treatment to 2-week treatment followed by 1-week washout, the same dosing schedule as used for BTZ.

In a clinical study in patients with relapsed or refractory MM (*Eur J Haematol.* 2009;83:449-54), the combination of BTZ with DEX 20 mg was administered from the early stage of treatment (once daily 4 times a week for 2 weeks followed by 1-week washout). The combination showed high tumor regression effect as compared with BTZ alone. Therefore, in the expanded cohort in Study B2207, from Cycle 2 onward, DEX 20 mg was administered once daily 4 times a week in combination with panobinostat 20 mg once daily 3 times a week and BTZ 1.3 mg/m^2 once daily twice a week. All 3 drugs were administered for 2 weeks followed by a 1-week washout. Panobinostat used in combination with BTZ and DEX showed favorable efficacy with a response rate of 73.3%. Therefore, in Studies D2308 and DUS71, the dose and dosing interval of these drugs were determined as follows: panobinostat 20 mg once daily 3 times a week for 2 weeks, followed by 1-week washout; BTZ 1.3 mg/m^2 once daily twice a week for 2 weeks, followed by 1-week washout; and DEX 20 mg once daily 4 times a week for 2 weeks, followed by 1-week washout. The proposed dosage and the dosing interval of panobinostat were determined based on those used in Studies D2308 and DUS71.

PMDA asked the applicant to explain the use of panobinostat in patients with relapsed or refractory MM for whom BTZ or DEX cannot be used.

The applicant responded as follows:

The proposed dosage and dosing interval of panobinostat were determined based on the rules used in Studies D2308 and DUS71, in which panobinostat was administered in combination with BTZ and DEX. Treatment with panobinostat is therefore not recommendable for patients with relapsed or refractory MM who cannot use BTZ or DEX.

PMDA considers as follows:
Based on the review in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety," panobinostat should be administered orally at 20 mg once daily 3 times a week for 2 weeks (Days 1, 3, 5, 8, 10, and 12), followed by a 9-day rest period (Days 13-21), as per Studies D2308 and DUS71. Repeating the 3-week cycle is acceptable.

Since the efficacy and safety of panobinostat are unknown in combination with drugs other than BTZ and DEX, the "Dosage and Administration" section of the package insert of panobinostat should clearly advise that panobinostat be administered in combination with BTZ and DEX. The rules for concomitant use with BTZ and DEX in Studies D2308 and DUS71 should be considered as guidelines on the administration of panobinostat, and these rules should be highlighted in the "Precautions for Dosage and Administration" section, etc. of the package insert in an appropriate manner.

4.(iii).B.(5).2) Dose adjustment
The applicant explained the proposed criteria for the start, interruption, dose reduction, and discontinuation of panobinostat, as follows:
In Study D2308, the criteria for the start, interruption, dose reduction, and discontinuation of panobinostat were defined, and panobinostat was tolerable in patients who complied with these criteria. Adverse events requiring attention in treatment with panobinostat, such as thrombocytopenia, neutropenia, diarrhea, nausea, vomiting, and QT prolongation need to be controlled by proper dose adjustment. For this purpose, the proposed "Precautions for Dosage and Administration" section mentions the following: (i) platelet count, neutrophil count, QTc interval, and blood electrolytes (potassium, magnesium, and phosphate in blood) as criteria for the start of treatment; (ii) platelet count, neutrophil count, diarrhea, nausea, vomiting, and QTc interval as criteria for the interruption, dose reduction, and discontinuation of treatment; (iii) and other adverse drug reactions. Since dose reduction to <10 mg was not investigated in Study D2308, the package insert advises against reducing the dose to <10 mg.

However, the proposed dose adjustment criteria are different in some aspects from those used in Study D2308, as detailed below:

- The criterion for the start of treatment according to neutrophil count was ≥1500/μL in Study D2308 and ≥1000/μL in Study DUS71. The incidence of neutrophil count decreased (75.0% in the panobinostat group in Study D2308, 70.4% in Study DUS71) and the incidence of febrile neutropenia (1.0% in the panobinostat group in Study D2308, 1.8% in Study DUS71), etc. were similar for the two studies. The proposed criterion was determined to be ≥1000/μL as per Study DUS71.

- The criterion for the start of treatment according to QTc interval was <450 ms in Study D2308. However, QTcF >500 ms was not observed in the panobinostat group in Study D2308, and QTcF interval of >480 ms and ≤500 ms was observed only in 5 patients (1.3%). Therefore, the proposed criterion was determined to be <480 ms.

- In Study D2308, the criteria for the interruption, dose reduction, and discontinuation of panobinostat due to neutrophil count had been determined as follows: (i) if neutrophil count is ≥500/μL and <750/μL, panobinostat should be interrupted until the count recovers to ≥1000/μL, and (ii) if neutrophil count is ≥750/μL and <1000/μL, neither treatment interruption nor dose reduction is necessary. In order to control neutrophil count more strictly, however, the proposed criteria specify that panobinostat should be interrupted if neutrophil count decreases to <1000/μL.

- In Study D2308, the criteria for the interruption, dose reduction, and discontinuation of panobinostat due to other adverse drug reactions were determined as follows: (i) in case of a Grade ≥3 adverse drug reaction, panobinostat should be interrupted until the adverse drug reaction improves to Grade ≤1, and (ii) when the treatment is resumed, each dose should be reduced by 1 level. In addition to (i) and (ii), the proposed criteria specify the action to be taken (i.e., reduction of the dose again by 1 level) when a Grade ≥3 adverse drug reaction recurs during the resumed treatment.

After the application for panobinostat was submitted in Japan, panobinostat was approved in the US in February 2015. PMDA asked the applicant to explain the necessity of revising the proposed package insert.

The applicant responded as follows:
In Study X2101, C_{max} of panobinostat in patients with mild, moderate, and severe hepatic impairment increased by 1.57, 1.83, and 1.69 times that in patients with solid cancer having normal hepatic function, respectively, and AUC_{inf} by 1.43, 2.05, and 1.81 times, respectively [see "4.(ii).A.(5) Foreign phase I study in patients with hepatic impairment"]. Based on these results, the US labeling defines the starting dose of panobinostat in patients with mild and moderate hepatic impairment to be 15 and 10 mg, respectively, and warns that panobinostat should not be used in patients with severe hepatic impairment. Accordingly, the "Precautions for Dosage and Administration" section of the proposed package insert was revised to add precautionary statements encouraging healthcare professionals to consider dose reduction of panobinostat and to closely monitor patient condition for possible adverse events when using panobinostat in patients with hepatic impairment.

PMDA considers as follows:
In Study D2308, the incidence of neutropenia was higher in Japanese patients than in non-Japanese patients. Therefore, the criterion for the start of treatment according to neutrophil count should be defined based on the rule stipulated in Study D2308. The QTc interval-related criterion for the start of treatment should remain as <450 ms based on the rule employed in Study D2308, because the rationale for the change to <480 ms is unclear. The criteria for the interruption, dose reduction, and discontinuation of panobinostat following the recurrence of an adverse drug reaction should be clearly established not only for "other adverse drug reactions" but also for all important adverse drug reactions listed.

Patients with hepatic impairment require close attention during treatment with panobinostat due to increased exposure to panobinostat. No study data are available on patients with hepatic impairment who received the starting dose of 15 or 10 mg. The applicant therefore plans to advise healthcare professionals to consider dose reduction in patients with hepatic impairment but without indicating any specific dose range; this is acceptable. The "Precautions for Dosage and Administration" section of the package insert should include the precautionary statements that, in patients with hepatic impairment, dose reduction should be considered according to the condition of the patient and that patients' condition should be closely monitored for possible adverse events. Since only 1 patient with severe hepatic impairment was investigated in Study X2101, safety information of panobinostat in patients with hepatic impairment should be further collected after the market launch and new findings should be provided to healthcare professionals in an appropriate manner once available.

4.(iii).B.(5).3) Treatment cycles
The applicant explained treatment cycles as follows:
The treatment cycles for panobinostat in Studies D2308 and DUS71 were designed with reference to the phase III study of BTZ in patients with MM that compared the efficacy, etc. between BTZ monotherapy and a high dose DEX (*N Engl J Med.* 2005;352:2487-98; [the APEX study]). Each cycle consisted of 3 weeks. Panobinostat was administered for 8 cycles in Treatment Phase 1 and another 8 cycles in Treatment Phase 2 (total 16 cycles). Study DUS71 was conducted in patients with BTZ-refractory MM, who had limited post-panobinostat therapeutic options. These patients were allowed to continue receiving panobinostat after the 8 cycles of Treatment Phase 2 if panobinostat was assessed as clinically useful by the investigator.

PMDA asked the applicant to describe patients who received panobinostat for >8 cycles in Treatment Phase 2.

The applicant responded as follows:
In Study D2308, there were no patients who received panobinostat for >8 cycles in Treatment Phase 2. In Study DUS71, 5 of 55 patients (9.1%) received panobinostat for >8 cycles in Treatment Phase 2. Panobinostat was discontinued in 3 of the 5 patients because of progressive disease (PD). Of the 3 patients, 1 patient achieved MR and then PR, and another patient continued to have PR. In 4 of the 5

patients, adverse events occurred after the completion of Cycle 8 in Treatment Phase 2. Grade ≥3 events observed were cellulitis/pulmonary embolism and alcoholism (1 patient each), but a causal relationship to panobinostat was ruled out for all of the events.

Thus, only limited clinical data are available on patients receiving panobinostat for >8 cycles in Treatment Phase 2. Therefore, the "Precautions for Dosage and Administration" section in the package insert included the precautionary statement that the efficacy and safety of panobinostat administered for >16 cycles (48 weeks) have not been established.

PMDA accepted the explanation of the applicant.

4.(iii).B.(5).4) Concomitant use with other antineoplastic drugs

PMDA asked the applicant to explain the possibility that panobinostat is concomitantly administered with antineoplastic drugs other than BTZ and DEX.

The applicant responded as follows:

Panobinostat is reported to have a mechanism of action that yields clinical benefit when concomitantly administered with antineoplastic drugs other than BTZ (*Ther Adv Hematol.* 2014;5:197-210). Therefore, in addition to Study B2206 that investigated the safety, etc. of combination therapy with panobinostat, lenalidomide, and DEX in patients with MM [see "4.(iii).A *Reference data* (2).2) Foreign phase I study"], foreign clinical studies were conducted on the use of panobinostat in combination with BTZ, thalidomide, and DEX and in combination with carfirzomib (unapproved in Japan) (e.g., *Blood.* 2014;124:Abstract 32).

The efficacy and safety of panobinostat in combination with antineoplastic drugs other than BTZ and DEX are currently unknown, and there are no clinical data that validate the benefit of such combination therapy. Therefore, the use of panobinostat in combination with antineoplastic drugs other than BTZ and DEX should not be recommended.

PMDA considers as follows:

The explanation of the applicant is acceptable. Therefore, the "Precautions for Dosage and Administration" section of the package insert should highlight that the efficacy and safety of panobinostat in combination with antineoplastic drugs other than BTZ and DEX have not been established.

4.(iii).B.(6) Post-marketing surveillance

The applicant explained the plan for post-marketing surveillance as follows:

In order to evaluate the safety, etc. of panobinostat in routine clinical practice after the market launch, the applicant plans to conduct post-marketing surveillance in all patients with relapsed or refractory MM who have received panobinostat.

The proposed priority investigation items of the post-marketing surveillance are QT prolongation, bone marrow depression, hemorrhage, infection, hepatic impairment, renal dysfunction, and diarrhea; these items were selected based on the incidence of adverse events shown by the pooled analysis of clinical study data on the safety of the combination with panobinostat, BTZ, and DEX.

The target sample size was determined as 350 based on the following hypothesis: (i) the registration period for participating patients was assumed to be 1 year from the start of marketing of panobinostat, and (ii) of 2100 patients with relapsed or refractory MM who were expected to be treated with BTZ a year, 350 patients were assumed to receive concomitant panobinostat during the registration period. This sample size would have a ≥95% probability to detect 1 patient experiencing hepatic dysfunction. According to the pooled analysis of clinical studies in patients with MM, hepatic dysfunction was the least frequent serious adverse event among the priority investigation items.

The follow-up period for the post-marketing surveillance was determined to be up to 1 year (48 weeks) In Study D2308, the median treatment period in the panobinostat group was 5 months, and most of the adverse events included in the priority investigation items occurred within 6 months after the start of

treatment with panobinostat. Therefore, a 1-year follow-up period would be sufficient to understand the safety profile of panobinostat.

PMDA considers as follows:
Only limited information is available on the safety of panobinostat in Japanese patients with relapsed or refractory MM. Relevant information should therefore be collected from all patients receiving panobinostat for a certain period after the market launch in a prompt and unbiased manner, and obtained information should be provided to healthcare professionals immediately.

Nausea, vomiting, and dehydration require attention during treatment with panobinostat, and these events should also be included in the priority investigation items. The target sample size proposed by the applicant is appropriate. The follow-up period should be reconsidered taking account of the occurrences of the events added to the priority investigation items.

4.(iv) Adverse events, etc. observed in clinical studies
Deaths reported in clinical data submitted for safety evaluation are described in "4.(iii) Summary of clinical efficacy and safety." Major adverse events other than death were as follows.

4.(iv).(1) Japanese phase I study (Study A1101)
All patients experienced adverse events. All patients also experienced adverse events for which a causal relationship to panobinostat could not be ruled out. Adverse events with an incidence of ≥40% in any group are shown in the following table.

Adverse events with an incidence of ≥40% in any group

System organ class Preferred tem (MedDRA ver.12.1)	Number of patients (%)					
	10 mg/m^2 N = 3		15 mg/m^2 N = 3		20 mg/m^2 N = 8	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	1 (33.3)	3 (100)	3 (100)	8 (100)	8 (100)
Blood and lymphatic system disorders						
Thrombocytopenia	3 (100)	1 (33.3)	3 (100)	2 (66.7)	8 (100)	5 (62.5)
Leukopenia	3 (100)	0	1 (33.3)	1 (33.3)	5 (62.5)	2 (25.0)
Neutropenia	2 (66.7)	0	1 (33.3)	1 (33.3)	5 (62.5)	3 (37.5)
Gastrointestinal disorders						
Nausea	1 (33.3)	0	2 (66.7)	0	4 (50.0)	0
Stomatitis	2 (66.7)	0	1 (33.3)	0	3 (37.5)	0
General disorders and administration site conditions						
Fatigue	2 (66.7)	0	2 (66.7)	1 (33.3)	3 (37.5)	1 (12.5)
Pyrexia	0	0	1 (33.3)	0	4 (50.0)	0
Investigations						
Blood thyroid stimulating hormone increased	0	0	2 (66.7)	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	1 (33.3)	0	2 (66.7)	1 (33.3)	5 (62.5)	0
Hypoalbuminaemia	1 (33.3)	0	3 (100)	0	2 (25.0)	0
Hyponatraemia	0	0	2 (66.7)	1 (33.3)	0	0
Nervous system disorders						
Dysgeusia	2 (66.7)	0	1 (33.3)	0	1 (12.5)	0
Skin and subcutaneous tissue disorders						
Rash	2 (66.7)	0	0	0	3 (37.5)	0

Serious adverse events were observed in 1 of 3 patients (33.3%) in the 15 mg/m^2 group and in 2 of 8 patients (25.0%) in the 20 mg/m^2 group. The serious adverse events observed were hemicephalalgia (1 patient [33.3%]) in the 15 mg/m^2 group and ALT increased, AST increased, and femoral neck fracture (1 patient each [12.5%]) in the 20 mg/m^2. A causal relationship to panobinostat could not be ruled out for ALT increased and AST increased (1 patient each) in the 20 mg/m^2 group.

Adverse events leading to the discontinuation of panobinostat were reported by 2 of 14 patients (14.3%) in the 20 mg/m^2 group. These were ALT increased, AST increased, and femoral neck fracture (1 patient each [7.1%]). A causal relationship to panobinostat could not be ruled out for ALT increased and AST

increased (1 patient each).

4.(iv).(2) Japanese phase II study (Study B1101)

All patients experienced adverse events. All patients also experienced adverse events for which a causal relationship to panobinostat could not be ruled out. Adverse events with an incidence of ≥40% in any group are shown in the following table.

Adverse events with an incidence of ≥40% in any group

System organ class Preferred term (MedDRA ver.11.0)	Number of patients (%)					
	10 mg N = 3		15 mg N = 4		20 mg N = 6	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	1 (33.3)	4 (100)	2 (50.0)	6 (100)	5 (83.3)
Blood and lymphatic system disorders						
Thrombocytopenia	2 (66.7)	0	2 (50.0)	1 (25.0)	3 (50.0)	0
Gastrointestinal disorders						
Diarrhoea	3 (100)	0	3 (75.0)	0	4 (66.7)	0
Nausea	3 (100)	1 (33.3)	3 (75.0)	0	4 (66.7)	0
Vomiting	2 (66.7)	1 (33.3)	2 (50.0)	0	4 (66.7)	0
General disorders and administration site conditions						
Fatigue	0	0	1 (25.0)	0	4 (66.7)	0
Pyrexia	2 (66.7)	0	0	0	3 (50.0)	0
Investigations						
Platelet count decreased	0	0	2 (50.0)	1 (25.0)	3 (50.0)	3 (50.0)
Weight decreased	2 (66.7)	0	2 (50.0)	1 (25.0)	1 (16.7)	0
Blood albumin decreased	0	0	0	0	3 (50.0)	0
Haemoglobin decreased	0	0	0	0	3 (50.0)	1 (16.7)
Metabolism and nutrition disorders						
Anorexia	2 (66.7)	0	1 (25.0)	0	4 (66.7)	0
Nervous system disorders						
Dizziness	1 (33.3)	0	2 (50.0)	0	1 (16.7)	0
Dysgeusia	2 (66.7)	0	0	0	2 (33.3)	0
Respiratory, thoracic and mediastinal disorders						
Cough	0	0	2 (50.0)	0	1 (16.7)	0

Serious adverse events were observed in 1 of 3 patients (33.3%) in the 10 mg group and in 1 of 6 patients (16.7%) in the 20 mg group. The serious adverse events observed were anorexia (1 patient [33.3%]) in the 10 mg group and atrial fibrillation (1 patient [16.7%]) in the 20 mg group. A causal relationship to panobinostat could not be ruled out for either event.

There were no adverse events leading to the discontinuation of panobinostat.

4.(iv).(3) Global phase III study (Study D2308)

Adverse events were observed in 380 of 381 patients (99.7%) in the panobinostat group and in 376 of 377 patients (99.7%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 345 of 381 patients (90.6%) and in 284 of 377 patients (75.3%), respectively. Adverse events with an incidence of ≥10% in either group are shown in the following table.

Adverse events with an incidence of ≥10% in either group

System organ class Preferred term (MedDRA ver.16.0)	Number of patients (%)			
	Panobinostat N = 381		Placebo N =377	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	380 (99.7)	364 (95.5)	376 (99.7)	310 (82.2)
Blood and lymphatic system disorders				
Thrombocytopenia	246 (64.6)	217 (57.0)	154 (40.8)	94 (24.9)
Anaemia	158 (41.5)	63 (16.5)	126 (33.4)	60 (15.9)
Neutropenia	114 (29.9)	92 (24.1)	40 (10.6)	30 (8.0)
Leukopenia	62 (16.3)	35 (9.2)	31 (8.2)	12 (3.2)
Lymphopenia	52 (13.6)	47 (12.3)	35 (9.3)	28 (7.4)
Gastrointestinal disorders				
Diarrhoea	260 (68.2)	97 (25.5)	157 (41.6)	30 (8.0)
Nausea	138 (36.2)	21 (5.5)	78 (20.7)	2 (0.5)
Constipation	102 (26.8)	4 (1.0)	123 (32.6)	4 (1.1)
Vomiting	98 (25.7)	28 (7.3)	49 (13.0)	5 (1.3)
Abdominal pain	51 (13.4)	9 (2.4)	40 (10.6)	3 (0.8)
Dyspepsia	47 (12.3)	1 (0.3)	43 (11.4)	1 (0.3)
Abdominal pain upper	44 (11.5)	3 (0.8)	36 (9.5)	1 (0.3)
General disorders and administration site conditions				
Fatigue	157 (41.2)	65 (17.1)	110 (29.2)	33 (8.8)
Oedema peripheral	109 (28.6)	8 (2.1)	72 (19.1)	1 (0.3)
Pyrexia	99 (26.0)	5 (1.3)	56 (14.9)	7 (1.9)
Asthenia	84 (22.0)	36 (9.4)	55 (14.6)	14 (3.7)
Infections and infestations				
Upper respiratory tract infection	68 (17.8)	9 (2.4)	55 (14.6)	6 (1.6)
Pneumonia	65 (17.1)	48 (12.6)	48 (12.7)	39 (10.3)
Nasopharyngitis	49 (12.9)	0	47 (12.5)	2 (0.5)
Herpes zoster	18 (4.7)	4 (1.0)	40 (10.6)	7 (1.9)
Investigations				
Weight decreased	44 (11.5)	7 (1.8)	17 (4.5)	2 (0.5)
Platelet count decreased	43 (11.3)	35 (9.2)	17 (4.5)	13 (3.4)
Blood creatinine increased	38 (10.0)	4 (1.0)	22 (5.8)	6 (1.6)
Metabolism and nutrition disorders				
Decreased appetite	107 (28.1)	12 (3.1)	47 (12.5)	4 (1.1)
Hypokalaemia	104 (27.3)	73 (19.2)	53 (14.1)	24 (6.4)
Hyponatraemia	49 (12.9)	37 (9.7)	19 (5.0)	13 (3.4)
Hypophosphataemia	43 (11.3)	33 (8.7)	32 (8.5)	24 (6.4)
Musculoskeletal and connective tissue disorders				
Back pain	48 (12.6)	3 (0.8)	47 (12.5)	5 (1.3)
Pain in extremity	40 (10.5)	1 (0.3)	54 (14.3)	3 (0.8)
Nervous system disorders				
Neuropathy peripheral	117 (30.7)	26 (6.8)	133 (35.3)	21 (5.6)
Dizziness	71 (18.6)	11 (2.9)	62 (16.4)	9 (2.4)
Headache	52 (13.6)	3 (0.8)	40 (10.6)	1 (0.3)
Peripheral sensory neuropathy	42 (11.0)	9 (2.4)	46 (12.2)	7 (1.9)
Neuralgia	38 (10.0)	5 (1.3)	44 (11.7)	3 (0.8)
Psychiatric disorders				
Insomnia	73 (19.2)	0	61 (16.2)	1 (0.3)
Respiratory, thoracic and mediastinal disorders				
Cough	81 (21.3)	4 (1.0)	70 (18.6)	0
Dyspnoea	56 (14.7)	9 (2.4)	44 (11.7)	9 (2.4)
Vascular disorders				
Hypotension	53 (13.9)	11 (2.9)	35 (9.3)	5 (1.3)

Serious adverse events were observed in 228 of 381 patients (59.8%) in the panobinostat group and in 157 of 377 patients (41.6%) in the placebo group. Serious adverse events reported by ≥5 patients were, in the panobinostat group, pneumonia (56 patients [14.7%]), diarrhoea (43 patients [11.3%]), thrombocytopenia (28 patients [7.3%]), pyrexia (16 patients [4.2%]), asthenia (15 patients [3.9%]), anaemia (14 patients [3.7%]), vomiting (12 patients [3.1%]), fatigue and dehydration (11 patients each [2.9%]), sepsis, septic shock, and orthostatic hypotension (9 patients each [2.4%]), urinary tract infection and hypokalaemia (8 patients each [2.1%]), nausea, gastroenteritis, and renal failure acute (7 patients each [1.8%]), ileus, infection, dizziness, loss of consciousness, syncope, respiratory failure, and hypotension (5 patients each [1.3%]); and, in the placebo group, pneumonia (40 patients [10.6%]), pyrexia (11 patients [2.9%]), diarrhoea and renal failure acute (9 patients each [2.4%]),

thrombocytopenia (8 patients [2.1%]), sepsis and dyspnoea (7 patients each [1.9%]), asthenia (6 patients [1.6%]), dehydration and herpes zoster (5 patients each [1.3%]). A causal relationship to the study drug could not be ruled out, in the panobinostat group, for pneumonia (31 patients), diarrhoea (30 patients), thrombocytopenia (22 patients), vomiting (11 patients), fatigue (10 patients), anaemia (9 patients), orthostatic hypotension (7 patients), asthenia, hypokalaemia, and nausea (6 patients each), pyrexia (5 patients), dehydration, ileus, and infection (4 patients each), sepsis, loss of consciousness, syncope, and hypotension (3 patients each), urinary tract infection, gastroenteritis, and dizziness (2 patients each), and septic shock and respiratory failure (1 patient each); and in the placebo group, for pneumonia (13 patients), diarrhoea and thrombocytopenia (6 patients each), pyrexia (4 patients), dyspnoea (3 patients), dehydration (2 patients), sepsis and herpes zoster (1 patient each).

Adverse events leading to the discontinuation of study drug were reported by 138 of 381 patients (36.2%) in the panobinostat group and in 77 of 377 patients (20.4%) in the placebo group. Adverse events leading to the discontinuation of study drug reported by ≥5 patients were, in the panobinostat group, diarrhoea (17 patients [4.5%]), neuropathy peripheral (14 patients [3.7%]), asthenia and fatigue (11 patients each [2.9%]), thrombocytopenia (6 patients [1.6%]), and pneumonia (5 patients [1.3%]); and, in the placebo group, fatigue (11 patients [2.9%]), pneumonia (8 patients [2.1%]), neuropathy peripheral (7 patients [1.9%]), and diarrhoea (6 patients [1.6%]). A causal relationship to the study drug could not be ruled out, in the panobinostat group, for diarrhoea (12 patients), fatigue (11 patients), neuropathy peripheral (7 patients), thrombocytopenia and asthenia (5 patients each), pneumonia (3 patients), and peripheral sensory neuropathy (1 patient); and in the placebo group, for fatigue (10 patients), diarrhoea (6 patients), neuropathy peripheral (5 patients), and pneumonia (3 patients).

4.(iv).(4) Foreign phase I study (Study A2101)

Adverse events were observed in all patients. Adverse events for which a causal relationship to panobinostat could not be ruled out were observed in 2 of 3 patients (66.7%) in the 2.4 mg/m^2 group, 2 of 3 patients (66.7%) in the 4.8 mg/m^2 group, 4 of 7 patients (57.1%) in the 7.2 mg/m^2 group, and 8 of 8 patients (100%) in the 9.0 mg/m^2 group in Group 1; in 1 of 1 patient (100%) in the 4.8 mg/m^2 group, 1 of 1 patient (100%) in the 9.6 mg/m^2 group, 3 of 3 patients (100%) in the 15.0 mg/m^2 group, and 1 of 1 patient (100%) in the 20.0 mg/m^2 group in Group 2; in 8 of 8 patients (100%) in the 10.0 mg/m^2 group, 8 of 8 patients (100%) in the 15.0 mg/m^2 group, and 30 of 31 patients (96.8%) in the 20.0 mg/m^2 group in Group 3; and in 6 of 6 patients (100%) in the 20.0 mg/m^2 group and 3 of 3 patients (100%) in the 25.0 mg/m^2 group in Group 4. Serious adverse events were observed in 1 of 2 patients (50.0%) in the 1.2 mg/m^2 group, 1 of 3 patients (33.3%) in the 4.8 mg/m^2 group, 3 of 7 patients (42.9%) in the 7.2 mg/m^2 group, and 4 of 8 patients (50.0%) in the 9.0 mg/m^2 group in Group 1; in 1 of 1 patient (100%) in the 4.8 mg/m^2 group, 1 of 3 patients (33.3%) in the 15.0 mg/m^2 group, and 1 of 1 patient (100%) in the 20.0 mg/m^2 group in Group 2; in 4 of 8 patients (50.0%) in the 10.0 mg/m^2 group, 5 of 8 patients (62.5%) in the 15.0 mg/m^2 group, 22 of 31 patients (71.0%) in the 20.0 mg/m^2 group in Group 3; and in 4 of 6 patients (66.7%) in the 20.0 mg/m^2 group and 3 of 3 patients (100%) in the 25.0 mg/m^2 group in Group 4. Serious adverse events reported by ≥2 patients in any group were, in Group 1, thrombocytopenia (3 patients [37.5%]) in the 9.0 mg/m^2 group; in Group 3, thrombocytopenia (7 patients [22.6%]), anaemia, neutropenia, pneumonia, and dyspnoea (3 patients each [9.7%]), and pleural effusion (2 patients [6.5%]) in the 20.0 mg/m^2 group; and, in Group 4, dehydration (2 patients [33.3%]) in the 20.0 mg/m^2 group and dehydration (2 patients [66.7%]) in the 25.0 mg/m^2 group. A causal relationship to panobinostat could not be ruled out for thrombocytopenia (3 patients) in the 9.0 mg/m^2 group in Group 1, and for thrombocytopenia (7 patients), neutropenia (2 patients), anaemia and dyspnoea (1 patient each) in the 20.0 mg/m^2 group in Group 3.

Adverse events leading to the discontinuation of panobinostat were reported by 1 of 2 patients (50.0%) in the 1.2 mg/m^2 group, 2 of 7 patients (28.6%) in the 7.2 mg/m^2 group, and 1 of 8 patients (12.5%) in the 9.0 mg/m^2 group in Group 1; in 1 of 1 patient (100%) in the 4.8 mg/m^2 group and 1 of 1 patient (100%) in the 20.0 mg/m^2 group in Group 2; in 1 of 8 patients (12.5%) in the 10.0 mg/m^2 group and 7 of 31 patients (22.6%) in the 20.0 mg/m^2 group in Group 3; and in 4 of 6 patients (66.7%) in the 20.0 mg/m^2 group and 2 of 3 patients (66.7%) in the 25.0 mg/m^2 group in Group 4. There were no adverse events leading to the discontinuation of panobinostat reported by ≥2 patients in any group.

4.(iv).(5) Foreign phase I/II study (Study A2102)

Adverse events were observed in all patients. Adverse events for which a causal relationship to panobinostat could not be ruled out were observed in 2 of 3 patients (66.7%) in the 4.8 mg/m^2 group, 2 of 3 patients (66.7%) in the 7.2 mg/m^2 group, 1 of 1 patient (100%) in the 9.0 mg/m^2 group, 3 of 3 patients (100%) in the 11.5 mg/m^2 group, and 5 of 5 patients (100%) in the 14.0 mg/m^2 group.

Serious adverse events were observed in 1 of 3 patients (33.3%) in the 4.8 mg/m^2 group, 2 of 3 patients (66.7%) in the 7.2 mg/m^2 group, 3 of 3 patients (100%) in the 11.5 mg/m^2 group, and 4 of 5 patients (80.0%) in the 14.0 mg/m^2 group. The serious adverse events observed were, in the 4.8 mg/m^2 group, febrile neutropenia and hypoxia (1 patient each [33.3%]); in the 7.2 mg/m^2 group, atrial fibrillation, febrile neutropenia, acute myocardial infarction, and troponin increased (1 patient each [33.3%]); in the 11.5 mg/m^2 group, febrile neutropenia (2 patients [66.7%]), neutropenia, thrombocytopenia, electrocardiogram QT prolonged, ALT increased, and hypotension (1 patient each [33.3%]); and, in the 14.0 mg/m^2 group, electrocardiogram QT corrected interval prolonged (2 patients [40.0%]), staphylococcal bacteraemia, febrile neutropenia, pulmonary haemorrhage, staphylococcal sepsis, thrombocytopenia, pleural effusion, pyrexia, pericardial effusion, respiratory distress, epigastric discomfort, and hypokalaemia (1 patient each [20.0%]). A causal relationship to panobinostat could not be ruled out for atrial fibrillation (1 patient) in the 7.2 mg/m^2 group; for thrombocytopenia, neutropenia, electrocardiogram QT prolonged, and ALT increased (1 patient each) in the 11.5 mg/m^2 group; and for electrocardiogram QT corrected interval prolonged (2 patients), pulmonary haemorrhage, staphylococcal sepsis, thrombocytopenia, pericardial effusion, respiratory distress, epigastric discomfort, and hypokalaemia (1 patient each) in the 14 mg/m^2 group.

Adverse events leading to the discontinuation of panobinostat were reported by 1 of 3 patients (33.3%) in the 7.2 mg/m^2 group, 1 of 3 patients (33.3%) in the 11.5 mg/m^2 group, and 3 of 5 patients (60.0%) in the 14.0 mg/m^2 group. These were atrial fibrillation (1 patient [33.3%]) in the 7.2 mg/m^2 group, electrocardiogram QT prolonged (1 patient [33.3%]) in the 11.5 mg/m^2 group, electrocardiogram QT corrected interval prolonged (2 patients [40.0%]), pulmonary haemorrhage, and staphylococcal sepsis (1 patient each [20.0%]) in the 14.0 mg/m^2 group. A causal relationship to panobinostat could not be ruled out for all events.

4.(iv).(6) Foreign phase I study (Study B2101)

4.(iv).(6).1) Three-times-a-week (every week) regimen

Adverse events were observed in all patients. Adverse events for which a causal relationship to panobinostat could not be ruled out were observed in 2 of 3 patients (66.7%) in the 15 mg group, 22 of 22 patients (100%) in the 20 mg group, 12 of 14 patients (85.7%) in the 20 mg (fed administration) group, and 8 of 10 patients (80.0%) in the 30 mg group. Adverse events with an incidence of ≥40% in any group are shown in the following table.

Adverse events with an incidence of ≥40% in any group

System organ class Preferred term (MedDRA ver.13.0)	Number of patients (%)							
	15 mg N = 3		20 mg N = 22		20 mg (fed administration) N = 14		30 mg N = 10	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	22 (100)	16 (72.7)	14 (100)	9 (64.3)	10 (100)	7 (70.0)
Blood and lymphatic system disorders								
Anaemia	1 (33.3)	0	2 (9.1)	2 (9.1)	3 (21.4)	1 (7.1)	4 (40.0)	1 (10.0)
Thrombocytopenia	0	0	10 (45.5)	6 (27.3)	5 (35.7)	5 (35.7)	5 (50.0)	3 (30.0)
Gastrointestinal disorders								
Diarrhoea	1 (33.3)	1 (33.3)	11 (50.0)	1 (4.5)	8 (57.1)	0	7 (70.0)	1 (10.0)
Nausea	1 (33.3)	0	15 (68.2)	0	12 (85.7)	0	5 (50.0)	0
Vomiting	1 (33.3)	0	4 (18.2)	0	8 (57.1)	0	4 (40.0)	0
General disorders and administration site conditions								
Fatigue	1 (33.3)	0	13 (59.1)	2 (9.1)	10 (71.4)	0	6 (60.0)	0
Oedema peripheral	0	0	6 (27.3)	0	8 (57.1)	0	2 (20.0)	0
Investigations								
Weight decreased	0	0	9 (40.9)	0	6 (42.9)	0	3 (30.0)	0
Metabolism and nutrition disorders								
Anorexia	1 (33.3)	0	16 (72.7)	0	8 (57.1)	0	6 (60.0)	0
Musculoskeletal and connective tissue disorders								
Arthralgia	3 (100)	1 (33.3)	3 (13.6)	0	2 (14.3)	0	1 (10.0)	0
Pain in extremity	2 (66.7)	0	2 (9.1)	0	3 (21.4)	0	3 (30.0)	0
Nervous system disorders								
Dizziness	0	0	4 (18.2)	0	8 (57.1)	0	3 (30.0)	0
Headache	0	0	2 (9.1)	0	4 (28.6)	0	4 (40.0)	0

Serious adverse events were observed in 1 of 3 patients (33.3%) in the 15 mg group, 9 of 22 patients (40.9%) in the 20 mg group, 7 of 14 patients (50.0%) in the 20 mg (fed administration) group, and 6 of 10 patients (60.0%) in the 30 mg group. The serious adverse events observed were, in the 15 mg group, nausea, asthenia, general physical health deterioration, and anorexia (1 patient each [33.3%]); in the 20 mg group, skin infection and rash (2 patients each [9.1%]), dyspnoea, pleural effusion, pyrexia, pleuritic pain, atrial fibrillation, atrial flutter, cardiac failure, tachycardia, catheter sepsis, pseudomonas infection, streptococcal infection, pain of skin, cancer pain, renal dysfunction, and peripheral ischaemia (1 patient each [4.5%]); in the 20 mg (fed administration) group, dyspnoea (2 patients [14.3%]) and pleural effusion, sinus bradycardia, abdominal pain, hypovolaemia, lumbar vertebral fracture, and bone pain (1 patient each [7.1%]); and, in the 30 mg group, dyspnoea, back pain, pleural effusion, pyrexia, cough, respiratory failure, diarrhoea, pneumonia, and thrombocytopenia (1 patient each [10.0%]). A causal relationship to panobinostat could not be ruled out for atrial flutter, cardiac failure, renal dysfunction, and peripheral ischaemia (1 patient each) in the 20 mg group; for hypovolaemia (1 patient) in the 20 mg (fed administration) group; and for thrombocytopenia and diarrhoea (1 patient each) in the 30 mg group.

Adverse events leading to the discontinuation of panobinostat were reported by 6 of 22 patients (27.3%) in the 20 mg group, 3 of 14 patients (21.4%) in the 20 mg (fed administration) group, and 3 of 10 patients (30.0%) in the 30 mg group. These were, in the 20 mg group, neutropenia, thrombocytopenia, diarrhoea, nausea, skin infection, and rash (1 patient each [4.5%]); in the 20 mg (fed administration) group, sinus bradycardia, anorexia, and bone pain (1 patient each [7.1%]); and, in the 30 mg group, diarrhoea, anorexia, and pleural effusion (1 patient each [10.0%]). A causal relationship to panobinostat could not be ruled out for neutropenia, thrombocytopenia, diarrhoea, and nausea (1 patient each) in the 20 mg group; and for diarrhoea (1 patient) in the 30 mg group.

4.(iv).(6).2) Three-times-a-week (every other week) regimen

Adverse events were observed in all patients. Adverse events for which a causal relationship to panobinostat could not be ruled out were also observed in all patients. Adverse events with an incidence of ≥40% in either group are shown in the following table.

Adverse events with an incidence of ≥40% in either group

System organ class Preferred term (MedDRA ver.13.0)	Number of patients (%)			
	30 mg N = 21		45 mg N = 2	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	21 (100)	18 (85.7)	2 (100)	2 (100)
Blood and lymphatic system disorders				
Anaemia	5 (23.8)	3 (14.3)	1 (50.0)	0
Thrombocytopenia	8 (38.1)	6 (28.6)	2 (100)	2 (100)
Gastrointestinal disorders				
Diarrhoea	11 (52.4)	1 (4.8)	2 (100)	1 (50.0)
Nausea	12 (57.1)	0	0	0
Stomatitis	2 (9.5)	0	1 (50.0)	0
Vomiting	9 (42.9)	0	0	0
General disorders and administration site conditions				
Fatigue	16 (76.2)	1 (4.8)	2 (100)	0
Pyrexia	9 (42.9)	1 (4.8)	0	0
Infections and infestations				
Herpes simplex	0	0	1 (50.0)	0
Metabolism and nutrition disorders				
Anorexia	15 (71.4)	0	1 (50.0)	0
Vascular disorders				
Hypertension	1 (4.8)	0	1 (50.0)	0

Serious adverse events were observed in 10 of 21 patients (47.6%) in the 30 mg group and in 1 of 2 patients (50.0%) in the 45 mg group. The serious adverse events observed were, in the 30 mg group, dyspnoea (3 patients [14.3%]), thrombocytopenia (2 patients [9.5%]), vertigo, diarrhoea, vomiting, asthenia, catheter thrombosis, general physical health deterioration, pyrexia, infection, pseudomonal sepsis, pyelonephritis, skin infection, bacteria stool identified, dehydration, bone pain, musculoskeletal chest pain, transient ischaemic attack, urinary retention, and pleural effusion (1 patient each [4.8%]); and, in the 45 mg group, thrombocytopenia (1 patient [50.0%]). A causal relationship to panobinostat could not be ruled out for thrombocytopenia (2 patients) in the 30 mg group and thrombocytopenia (1 patient) in the 45 mg group.

Adverse events leading to the discontinuation of panobinostat were reported by 5 of 21 patients (23.8%) in the 30 mg group and 1 of 2 patients (50.0%) in the 45 mg group. These were, in the 30 mg group, fatigue (2 patients [9.5%]), and neutropenia, thrombocytopenia, nausea, pyrexia, hyperbilirubinaemia, and lethargy (1 patient each [4.8%]); and, in the 45 mg group, fatigue (1 patient [50.0%]). A causal relationship to panobinostat could not be ruled out for fatigue (2 patients), and neutropenia, thrombocytopenia, and nausea (1 patient each) in the 30 mg group, and for fatigue (1 patient) in the 45 mg group.

4.(iv).(6).3) Twice-a-week (every week) regimen

Adverse events were observed in all patients. Adverse events for which a causal relationship to panobinostat could not be ruled out were observed in 3 of 3 patients (100%) in the 30 mg group, 14 of 15 patients (93.3%) in the 45 mg group, and 3 of 4 patients (75.0%) in the 60 mg group. Adverse events with an incidence of ≥40% in any group are shown in the following table.

Adverse events with an incidence of ≥40% in any group

System organ class Preferred term (MedDRA ver.13.0)	Number of patients (%)					
	30 mg N = 3		45 mg N = 15		60 mg N = 4	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	15 (100)	12 (80.0)	4 (100)	4 (100)
Blood and lymphatic system disorders						
Anaemia	1 (33.3)	1 (33.3)	7 (46.7)	4 (26.7)	2 (50.0)	1 (25.0)
Thrombocytopenia	1 (33.3)	1 (33.3)	8 (53.3)	5 (33.3)	3 (75.0)	3 (75.0)
Gastrointestinal disorders						
Diarrhoea	1 (33.3)	0	9 (60.0)	0	1 (25.0)	0
Dry mouth	0	0	3 (20.0)	0	2 (50.0)	0
Dyspepsia	2 (66.7)	0	0	0	1 (25.0)	0
Nausea	2 (66.7)	0	10 (66.7)	0	1 (25.0)	0
Stomatitis	1 (33.3)	0	0	0	2 (50.0)	0
Vomiting	2 (66.7)	0	5 (33.3)	0	3 (75.0)	0
General disorders and administration site conditions						
Fatigue	2 (66.7)	0	9 (60.0)	1 (6.7)	3 (75.0)	1 (25.0)
Oedema peripheral	2 (66.7)	0	5 (33.3)	0	2 (50.0)	0
Pyrexia	2 (66.7)	0	2 (13.3)	0	2 (50.0)	0
Infections and infestations						
Upper respiratory tract infection	2 (66.7)	0	0	0	0	0
Metabolism and nutrition disorders						
Anorexia	2 (66.7)	0	9 (60.0)	0	2 (50.0)	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	2 (66.7)	0	2 (13.3)	0	0	0
Psychiatric disorders						
Insomnia	0	0	0	0	2 (50.0)	1 (25.0)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	3 (100)	0	2 (13.3)	0	2 (50.0)	1 (25.0)

Serious adverse events were observed in 1 of 3 patients (33.3%) in the 30 mg group, 5 of 15 patients (33.3%) in the 45 mg group, and 2 of 4 patients (50.0%) in the 60 mg group. The serious adverse events observed were, in the 30 mg group, hypercalcaemia, mental status changes, and respiratory distress (1 patient each [33.3%]); in the 45 mg group, upper gastrointestinal haemorrhage, asthenia, pain, pyrexia, atelectasis, and respiratory arrest (1 patient each [6.7%]); and, in the 60 mg group, thrombocytopenia, headache, insomnia, psychotic disorder, pulmonary embolism, and respiratory failure (1 patient each [25.0%]). A causal relationship to panobinostat could not be ruled out for asthenia (1 patient) in the 45 mg group and for thrombocytopenia (1 patient) in the 60 mg group.

Adverse events leading to the discontinuation of panobinostat were reported by 2 of 3 patients (66.7%) in the 30 mg group and 5 of 15 patients (33.3%) in the 45 mg group. These were, in the 30 mg group, performance status decreased and respiratory distress (1 patient each [33.3%]); and in the 45 mg group, thrombocytopenia, dry mouth, nausea, vomiting, asthenia, fatigue, pain, electrocardiogram QT prolonged, and respiratory arrest (1 patient each [6.7%]). A causal relationship to panobinostat could not be ruled out for performance status decreased (1 patient) in the 30 mg group and thrombocytopenia, dry mouth, nausea, vomiting, asthenia, fatigue, and electrocardiogram QT prolonged (1 patient each) in the 45 mg group.

4.(iv).(7) Foreign phase I study (Study B2108)

Adverse events were observed in 3 of 4 patients (75.0%) in the single-dose phase and in 4 of 4 patients (100%) in the extension phase. Adverse events for which a causal relationship to panobinostat could not be ruled out were observed in 1 of 4 patients (25.0%) and 3 of 4 patients (75.0%), respectively.

Adverse events with an incidence of ≥40% were fatigue and anorexia (3 patients each [75.0%]) and abdominal pain, nausea, vomiting, and insomnia (2 patients each [50.0%]) in the extension phase. Fatigue and vomiting (1 patient each) were Grade ≥3 events.

There were no serious adverse events or adverse events leading to the discontinuation of panobinostat.

4.(iv).(8) Foreign phase I study (Study B2109)
Adverse events were observed in 15 of 17 patients (88.2%) in the panobinostat combination therapy with DM (the Core Phase) and in 16 of 16 patients (100%) in the Extension Phase. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 8 of 17 patients (47.1%) and in 6 of 16 patients (37.5%), respectively.

Adverse events with an incidence of ≥30% were dyspnoea (7 patients [43.8%]) and fatigue (6 patients [37.5%]) in the Extension Phase. Of these, fatigue and dyspnoea (1 patient each) were Grade ≥3 events.

Serious adverse events were observed in 1 of 17 patients (5.9%) in the Core Phase and in 7 of 16 patients (43.8%) in the Extension Phase. The serious adverse events observed were, in the Core Phase, pneumonia (1 patient [5.9%]); and in the Extension Phase, pneumonia (2 patients [12.5%]), atrial fibrillation, pyrexia, sepsis, urinary tract infection, hypokalaemia, pain in extremity, cerebral haemorrhage, renal failure acute, respiratory distress, intermittent claudication, and peripheral ischaemia (1 patient each [6.3%]). A causal relationship to the study drug was ruled out for all of these events.

Adverse events leading to the discontinuation of study drug were reported by 4 of 16 patients (25.0%) in the Extension Phase. These were pneumonia, atrial fibrillation, cerebral haemorrhage, dyspnoea, and renal failure acute (1 patient each [6.3%]). A causal relationship to the study drug was ruled out for all of these events.

4.(iv).(9) Foreign phase I study (Study B2110)
Adverse events were observed in 13 of 14 patients (92.9%) in the Core Phase (panobinostat + KCZ) and in 13 of 13 patients (100%) in the Extension Phase. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 12 of 14 patients (85.7%) and in 13 of 13 patients (100%), respectively.

Adverse events with an incidence of ≥30% were nausea (9 patients [69.2%]), vomiting and diarrhoea (8 patients each [61.5%]), fatigue and anorexia (7 patients each [53.8%]), hypophosphataemia (6 patients [46.2%]), thrombocytopenia, oedema peripheral, dehydration, and hypokalaemia (4 patients each [30.8%]) in the Extension Phase. Fatigue and hypophosphataemia (3 patients each [23.1%]), vomiting (2 patients [15.4%]), and nausea, dehydration, and hypokalaemia (1 patient each [7.7%]) were Grade ≥3 events.

Serious adverse events were observed in 2 of 14 patients (14.3%) in the Core phase and in 7 of 13 patients (53.8%) in the Extension Phase. The serious adverse events observed were renal failure and dyspnoea exertional (1 patient each [7.1%]) in the Core Phase and myocardial infarction and dehydration (2 patients each [15.4%]), abdominal pain, constipation, diarrhoea, nausea, vomiting, catheter related complication, performance status decreased, pyrexia, electrocardiogram repolarisation abnormality, anorexia, decreased appetite, hyponatraemia, back pain, hypoxia, lung disorder, orthopnoea, and arterial occlusive disease (1 patient each [7.7%]) in the Extension Phase. A causal relationship to the study drug could not be ruled out for renal failure and dyspnoea exertional (1 patient each) in the Core Phase and for myocardial infarction, diarrhoea, nausea, vomiting, electrocardiogram repolarisation abnormality, anorexia, and arterial occlusive disease (1 patient each) in the Extension Phase.

Adverse events leading to the discontinuation of study drug were reported by 1 of 14 patients (7.1%) in the Core Phase and 3 of 13 patients (23.1%) in the Extension Phase. These were renal failure (1 patient [7.1%]) in the Core Phase; and myocardial infarction (2 patients [15.4%]), performance status decreased and hyponatraemia (1 patient each [7.7%]) in the Extension Phase. A causal relationship to the study drug could not be ruled out for renal failure (1 patient) in the Core Phase and for myocardial infarction and performance status decreased (1 patient each) in the Extension Phase.

4.(iv).(10) Foreign phase I study (Study B2111)
Adverse events were observed in 34 of 36 patients (94.4%) in the PK Evaluation Phase and in 26 of 29 patients (89.7%) in the Extension Phase. Adverse events for which a causal relationship to panobinostat could not be ruled out were observed in 28 of 36 patients (77.8%) and in 24 of 29 patients (82.8%), respectively.

Adverse events with an incidence of ≥30% were thrombocytopenia (15 patients [51.7%]), fatigue (14 patients [48.3%]), nausea (12 patients [41.4%]), diarrhoea and decreased appetite (10 patients each [34.5%]), and vomiting (9 patients [31.0%]) in the Extension Phase. Thrombocytopenia (11 patients [37.9%]), fatigue (5 patients [17.2%]), vomiting (2 patients [6.9%]), and nausea and diarrhoea (1 patient each [3.4%]) were Grade ≥3 events.

Serious adverse events were observed in 7 of 36 patients (19.4%) in the PK Evaluation Phase and in 7 of 29 patients (24.1%) in the Extension Phase. The serious adverse events observed were, in the PK Evaluation Phase, vomiting (3 patients [8.3%]), fatigue (2 patients [5.6%]), dysphagia, nausea, pyrexia, pneumonia, wound infection, dehydration, prostatitis, dyspnoea, hypotension, and wound haemorrhage (1 patient each [2.8%]); and, in the Extension Phase, neutropenia, abdominal pain, anal fistula, nausea, oesophageal obstruction, vomiting, anal abscess, pneumonia, sepsis, electrocardiogram abnormal, and spinal cord compression (1 patient each [3.4%]). A causal relationship to panobinostat could not be ruled out for fatigue and vomiting (1 patient each) in the PK Evaluation Phase and for electrocardiogram abnormal and neutropenia (1 patient each) in the Extension Phase.

Adverse events leading to the discontinuation of panobinostat were reported by 1 of 36 patients (2.8%) in the PK Evaluation Phase and 4 of 29 patients (13.8%) in the Extension Phase. These were, in the PK Evaluation Phase, fatigue, nausea, and vomiting (1 patient each [2.8%]); and in the Extension Phase, blood bilirubin increased, electrocardiogram abnormal, diarrhoea, and thrombocytopenia (1 patient each [3.4%]). A causal relationship to panobinostat could not be ruled out for fatigue (1 patient) in the PK Evaluation Phase and for blood bilirubin increased, electrocardiogram abnormal, diarrhoea, and thrombocytopenia (1 patient each) in the Extension Phase.

4.(iv).(11) Foreign phase I study (Study B2207)

4.(iv).(11).1) Dose escalation cohort

Adverse events were observed in all patients studied. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 6 of 7 patients (85.7%) in the panobinostat 10 mg + BTZ 1.0 mg/m^2 group, 5 of 7 patients (71.4%) in the panobinostat 20 mg + BTZ 1.0 mg/m^2 group, 17 of 17 patients (100%) in the panobinostat 20 mg + BTZ 1.3 mg/m^2group, 7 of 7 patients (100%) in the panobinostat 30 mg + BTZ 1.3 mg/m^2 group, and 9 of 9 patients (100%) in the panobinostat 25 mg + BTZ 1.3 mg/m^2 group. Adverse events with an incidence of ≥40% in any group are shown in the following table.

Adverse events with an incidence of ≥40% in any group

System organ class Preferred term (MedDRA ver.16.0)	Number of patients (%)									
	Panobinostat 10 mg + BTZ 1.0 mg/m^2 N = 7		Panobinostat 20 mg + BTZ 1.0 mg/m^2 N = 7		Panobinostat 20 mg + BTZ 1.3 mg/m^2 N = 17		Panobinostat 30 mg + BTZ 1.3 mg/m^2 N = 7		Panobinostat 25 mg + BTZ 1.3 mg/m^2 N = 9	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	7 (100)	6 (85.7)	7 (100)	6 (85.7)	17 (100)	17 (100)	7 (100)	7 (100)	9 (100)	9 (100)
Blood and lymphatic system disorders										
Thrombocytopenia	6 (85.7)	6 (85.7)	6 (85.7)	6 (85.7)	16 (94.1)	14 (82.4)	7 (100)	7 (100)	9 (100)	7 (77.8)
Neutropenia	4 (57.1)	2 (28.6)	4 (57.1)	3 (42.9)	15 (88.2)	11 (64.7)	7 (100)	7 (100)	7 (77.8)	7 (77.8)
Anaemia	3 (42.9)	1 (14.3)	6 (85.7)	4 (57.1)	10 (58.8)	2 (11.8)	5 (71.4)	1 (14.3)	5 (55.6)	2 (22.2)
Leukopenia	0	0	0	0	6 (35.3)	5 (29.4)	3 (42.9)	2 (28.6)	1 (11.1)	1 (11.1)
Gastrointestinal disorders										
Diarrhoea	3 (42.9)	0	2 (28.6)	0	14 (82.4)	4 (23.5)	7 (100)	1 (14.3)	6 (66.7)	2 (22.2)
Nausea	3 (42.9)	0	1 (14.3)	0	13 (76.5)	1 (5.9)	5 (71.4)	0	6 (66.7)	0
Vomiting	1 (14.3)	0	1 (14.3)	0	7 (41.2)	2 (11.8)	4 (57.1)	1 (14.3)	5 (55.6)	0
Constipation	4 (57.1)	0	0	0	3 (17.6)	0	1 (14.3)	0	2 (22.2)	0
General disorders and administration site conditions										
Pyrexia	3 (42.9)	0	3 (42.9)	0	8 (47.1)	1 (5.9)	5 (71.4)	0	6 (66.7)	1 (11.1)
Fatigue	4 (57.1)	0	4 (57.1)	0	7 (41.2)	2 (11.8)	4 (57.1)	2 (28.6)	3 (33.3)	0
Asthenia	1 (14.3)	0	1 (14.3)	1 (14.3)	8 (47.1)	4 (23.5)	5 (71.4)	5 (71.4)	5 (55.6)	4 (44.4)
Infections and infestations										
Respiratory tract infection	0	0	0	0	5 (29.4)	3 (17.6)	3 (42.9)	0	3 (33.3)	1 (11.1)
Metabolism and nutrition disorders										
Decreased appetite	0	0	2 (28.6)	0	10 (58.8)	0	3 (42.9)	1 (14.3)	5 (55.6)	0
Hypokalaemia	3 (42.9)	1 (14.3)	0	0	5 (29.4)	1 (5.9)	2 (28.6)	2 (28.6)	3 (33.3)	1 (11.1)
Hyperglycaemia	1 (14.3)	0	0	0	4 (23.5)	2 (11.8)	3 (42.9)	0	3 (33.3)	2 (22.2)
Nervous system disorders										
Dizziness	1 (14.3)	0	0	0	7 (41.2)	0	3 (42.9)	1 (14.3)	2 (22.2)	1 (11.1)
Headache	2 (28.6)	0	0	0	3 (17.6)	0	3 (42.9)	0	0	0
Respiratory, thoracic and mediastinal disorders										
Dyspnoea	2 (28.6)	0	0	0	3 (17.6)	1 (5.9)	3 (42.9)	0	2 (22.2)	0
Vascular disorders										
Hypertension	0	0	1 (14.3)	0	2 (11.8)	1 (5.9)	3 (42.9)	0	1 (11.1)	0

Serious adverse events were observed in 4 of 7 patients (57.1%) in the panobinostat 10 mg + BTZ 1.0 mg/m^2 group, 2 of 7 patients (28.6%) in the panobinostat 20 mg + BTZ 1.0 mg/m^2 group, 13 of 17 patients (76.5%) in the panobinostat 20 mg + BTZ 1.3 mg/m^2 group, 3 of 7 patients (42.9%) in the panobinostat 30 mg + BTZ 1.3 mg/m^2 group, and 7 of 9 patients (77.8%) in the panobinostat 25 mg + BTZ 1.3 mg/m^2 group. Serious adverse events reported by ≥2 patients in any group were pyrexia (2 patients [28.6%]) in the panobinostat 10 mg + BTZ 1.0 mg/m^2 group; thrombocytopenia (2 patients [28.6%]) in the panobinostat 20 mg + BTZ 1.0 mg/m^2 group; pyrexia, device related infection, respiratory tract infection, renal failure, and hypotension (2 patients each [11.8%]) in the panobinostat 20 mg + BTZ 1.3 mg/m^2 group; and neutropenia, thrombocytopenia, diarrhoea, and pyrexia (2 patients each [22.2%]) in the panobinostat 25 mg + BTZ 1.3 mg/m^2 group. A causal relationship to the study drug could not be ruled out for thrombocytopenia (1 patient) in the panobinostat 20 mg + BTZ 1.0 mg/m^2 group, for pyrexia, respiratory tract infection, renal failure, and hypotension (1 patient each) in the panobinostat 20 mg + BTZ 1.3 mg/m^2 group, and for thrombocytopenia (2 patients) and pyrexia, diarrhoea, and neutropenia (1 patient each) in the panobinostat 25 mg + BTZ 1.3 mg/m^2 group.

Adverse events leading to the discontinuation of study drug were reported by 1 of 7 patients (14.3%) in the panobinostat 10 mg + BTZ 1.0 mg/m^2 group, 2 of 7 patients (28.6%) in the panobinostat 20 mg + BTZ 1.0 mg/m^2 group, 8 of 17 patients (47.1%) in the panobinostat 20 mg + BTZ 1.3 mg/m^2 group, 4 of 7 patients (57.1%) in the panobinostat 30 mg + BTZ 1.3 mg/m^2 group, and 3 of 9 patients (33.3%) in the panobinostat 25 mg + BTZ 1.3 mg/m^2 group. These were weight decreased (1 patient [14.3%]) in the panobinostat 10 mg + BTZ 1.0 mg/m^2 group; thrombocytopenia (2 patients) in the panobinostat 20 mg + BTZ 1.0 mg/m^2 group; anaemia, neutropenia, thrombocytopenia, myocardial infarction, supraventricular extrasystoles, chills, pyrexia, bacteraemia, tooth infection, rheumatoid arthritis, syncope, and orthostatic hypotension (1 patient each [5.9%]) in the panobinostat 20 mg + BTZ 1.3 mg/m^2 group; asthenia (2 patients [28.6%]), thrombocytopenia, *Pneumocystis jirovecii* infection, pneumonia, and respiratory failure (1 patient each [14.3%]) in the panobinostat 30 mg + BTZ 1.3 mg/m^2 group; and ileus, nausea, neuropathy peripheral, urinary retention, and shock (1 patient each [11.1%]) in the panobinostat 25 mg + BTZ 1.3 mg/m^2 group. A causal relationship to the study drug could not be ruled out for weight decreased (1 patient) in the panobinostat 10 mg + BTZ 1.0 mg/m^2 group, for thrombocytopenia (1 patient) in the panobinostat 20 mg + BTZ 1.0 mg/m^2 group, for thrombocytopenia, bacteraemia, pyrexia, neutropenia, syncope, rheumatoid arthritis, orthostatic hypotension, anaemia, and supraventricular extrasystoles (1 patient each) in the panobinostat 20 mg + BTZ 1.3 mg/m^2 group, for asthenia (2 patients), thrombocytopenia and pneumonia (1 patient each) in the panobinostat 30 mg + BTZ 1.3 mg/m^2 group, and for neuropathy peripheral, nausea, ileus, and shock (1 patient each) in the panobinostat 25 mg + BTZ 1.3 mg/m^2 group.

4.(iv).(11).2) Expanded cohort

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were also observed in all patients. Adverse events with an incidence of ≥40% are shown in the following table.

Adverse events with an incidence of ≥40%

System organ class Preferred term (MedDRA ver.13.0)	Number of patients (%) Panobinostat 20 mg + BTZ 1.3 mg/m^2 + DEX 20 mg N = 15	
	All Grades	Grade ≥3
All adverse events	15 (100)	13 (86.7)
Blood and lymphatic system disorders		
Thrombocytopenia	11 (73.3)	10 (66.7)
Neutropenia	9 (60.0)	7 (46.7)
Leukopenia	6 (40.0)	3 (20.0)
Gastrointestinal disorders		
Diarrhoea	13 (86.7)	3 (20.0)
Nausea	10 (66.7)	0
Constipation	8 (53.3)	0
Abdominal pain	7 (46.7)	1 (6.7)
Vomiting	7 (46.7)	0
Abdominal discomfort	6 (40.0)	1 (6.7)
General disorders and administration site conditions		
Fatigue	11 (73.3)	3 (20.0)
Asthenia	7 (46.7)	2 (13.3)
Pyrexia	7 (46.7)	0
Infections and infestations		
Upper respiratory tract infection	6 (40.0)	0
Metabolism and nutrition disorders		
Decreased appetite	9 (60.0)	0
Nervous system disorders		
Dizziness	7 (46.7)	2 (13.3)
Neuropathy peripheral	7 (46.7)	1 (6.7)
Dysgeusia	6 (40.0)	0
Respiratory, thoracic and mediastinal disorders		
Cough	6 (40.0)	0

Serious adverse events were observed in 6 of 15 patients (40.0%). Those events were thrombocytopenia (4 patients [26.7%]), dehydration (2 patients [13.3%]), and neutropenia, myocardial infarction, nausea,

pyrexia, bronchitis, pyelonephritis, urinary tract infection, injury, hypokalaemia, aphasia, autonomic neuropathy, cerebral haemorrhage, dizziness, ischaemic stroke, stupor, syncope, transient ischaemic attack, and dyspnoea (1 patient each [6.7%]). A causal relationship to the study drug could not be ruled out for thrombocytopenia (4 patients) and neutropenia and nausea (1 patient each).

Adverse events leading to the discontinuation of study drug were reported by 5 of 15 patients (33.3%). These were neuropathy peripheral (2 patients [13.3%]) and myocardial infarction, asthenia, fatigue, and transient ischaemic attack (1 patient each [6.7%]). A causal relationship to the study drug could not be ruled out for neuropathy peripheral (2 patients) and asthenia and fatigue (1 patient each).

4.(iv).(12) Foreign phase I study (Study X2101)

Adverse events were observed in all patients. Adverse events for which a causal relationship to panobinostat could not be ruled out were observed in 22 of 25 patients (88.0%).

Adverse events with an incidence of ≥30% were nausea and fatigue (19 patients each [76.0%]), decreased appetite (17 patients [68.0%]), vomiting (16 patients [64.0%]), diarrhoea (13 patients [52.0%]), oedema peripheral (10 patients [40.0%]), and anaemia and dyspnoea (8 patients each [32.0%]). Fatigue (10 patients [40.0%]), nausea (5 patients [20.0%]), vomiting and diarrhoea (3 patients each [12.0%]), and anaemia (2 patients [8.0%]) were Grade ≥3 events.

Serious adverse events were observed in 13 of 25 patients (52.0%). Those events were nausea, vomiting, diarrhoea, dyspnoea, pneumonia, fatigue, and ascites (2 patients each [8.0%]), and pyrexia, thrombocytopenia, performance status decreased, dehydration, gastrointestinal obstruction, asthenia, haemorrhage urinary tract, vaginal haemorrhage, failure to thrive, confusional state, infection, deep vein thrombosis, post procedural haemorrhage, blood creatinine increased, vasculitis, and anaemia (1 patient each [4.0%]). A causal relationship to panobinostat could not be ruled out for nausea, vomiting, diarrhoea, and fatigue (2 patients each), and for pyrexia, pneumonia, thrombocytopenia, performance status decreased, dehydration, asthenia, haemorrhage urinary tract, deep vein thrombosis, post procedural haemorrhage, blood creatinine increased, vasculitis, and anaemia (1 patient each).

Adverse events leading to the discontinuation of panobinostat were reported by 4 of 25 patients (16.0%). Those events were fatigue (2 patients [8.0%]) and decreased appetite, dysgeusia, vomiting, nausea, vasculitis, and blood bilirubin increased (1 patient each [4.0%]). A causal relationship to panobinostat could not be ruled out for fatigue (2 patients), decreased appetite, dysgeusia, vomiting, nausea, and vasculitis (1 patient each).

4.(iv).(13) Foreign phase I study (Study X2105)

Adverse events were observed in all patients. Adverse events for which a causal relationship to panobinostat could not be ruled out were also observed in all patients.

Adverse events with an incidence of ≥30% were fatigue (27 patients [73.0%]), nausea (21 patients [56.8%]), diarrhoea (18 patients [48.6%]), dyspnoea (15 patients [40.5%]), anaemia (14 patients [37.8%]), decreased appetite (13 patients [35.1%]), and thrombocytopenia (12 patients [32.4%]). Of these, fatigue (10 patients [27.0%]), thrombocytopenia (7 patients [18.9%]), dyspnoea (5 patients [13.5%]), anaemia and diarrhoea (2 patients each [5.4%]), and nausea (1 patient [2.7%]) were Grade ≥3 events.

Serious adverse events were observed in 20 of 37 patients (54.1%). Those events were dyspnoea (4 patients [10.8%]), dehydration (3 patients [8.1%]), anaemia, pyrexia, thrombocytopenia, hypoxia, pulmonary embolism, abdominal pain, and urinary tract infection (2 patients each [5.4%]), and ascites, general physical health deterioration, cholecystitis, cardiac arrest, hypotension, constipation, disease progression, metastases to lung, lymphangiosis carcinomatosa, sepsis, vena cava thrombosis, fatigue, haemorrhage urinary tract, international normalised ratio increased, renal failure acute, staphylococcal bacteraemia, rash maculo-papular, vasculitis, and hyperkalaemia (1 patient each [2.7%]). A causal relationship to panobinostat could not be ruled out for anaemia and thrombocytopenia (2 patients each), pyrexia, constipation, fatigue, dehydration, urinary tract infection, rash maculo-papular, and vasculitis (1 patient each).

Adverse events leading to the discontinuation of panobinostat were reported by 8 of 37 patients (21.6%). These were fatigue (3 patients [8.1%]), pulmonary embolism, hyponatraemia, cognitive disorder, lung infection, and urinary tract infection (1 patient each [2.7%]). A causal relationship to panobinostat could not be ruled out for fatigue (2 patients) and urinary tract infection (1 patient).

4.(iv).(14) Foreign phase II study (Study DUS71)
Adverse events were observed in 54 of 55 patients (98.2%), and those for which a causal relationship to the study drug could not be ruled out were observed in 51 of 55 patients (92.7%).

Adverse events with an incidence of ≥30% were diarrhoea (39 patients [70.9%]), fatigue (37 patients [67.3%]), thrombocytopenia (36 patients [65.5%]), nausea (33 patients [60.0%]), anaemia (26 patients [47.3%]), decreased appetite (23 patients [41.8%]), oedema peripheral (22 patients [40.0%]), dizziness (21 patients [38.2%]), dyspnoea (20 patients [36.4%]), constipation (19 patients [34.5%]), and upper respiratory tract infection (18 patients [32.7%]). Thrombocytopenia (35 patients), diarrhoea and fatigue (11 patients each), anaemia (8 patients), nausea (3 patients), dizziness and dyspnoea (2 patients each) were Grade ≥3 events.

Serious adverse events were observed in 39 of 55 patients (70.9%). Those reported by ≥2 patients were thrombocytopenia (16 patients [29.1%]), pneumonia (8 patients [14.5%]), pyrexia (5 patients [9.1%]), anaemia, sepsis, and renal failure acute (4 patients each [7.3%]), septic shock, diarrhoea, dehydration, back pain, and hypotension (3 patients each [5.5%]), asthenia, cellulitis, influenza, hypercalcaemia, renal dysfunction, and dyspnoea (2 patients each [3.6%]). A causal relationship to the study drug could not be ruled out for thrombocytopenia (14 patients), pneumonia, anaemia, and diarrhoea (3 patients each), sepsis, septic shock, and dyspnoea (2 patients each), pyrexia, renal failure acute, dehydration, hypotension, and asthenia (1 patient each).

Adverse events leading to the discontinuation of study drug were reported by 10 of 55 patients (18.2%). Those events were fatigue (4 patients [7.3%]), diarrhoea, asthenia, and pneumonia (2 patients each [3.6%]), weight decreased, decreased appetite, back pain, muscle spasms, neoplasm malignant, neuropathy peripheral, confusional state, depression, and pneumonitis (1 patient each [1.8%]). A causal relationship to the study drug could not be ruled out for fatigue (4 patients), diarrhoea and asthenia (2 patients each), pneumonia, weight decreased, decreased appetite, muscle spasms, neuropathy peripheral, and pneumonitis (1 patient each).

4.(iv).(15) Japanese phase II study (Study B1201)
Adverse events were observed in all patients, and those for which a causal relationship to panobinostat could not be ruled out were also observed in all patients.

Serious adverse events were observed in 2 of 4 patients (50.0%). Those were dizziness, sepsis, skin ulcer, and neoplasm progression (1 patient each [25.0%]). A causal relationship to panobinostat could not be ruled out for dizziness, sepsis, and skin ulcer (1 patient each).

An adverse event leading to the discontinuation of panobinostat was reported by 1 of 4 patients (25.0%). The event was sepsis, and its causal relationship to panobinostat could not be ruled out.

4.(iv).(16) Foreign phase I/II study (Study B2102)
Adverse events were observed in all patients, and those for which a causal relationship to panobinostat could not be ruled out were observed in 114 of 120 patients (95.0%) in Group 1 and in 47 of 56 patients (83.9%) in Group 2.

Serious adverse events were observed in 81 of 120 patients (67.5%) in Group 1 and in 42 of 56 patients (75.0%) in Group 2. Serious adverse events reported by ≥2 patients in any group were, in Group 1, febrile neutropenia (26 patients [21.7%]), fatigue (13 patients [10.8%]), pyrexia (7 patients [5.8%]), sepsis and pneumonia (4 patients each [3.3%]), neutropenia and abdominal pain (3 patients each [2.5%]), bronchopulmonary aspergillosis, thrombocytopenia, diarrhoea, dyspnoea, hypotension, neutropenic infection, staphylococcal infection, renal failure acute, anaemia, and pneumonia fungal (2 patients each

[1.7%]); and, in Group 2, febrile neutropenia and pyrexia (8 patients each [14.33%]), thrombocytopenia, dyspnoea, tumour lysis syndrome, and chest pain (2 patients each [3.6%]). A causal relationship to panobinostat could not be ruled out for fatigue (8 patients), febrile neutropenia (5 patients), neutropenia (3 patients), pneumonia, thrombocytopenia, renal failure acute, abdominal pain, and diarrhoea (1 patient each) in Group 1, and for tumour lysis syndrome and chest pain (1 patient each) in Group 2.

Adverse events leading to the discontinuation of panobinostat were reported by 34 of 120 patients (28.3%) in Group 1 and 10 of 56 patients (17.9%) in Group 2. Adverse events leading to the discontinuation of panobinostat reported by ≥2 patients in either group were fatigue (10 patients [8.3%]), anorexia and thrombocytopenia (4 patients each [3.3%]), and febrile neutropenia (2 patients [1.7%]) in Group 1. A causal relationship to panobinostat could not be ruled out for fatigue (10 patients), anorexia (4 patients), and thrombocytopenia (3 patients).

4.(iv).(17) Foreign phase I study (Study B2206)
Adverse events were observed in all patients, and those for which a causal relationship to the study drug could not be ruled out were observed in 45 of 46 patients (97.8%).

Serious adverse events were observed in 32 of 46 patients (69.6%). Serious adverse events reported by ≥3 patients were pyrexia (8 patients [17.4%]), febrile neutropenia (7 patients [15.2%]), respiratory tract infection (5 patients [10.9%]), thrombocytopenia, respiratory failure, and pneumonia (4 patients each [8.7%]), and diarrhoea (3 patients [6.5%]). A causal relationship to the study drug could not be ruled out for febrile neutropenia (4 patients), pneumonia, thrombocytopenia, pyrexia, and respiratory tract infection (2 patients each), and respiratory failure (1 patient).

Adverse events leading to the discontinuation of study drug were reported by 22 of 46 patients (47.8%). Adverse events leading to the discontinuation of study drug reported by ≥2 patients were fatigue (5 patients [10.9%]), thrombocytopenia (3 patients [6.5%]), febrile neutropenia, neutropenia, electrocardiogram QT prolonged, and decreased appetite (2 patients each [4.3%]). A causal relationship to the study drug could not be ruled out for fatigue (4 patients), decreased appetite, thrombocytopenia, electrocardiogram QT prolonged, and febrile neutropenia (2 patients each), and neutropenia (1 patient).

4.(iv).(18) Foreign phase II study (Study B2201)
Adverse events were observed in 138 of 139 patients (99.3%). Adverse events for which a causal relationship to panobinostat could not be ruled out were observed in 133 of 139 patients (95.7%).

Serious adverse events were observed in 50 of 139 patients (36.0%). Serious adverse events reported by ≥3 patients were pyrexia (6 patients [4.3%]), thrombocytopenia (5 patients [3.6%]), angina pectoris, asthenia, general physical health deterioration, and squamous cell carcinoma (3 patients each [2.2%]). A causal relationship to panobinostat could not be ruled out for thrombocytopenia (4 patients), angina pectoris (3 patients), pyrexia, general physical health deterioration, and asthenia (1 patient each).

Adverse events leading to the discontinuation of panobinostat were reported by 42 of 139 patients (30.2%). Adverse events leading to discontinuation of panobinostat reported by ≥3 patients were thrombocytopenia (7 patients [5.0%]), fatigue (4 patients [2.9%]), neutropenia and electrocardiogram QT prolonged (3 patients each [2.2%]). A causal relationship to panobinostat could not be ruled out for any of these adverse events.

4.(iv).(19) Foreign phase II study (Study B2202)
Adverse events were observed in 28 of 29 patients (96.6%), and those for which a causal relationship to panobinostat could not be ruled out were observed in 21 of 29 patients (72.4%).

Serious adverse events were observed in 4 of 29 patients (13.8%). The serious adverse events observed were leukocytosis, splenic infarction, cardiac failure, gastrointestinal haemorrhage, pyrexia, electrocardiogram QT prolonged, pulmonary embolism, and deep vein thrombosis (1 patient each [3.4%]). A causal relationship to panobinostat could not be ruled out for electrocardiogram QT prolonged and pulmonary embolism (1 patient each).

Adverse events leading to the discontinuation of panobinostat were reported by 6 of 29 patients (20.7%). These were electrocardiogram QT prolonged (2 patients [6.9%]), leukocytosis, neutropenia, thrombocytopenia, and white blood cell count increased (1 patient each [3.4%]). A causal relationship to panobinostat could not be ruled out for electrocardiogram QT prolonged (2 patients) and neutropenia (1 patient).

4.(iv).(20) Foreign phase II study (Study B2203)

Adverse events were observed in all patients. Adverse events for which a causal relationship to panobinostat could not be ruled out were observed in 35 of 38 patients (92.1%).

Serious adverse events were observed in 17 of 38 patients (44.7%). Serious adverse events reported by ≥2 patients were pneumonia and hypercalcaemia (4 patients each [10.5%]), thrombocytopenia (3 patients [7.9%]), diarrhoea, nausea, vomiting, pyrexia, and dehydration (2 patients each [5.3%]). A causal relationship to panobinostat could not be ruled out for nausea (2 patients) and diarrhoea and vomiting (1 patient each).

Adverse events leading to the discontinuation of panobinostat were reported by 8 of 38 patients (21.1%). Those were blood creatinine increased (3 patients [7.9%]), M protein present, cerebrovascular accident, neuropathy peripheral, renal failure, and renal failure acute (1 patient each [2.6%]). A causal relationship to panobinostat could not be ruled out for blood creatinine increased in 2 of the 3 patients.

4.(iv).(21) Foreign phase II study (Study B2211)

Adverse events were observed in all patients. Adverse events for which a causal relationship to panobinostat could not be ruled out were observed in 17 of 27 patients (63.0%).

Serious adverse events were observed in 13 of 27 patients (48.1%). Serious adverse events reported by ≥2 patients were thrombocytopenia and pyrexia (4 patients each [14.8%]), and neutropenia and catheter site haemorrhage (2 patients each [7.4%]). A causal relationship to panobinostat could not be ruled out for thrombocytopenia and neutropenia (2 patients each).

Adverse events leading to the discontinuation of panobinostat were reported by 8 of 27 patients (29.6%). Adverse events leading to the discontinuation of panobinostat reported by ≥2 patients were thrombocytopenia and white blood cell count increased (2 patients each [7.4%]). A causal relationship to panobinostat could not be ruled out for thrombocytopenia (2 patients).

4.(iv).(22) Foreign phase II study (Study E2214)

Adverse events were observed in all patients, and those for which a causal relationship to panobinostat could not be ruled out were observed in 128 of 129 patients (99.2%).

Serious adverse events were observed in 46 of 129 patients (35.7%). Serious adverse events reported by ≥3 patients were thrombocytopenia (12 patients [9.3%]), anaemia and pneumonia (5 patients each [3.9%]), dyspnoea and sepsis (4 patients each [3.1%]), and atrial fibrillation (3 patients [2.3%]). A causal relationship to panobinostat could not be ruled out for thrombocytopenia (12 patients), anaemia (4 patients), atrial fibrillation (2 patients), and dyspnoea and pneumonia (1 patient each).

Adverse events leading to the discontinuation of panobinostat were reported by 20 of 129 patients (15.5%). Those reported by ≥2 patients were thrombocytopenia (7 patients [5.4%]), asthenia (3 patients [2.3%]), diarrhoea, vomiting, and dyspnoea (2 patients each [1.6%]). A causal relationship to panobinostat could not be ruled out for thrombocytopenia (6 patients), asthenia (3 patients), diarrhoea and vomiting (2 patients each), and dyspnoea (1 patient).

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

The assessment is ongoing. The results and PMDA's conclusion will be reported in Review Report (2).

2. PMDA's conclusion on the results of GCP on-site inspection

The assessment is ongoing. The results and PMDA's conclusion will be reported in Review Report (2).

IV. Overall Evaluation

Based on the submitted data, it is concluded that the efficacy of panobinostat in treatment of patients with relapsed or refractory multiple myeloma has been demonstrated and its safety is acceptable based on the observed clinical benefits. Panobinostat is considered to inhibit tumor growth by causing cell cycle arrest and apoptosis induction through the inhibition of deacetylation of histone or non-histone proteins. The proposed product is a drug with this new active ingredient, and is considered to have clinical significance as an option for the treatment of relapsed or refractory multiple myeloma. The proposed indications, dosage regimens, and post-marketing surveillance will be further discussed at the Expert Discussion.

PMDA considers that panobinostat may be approved if the product is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

May 18, 2015

I. Product Submitted for Registration

[Brand name]	Farydak Capsules 10 mg
	Farydak Capsules 15 mg
[Non-proprietary name]	Panobinostat Lactate
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	September 26, 2014

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for registration, 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) Efficacy

After the review described in "4.(iii).B.(2) Efficacy" in the Review Report (1), PMDA concluded that the efficacy of Panobinostat Lactate (hereinafter referred to as panobinostat) in patients with relapsed or refractory multiple myeloma (MM) was demonstrated based on the results of the global phase III study (Study D2308), which confirmed the superiority of the panobinostat combination therapy with bortezomib (BTZ) and dexamethasone (DEX) (panobinostat group) to the BTZ + DEX combination therapy (placebo group as control) in the primary endpoint of progression-free survival (PFS).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion. The following comments were also made by expert advisors.

- The limited number of Japanese patients enrolled in Study D2308 limited the comparison of efficacy between the Japanese subpopulation and the entire study population. Also, the rationale for the sample size of Japanese patients in Study D2308 should be clarified.

- An open-label uncontrolled study (Study D1201) is ongoing to evaluate the percentage of Japanese patients with relapsed or refractory MM who achieve complete response (CR) or near complete response (nCR) under the dosage regimen used in Study D2308. The results of Study D1201 may reveal a concern about the efficacy of panobinostat in Japanese patients. Therefore, the following actions should be considered for the study.

  - The protocol should be revised so that efficacy analyses are conducted on a regular basis, and early release of the interim analyses results should be planned. Because of limited information on the safety of panobinostat in Japanese patients, safety analyses should also be conducted in a similar manner so that relevant information is made available.

  - The final analysis results should be appropriately provided to healthcare professionals once available.

  - The latest efficacy and safety information should be checked to see whether additional measures are necessary.

- The interim analysis (data cut-off, [redacted], 20[redacted]) of Study D2308 revealed no statistically significant difference in the overall survival (OS) between the panobinostat and placebo groups. The data help determine the eligibility of patients for panobinostat therapy and should therefore be appropriately

provided to healthcare professionals through the package insert, etc. The results of final OS analysis should also be provided to healthcare professionals once available.

PMDA asked the applicant to explain the rationale for the sample size of Japanese patients in planning Study D2308.

The applicant responded as follows:
Relapsed or refractory MM, the target disease in Study D2308, is a rare disease. Considering the feasibility of the study, the target sample size of Japanese patients was determined as 30. The efficacy of panobinostat was considered to be consistent between the Japanese subpopulation and the entire study population when the primary endpoint of PFS showed a statistically significant difference and the hazard ratio was <1 in the Japanese subpopulation.

PMDA asked the applicant to explain the progress of Study D1201 and the latest efficacy and safety information.

The applicant responded as follows:
The target sample size in Study D1201 is 33. The enrollment of patients was started in [redacted] 20[redacted], and 11 patients have been enrolled as of [redacted], 20[redacted]. Although efficacy and safety data have yet to be finalized, the following data are available: (a) serious adverse events that require medical institutions to report within 24 hours after the first knowledge of the event, and (b) the measurements of monoclonal immunoglobulin (M protein) in serum and urine that are measured at the central laboratory facility. (a) Dizziness and asthenia were reported by 1 of 11 patients on Day 31 after the treatment with panobinostat. The patient was admitted to a hospital and recovered from both events on Day 35. A causal relationship of these events to panobinostat is unknown. A precautionary statement on these events are to be provided in the "Other adverse reactions" section of the package insert. (b) A total of 7 patients have completed the evaluation of the M protein-related efficacy of panobinostat in Cycle 2. In all of them, the M protein level at the end of Cycle 2 tended to be better than baseline.

PMDA considers as follows:
Complete response was achieved in Japanese patients in Study D2308, and the percentage of Japanese patients with complete response was similar to that in the entire study population. Considering these findings and the latest data of Study D1201, there are no data that negate the efficacy of panobinostat in Japanese patients.

Nevertheless, whether or not the ongoing Study D1201 achieves a complete response rate similar to that in the Japanese patients in Study D2308 is very critical in validating the efficacy of panobinostat in Japanese patients. Therefore, the protocol of Study D1201 should be revised appropriately to ensure the conduct of interim analyses and the publication of analyses results. The results of Study D1201 should be provided to healthcare professionals immediately once available [see "(5) Risk management plan (draft)"]. The package insert should also be promptly revised as appropriate based on the results of Study D1201.

PMDA instructed the applicant to take appropriate measures immediately after obtaining the final OS analysis results in Study D2308 and the results of Study D1201; the applicant agreed.

(2) Safety
After the review described in "4.(iii).B.(3) Safety" of the Review Report (1), PMDA determined that adverse events requiring attention during treatment with panobinostat were QT prolongation, bone marrow depression, hemorrhage, infection, hepatic dysfunction, renal dysfunction, diarrhea/nausea/vomiting/dehydration, cardiac disorders (cardiac failure, ischaemic heart disease, tachyarrhythmia), colitis ischaemic, and venous thromboembolism. Caution should be exercised against these adverse events during treatment with panobinostat.

PMDA also concluded that panobinostat is tolerable provided that the above adverse events are monitored and controlled in an appropriate manner by physicians with expertise 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 made by the expert advisors.

- Given the types and seriousness of adverse events that occurred after the administration of panobinostat, the need for monitoring patients on an inpatient basis or in a similar manner during the early stage of treatment should be considered.

- Abnormal electrocardiogram such as QT prolongation was observed in clinical studies. Cooperation with cardiologists is required for appropriate monitoring and control of these events. Information on the timing and frequency of these events is important and should therefore be provided appropriately to healthcare professionals.

- Panobinostat is indicated for the treatment of MM, which is common in elderly patients. In this population, diarrhea and dehydration may be fatal. Attention should therefore be paid to these events during treatment. In Study D2308, abnormality in electrolyte such as hypokalemia occurred more frequently in the panobinostat group than in the placebo group. Information on the relationship between abnormality in electrolyte and diarrhea should be provided appropriately.

- In Study D2308, the incidence of hypotension, orthostatic hypotension, syncope, and loss of consciousness were higher in the panobinostat group than in the placebo group. The need for safety measures against these events caused by panobinostat should be studied.

- The meeting of the Oncologic Drugs Advisory Committee of the US Food and Drug Administration (FDA), held on November 6, 2014, concluded that the benefits of panobinostat did not outweigh the risks (http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm435296.htm). The safety of panobinostat should therefore be evaluated extremely carefully. Given the frequency of blood transfusion (33.3% in the panobinostat group, 10.3% in the placebo group) and of G-CSF administration (13.1% in the panobinostat group, 4.2% in the placebo group) for the treatment of blood toxicity caused by the study drug in Study D2308, the cost-effectiveness of panobinostat is questionable and should be further investigated in future.

PMDA asked the applicant to explain (a) the incidence, timing of onset, etc. of electrocardiogram abnormalities such as QT prolongation, (b) the relationship between the electrolyte abnormalities and diarrhea after the administration of panobinostat, and (c) the incidence, etc. of hypotension, orthostatic hypotension, syncope, and loss of consciousness.

The applicant replied as follows:
The incidence of events related to QT prolongation caused by panobinostat are shown in the following table. These events occurred frequently in Cycle 1 but also occurred at a certain frequency in Cycle 2 onward. T wave changes, ST-T segment depression, and sinus tachycardia also showed a similar trend.

Incidence of events related to QT prolongation by treatment cycle

	Number of patients (%)							
	Study D2308				Study DUS71		Study B2207 (expanded cohort)	
	Panobinostat N = 381		Placebo N = 377		N = 55		N = 15	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Cycle 1	14/381 (3.4)	6/381 (1.6)	5/377 (1.3)	1/377 (0.3)	0/55	0/55	0/15	0/15
Cycle 2	9/352 (2.6)	5/352 (1.4)	5/357 (1.4)	2/357 (0.6)	3/50 (6.0)	3/50 (6.0)	0/15	0/15
Cycle 3	10/322 (3.1)	5/322 (1.6)	3/337 (0.9)	2/337 (0.6)	2/45 (4.4)	2/45 (4.4)	0/15	0/15
Cycle 4	6/285 (2.1)	3/285 (1.1)	3/309 (1.0)	3/309 (1.0)	2/39 (5.1)	2/39 (5.1)	0/13	0/13
Cycle 5	3/253 (1.2)	2/253 (0.8)	2/276 (0.7)	0/276	1/32 (3.1)	1/32 (3.1)	0/12	0/12
Cycle 6	1/229 (0.4)	0/229	4/252 (1.6)	2/252 (0.8)	0/30	0/30	1/11 (9.1)	1/11 (9.1)
Cycle 7	2/203 (1.0)	0/203	2/231 (0.9)	1/231 (0.4)	0/27	0/27	0/10	0/10
Cycle 8	1/184 (0.5)	1/184 (0.5)	0/212	0/212	0/24	0/24	0/7	0/7
Cycle 9	0/168	0/168	0/193	0/193	0/19	0/19	0/5	0/5
Cycle 10	0/157	0/157	0/182	0/182	0/16	0/16	0/5	0/5
Cycle 11	0/148	0/148	0/168	0/168	0/16	0/16	0/5	0/5
Cycle 12	1/138 (0.7)	0/138	0/152	0/152	0/16	0/16	0/5	0/5
Cycle 13	0/130	0/130	0/132	0/132	0/13	0/13	-	-
Cycle 14	0/124	0/124	0/125	0/125	0/12	0/12	-	-
Cycle 15	0/114	0/114	0/116	0/116	0/10	0/10	-	-
Cycle 16	0/108	0/108	0/109	0/109	0/8	0/8	-	-

-: Not applicable

The numbers of patients who had electrolyte abnormalities before the onset of diarrhea were 51 of 260 patients (19.6%) in the panobinostat group and 36 of 157 patients (22.9%) in the placebo group in Study D2308, 3 of 39 patients (7.7%) in Study DUS71, and 1 of 13 patients (7.7%) in Study B2207 (expanded cohort). On the other hand, the numbers of patients who had diarrhea before the onset of electrolyte abnormalities were 104 of 175 patients (59.4%) in the panobinostat group and 42 of 131 patients (32.1%) in the placebo group in Study D2308, 18 of 22 patients (81.8%) in Study DUS71, and 7 of 8 patients (87.5%) in Study B2207 (expanded cohort).

The incidence of hypotension, orthostatic hypotension, syncope, and loss of consciousness is shown in the following table. Serious hypotension was observed in 5 of 381 patients (1.3%) in the panobinostat group and 2 of 377 patients (0.5%) in the placebo group in Study D2308, and 3 of 55 patients (5.5%) in Study DUS71. A causal relationship to the study drug could not be ruled out in 3 patients in the panobinostat group in Study D2308, 1 patient in the placebo group in Study D2308, and 1 patient in Study DUS71. Serious orthostatic hypotension was observed in 9 of 381 patients (2.4%) in the panobinostat group and 1 of 377 patients (0.3%) in the placebo group in Study D2308, and 1 of 55 patients (1.8%) in Study DUS71. A causal relationship to the study drug could not be ruled out in 7 patients in the panobinostat group and 1 patient in the placebo group in Study D2308. Serious syncope was observed in 5 of 381 patients (1.3%) in the panobinostat group and 2 of 377 patients (0.5%) in the placebo group in Study D2308, and 1 of 15 patients (6.7%) in Study B2207 (expanded cohort). A causal relationship to the study drug could not be ruled out in 3 patients in the panobinostat group in Study D2308. Serious loss of consciousness was observed in 5 of 381 patients (1.3%) in the panobinostat group and in 1 of 377 patients (0.3%) in the placebo group in Study D2308. A causal relationship to the study drug could not be ruled out in 3 patients in the panobinostat group in Study D2308. Hypotension, orthostatic hypotension, syncope, or loss of consciousness following treatment with panobinostat did not result in death in any of the studies. Accordingly, the applicant explained that patients should be closely monitored for possible hypotension, orthostatic hypotension, syncope, and loss of consciousness following treatment with panobinostat and should be advised to be careful when operating potentially hazardous machines including cars.

Incidence of hypotension, orthostatic hypotension, syncope, and loss of consciousness

Preferred term (MedDRA/J ver.16.0)	Number of patients (%)							
	Study D2308				Study DUS71		Study B2207 (expanded cohort)	
	Panobinostat N = 381		Placebo N = 377		N = 55		N = 15	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypotension	53 (13.9)	11 (2.9)	35 (9.3)	5 (1.3)	11 (20.0)	5 (9.1)	3 (20.0)	0
Orthostatic hypotension	29 (7.6)	12 (3.1)	12 (3.2)	3 (0.8)	5 (9.1)	2 (3.6)	2 (13.3)	1 (6.7)
Syncope	23 (6.0)	14 (3.7)	9 (2.4)	6 (1.6)	5 (9.1)	5 (9.1)	1 (6.7)	1 (6.7)
Loss of consciousness	5 (1.3)	3 (0.8)	3 (0.8)	1 (0.3)	0	0	0	0

PMDA considers as follows:
In Study D2308, Japanese patients were hospitalized to receive panobinostat in Cycle 1, as advised in the "Warnings" section of the package insert of BTZ. Therefore, the package insert of panobinostat should also have a precautionary statement in the "Warnings" section so that patients receiving the combination therapy with panobinostat, BTZ, and DEX are hospitalized or placed under a similar condition during the early stage of the therapy. Given the types and seriousness of adverse events that occurred following treatment with panobinostat, physicians should be advised, through the "Warnings" section of the package insert, to read through the package insert, etc. carefully before the use of panobinostat.

The peak time of onset of panobinostat-induced abnormal electrocardiogram such as QT prolongation was not identified, but panobinostat-induced abnormal electrocardiogram was seen in all cycles. Through the package insert, etc., healthcare professionals should be informed of (a) the requirement that electrolyte tests and electrocardiography should be regularly performed before and during treatment with panobinostat, and of (b) the criteria used in clinical studies of panobinostat (i.e., the criteria for the start of treatment with panobinostat in relation to QTc interval and blood electrolyte levels; and the criteria for the interruption, dose reduction, and discontinuation of panobinostat in case of QT prolongation). Healthcare professionals should also be advised through written materials, etc. to carefully monitor and control panobinostat-induced abnormal electrocardiogram, such as QT prolongation, in coordination with cardiologists or in an environment that allows appropriate management of such events.

Diarrhea preceding electrolyte abnormalities was more frequent in the panobinostat group than in the placebo group. Therefore, through the package insert, etc., healthcare professionals should be advised to monitor blood electrolytes (e.g., potassium, magnesium, phosphate) before and during treatment with panobinostat and should be informed of the criteria for the interruption, dose reduction, and discontinuation of panobinostat in case of severe diarrhea.

Serious hypotension, orthostatic hypotension, syncope, and loss of consciousness were observed, and a causal relationship to panobinostat could not be ruled out for these events. Attention should therefore be paid to these events during treatment with panobinostat. The risks of panobinostat-induced hypotension, orthostatic hypotension, syncope, and loss of consciousness should be highlighted in the package insert, etc., along with a warning against the operation of potentially hazardous machines including cars. The occurrence of these events in clinical studies should also be mentioned.

(3) Clinical positioning and indication
As a result of the review in "4.(iii).B.(4) Clinical positioning and indication" in the Review Report (1), PMDA concluded that panobinostat combination therapy with BTZ and DEX is a therapeutic option for relapsed or refractory MM. Panobinostat should be indicated for "relapsed or refractory MM," as proposed by the applicant, with the following precautionary statements in the "Precautions for Indications" section. Prior regimens of patients enrolled in Study D2308 should be mentioned in the "Clinical Studies" section of the package insert.

Precautions for Indications

- Panobinostat should be administered to patients who are non-responsive to at least one of the standard regimens or who had a relapse after such regimen.

- Eligibility of the patient for the therapy should be determined based on a good understanding of the study results in the "Clinical Studies" section of the package insert, including prior regimens of patients enrolled in the clinical studies, and of the efficacy and safety of panobinostat.

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

Accordingly, PMDA instructed the applicant to include the above wording in the "Indications" and "Precautions for Indications" sections; the applicant agreed.

(4) Dosage and administration

After the review in "4.(iii).B.(5) Dosage and administration" in the Review Report (1), PMDA concluded that the dosage and administration of panobinostat should be determined as follows: "In combination with bortezomib and dexamethasone, the usual adult dosage is 20 mg of panobinostat administered orally once daily 3 times a week for 2 weeks (Days 1, 3, 5, 8, 10, and 12), followed by a 9-day rest period (Days 13-21). The 3-week treatment cycle is repeated. The dose may be adjusted according to the condition of the patient." The following cautions should be included in the "Precautions for Dosage and Administration" section of the package insert.

- The efficacy and safety of panobinostat monotherapy have not been established.

- Concomitant BTZ and DEX should be administered by physicians with a good understanding of the "Clinical Studies" section. The package inserts of the concomitant drugs should be read carefully.

- The efficacy and safety of panobinostat in combination with antineoplastic drugs other than BTZ and DEX have not been established.

- The efficacy and safety of panobinostat administered for >16 cycles (48 weeks) have not been established.

- Increased blood panobinostat concentration was reported in patients with hepatic impairment. In these patients, dose reduction should be considered and the condition of the patients should be closely monitored for possible adverse events.

- The criteria for the start of treatment with panobinostat regarding platelet count, neutrophil count, QTc interval, and blood electrolytes.

- The criteria for the interruption, dose reduction, and discontinuation of panobinostat in case of adverse drug reaction following the administration of panobinostat.

At the Expert Discussion, the expert advisors supported the above conclusion, making the following comment:

- Panobinostat is considered to be eliminated mostly by hepatic metabolism. It is therefore imperative that the risk of panobinostat therapy in patients with hepatic impairment be highlighted in the "Precautions for Dosage and Administration" section of the package insert. Because of the limited number of Japanese patients participating in Study B1101, which evaluated the PK of panobinostat, available data are not sufficient to evaluate the dose-proportionality of the PK of panobinostat in Japanese patients [see "4.(ii).A.(1).1) Japanese phase I study" in the Review Report (1)]. It is therefore reasonable for the applicant not to specify any concrete dose reduction range for patients with hepatic impairment receiving panobinostat.

Accordingly, PMDA instructed the applicant to revise the sections of "Dosage and Administration" and "Precautions for Dosage and Administration" as above; the applicant agreed.

(5) Risk management plan (draft)

In order to investigate the safety, etc. of panobinostat in routine clinical practice after the market launch, the applicant plans to conduct post-marketing surveillance targeting all patients who receive panobinostat for the treatment of relapsed or refractory MM.

After the review in "4.(iii).B.(6) Post-marketing surveillance" in the Review Report (1), PMDA concluded as follows: because of the limited information on the safety of panobinostat in Japanese patients with relapsed or refractory MM, relevant information should be collected in an efficient and unbiased manner from all patients treated with panobinostat for a certain period after the market launch, and available safety information should be provided to healthcare professionals immediately.

Also, nausea, vomiting, and dehydration should be added to the priority investigation items selected by the applicant, because attention should be paid to these events during the panobinostat therapy. The sample size proposed by the applicant is acceptable.

The follow-up period should be revised taking account of the incidence, etc. of the priority investigation items, including the added events (i.e., nausea, vomiting, and dehydration).

At the Expert Discussion, the expert advisors supported the above conclusion of PMDA, making the following comment:

- Panobinostat may be administered for a long-term period. The follow-up period should be long enough to gather safety information over the longest possible period.

Based on the review in the "(2) Safety" section and on the above discussion, PMDA instructed the applicant to re-consider the surveillance plan.

The applicant proposed to modify the surveillance plan as follows:

- Diarrhea/nausea/vomiting/dehydration and orthostatic hypotension/hypotension/syncope/loss of consciousness will be added to primary investigation items.

- Most of the adverse events observed in the panobinostat group of Study D2308, including those defined as priority investigation items, occurred within 6 months after the start of treatment; the incidence of these events did not increase during the 6 to 12 months or >12 months after the start of treatment. In Study D2308, there were no patients who received panobinostat for >16 cycles. However, since patients were allowed to have a washout period of up to 21 days before proceeding to the next cycle for the control of adverse events, panobinostat was administered for >48 weeks in 55 of 381 patients (14.4%) and for >56 weeks in 5 of 381 patients (1.3%). Therefore, the maximum follow-up period will be changed from 1 year to 16 cycles.

PMDA concluded as follows:

Because of the limited data on the efficacy and safety of panobinostat in Japanese patients, the results of the ongoing Study D1201 are crucial [see "(1) Efficacy"]. The efficacy specification section in the risk management plan should include the protocol of Study D1201 and the following descriptions, to ensure appropriate completion of Study D1201.

- An efficacy analysis should be performed approximately every 6 months, and the results of the analysis should be published on the website, etc. immediately.

- If the above analysis raises a new safety concern, discussion should be held on the necessity of changing the surveillance plan and of conducting additional pharmacovigilance activities and risk minimization activities; decisions resulting from the discussion should be published immediately.

- As soon as the final analysis results are made available, necessary measures, such as providing the information to healthcare professionals immediately, should be taken.

The results of the final OS analysis in Study D2308 will also be useful for healthcare professionals in appropriate decision making on eligibility of patients. PMDA concluded that the efficacy specification section in the risk management plan should contain the details of the OS analysis with a statement to the effect that results of the final OS analysis should be provided to healthcare professionals immediately.

PMDA instructed the applicant to appropriately respond to the above conclusions of PMDA; the applicant agreed.

Furthermore, based on the above discussion, PMDA concluded that the proposed risk management plan (draft) for panobinostat should include safety and efficacy specifications and that additional pharmacovigilance activities and risk minimization activities should be conducted as shown in the following tables.

Safety and efficacy specifications in risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• QT prolongation • Bone marrow depression • Haemorrhage • Infection • Hepatic dysfunction • Renal dysfunction • Diarrhoea/nausea/vomiting/dehydration • Hypotension/orthostatic hypotension/syncope/loss of consciousness	• Cardiac disorders (cardiac failure, ischaemic heart disease, tachyarrhythmia) • Colitis ischaemic • Venous thromboembolism • Effect on embryo-fetal development	• None
Efficacy specifications		
• Efficacy in routine clinical practice (post-marketing surveillance) • Evaluation of efficacy, etc. of panobinostat in combination with BTZ and DEX in patients with relapsed or refractory MM (extended study of post-marketing Japanese phase II study [Study D1201]) • Evaluation of OS in a randomized, double-blind, comparative study on panobinostat in combination with BTZ and DEX in patients with relapsed or refractory MM (a post-marketing global phase III study [the extended study of Study D2308])		

Outline of additional pharmacovigilance activities and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing surveillance (all-case surveillance) Target sample size, 350 Follow-up period, up to 16 cycles • Post-marketing clinical study (extension of Study D1201) • Post-marketing clinical study (extension of Study D2308)	• Information provision based on the early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals • Preparation and distribution of materials for patients • Measures to be taken to avoid drug administration error

Outline of the post-marketing surveillance (draft)

Objective	To investigate the safety, etc. of panobinostat in routine clinical practice
Survey method	All-patient surveillance by central registration method
Population	All patients who received panobinostat
Follow-up period	16 cycles
Planned sample size	350
Main investigation items	Priority investigation items: QT prolongation, bone marrow depression, hemorrhage, infection, hepatic dysfunction, renal dysfunction, diarrhoea/nausea/vomiting/dehydration, hypotension/orthostatic hypotension/syncope/loss of consciousness Other investigation items: patient characteristics (sex, age, reason for using panobinostat, the date of diagnosis of the primary disease, ECOG Performance Status, prior treatments, disease stage by International Staging System (ISS), type of myeloma, type of chromosomal abnormality, prior or concurrent diseases, history of allergy, history of adverse drug reactions, pregnancy/lactation status), status of treatment with panobinostat, BTZ, and DEX, concomitant drugs/therapies, clinical response, laboratory test, adverse events, pregnancy status

(6) Other

PMDA reached the following conclusion on the cytochrome P450 (CYP) 3A-mediated pharmacokinetic interaction of panobinostat: Based on the panobinostat exposure estimated by the Physiologically-based Pharmacokinetic (PBPK) Model, the package insert should include precautionary statements about decreased exposure to panobinostat used in combination with rifampicin [see "4.(ii).B.(2) Pharmacokinetic interactions" in the Review Report (1)].

The following comment was made by expert advisors at the Expert Discussion.

- In order to evaluate the appropriateness of the PBPK model, the model structure in the software used, physiological parameters, the reason for the change in the model, and the effect of the change in the model should also be checked.

PMDA asked the applicant to explain the reason for selecting the software used in the above analysis, the model structure in the software, physiological parameters, the reason for changing the model, and the effect of the change in the model.

The applicant responded as follows:

The analysis was performed using Simcyp, the software developed by Novartis (Switzerland). A Minimal PBPK model with a single adjusting compartment was used for the following reasons, among others: (i) panobinostat is considered to be eliminated by the metabolism in the gastrointestinal tract and in the liver and by renal excretion, and (ii), in the population pharmacokinetic analysis, a 3-compartment model including tissue compartments appeared to efficiently simulate the time-course of plasma panobinostat concentration after the administration of panobinostat. The default data in Simcyp were used for the physiological parameters and for concomitant drugs including rifampicin.

The reason why and how change was made in the PBPK model are as follows: during the early stage of the development of panobinostat, AUC of panobinostat following a single-dose administration at 20 mg was estimated based on the PBPK model (Simcyp ver. 8.1). The PBPK model was constructed based on the contribution rate of CYP3A-mediated metabolism to the elimination of panobinostat obtained from *in vitro* metabolic studies. As a result, the estimated value was approximately 8 times larger than the actual value (actual, 183 ± 102 ng·h/mL; estimated, 1414 ± 573 ng·h/mL). Subsequently, $AUC_{0\text{-}inf}$ of panobinostat following a single-dose administration at 20 mg was estimated based on another PBPK model (Simcyp ver. 13.0 [modified model]). The modified model was constructed based on the PK parameters of panobinostat alone (Studies B1101, B2101, B2102) and in combination with ketoconazole (Study B2110). As a result, the estimated value fell within twice the actual values (actual, 142 ± 50; estimated, 251 ± 122 ng·h/mL). Using the modified model, panobinostat exposure following the administration of panobinostat 20 mg on Day 7 in combination with rifampicin 600 mg once daily from Day 1 to Day 14 was estimated. The geometric mean ratios [90% CI] for C_{max} and AUC_{inf} of panobinostat alone versus panobinostat in combination with rifampicin were estimated to be 0.45 [0.41, 0.49] and 0.35 [0.32, 0.38], respectively.

In clinical studies, concomitant use of DEX tended to result in decreased exposure to panobinostat (the table below). Therefore the effect of the version upgrade of Simcyp does not change the conclusion that a concomitant potent CYP3A inducer reduces plasma panobinostat concentration. However, changes in model equations resulting from the version upgrade of Simcyp might have caused slight variation in estimated values.

Effect of concomitant DEX on panobinostat exposure in single-dose administration at 20 mg

Study identifier	DEX (dose)	n	C_{max} (ng/mL)	AUC_{inf} (h·ng/mL)
B2101	Not used	36	20.4 (59.5)	179 (64.1)[*2]
B2102	Not used	9	16.7 (64.6)	126 (61.1)[*3]
B2207	Not used	15	9.5 (60.4)	82.8 (60.8)
	Used (20 mg[*1])	12	8.1 (90.3)	68.5 (79.6)
B2206[*4]	Used (40 mg)	21	11.4 (77.9)	79.9 (59.8)

Geometric mean (CV%). [*1] For dosage regimen of DEX, see "4.(ii).A.(3).6) Foreign phase I study" of the Review Report (1). [*2] n = 22. [*3] n = 7. [*4] In each 28-day treatment cycle, panobinostat (5, 10, 20, 25 mg) was administered orally once daily 3 times a week, and oral lenalidomide hydrate (25 mg) was administered once daily from Day 1 to Day 21, followed by washout from Day 22 to Day 28. Also, oral DEX (40 mg) was concomitantly administered once daily from Day 1 to Day 4, from Day 9 to Day 12, and from Day 17 to Day 20 in Cycle 1 to Cycle 4, and from Day 1 to Day 4 in Cycle 5 onward.

PMDA considers as follows:
The applicant explained that the modified model, used for the investigation of the pharmacokinetic interaction of panobinostat mediated by CYP3A induction, was established in consideration of the elimination pathway of panobinostat; this explanation is generally acceptable. However, it is important to re-assess the appropriateness of the model when new clinical data become available. Any change made to the modified model may affect the estimation of the pharmacokinetic interaction of panobinostat mediated by CYP3A induction. Therefore, information on the pharmacokinetic interaction of panobinostat mediated by CYP3A induction should be further collected, and any new finding should be immediately provided to healthcare professionals, or any appropriate measures should be taken against it.

Also, data on the effect of concomitant DEX on panobinostat exposure should be provided appropriately to healthcare professionals through the package insert, etc.

PMDA instructed the applicant to take appropriate actions to the above issue; the applicant agreed.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1) PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2) PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-1). PMDA concluded that the conducted clinical studies were generally in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted application data. The following was noted in the sponsor's work as a matter to be improved, although it did not significantly affect the overall evaluation of the study.

Matter to be improved
Sponsor
- Inappropriate descriptions of the procedures for a clinical study in the protocol

IV. Overall Evaluation

PMDA concludes that the product may be approved with the following the indication, the dosage and administration, and the conditions for approval as shown below, provided that (i) the package insert contains appropriate precautionary statements, and information concerning the proper use of the product is disseminated appropriately after the market launch, and (ii) compliance with the proper use of the product is ensured under the supervision of physicians with expertise in the treatment of hematopoietic

malignancy and at medical institutions capable of emergency response. Since panobinostat is designated as an orphan drug, the re-examination period is 10 years. The drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication]
Relapsed or refractory multiple myeloma

[Dosage and administration]
In combination with bortezomib and dexamethasone, the usual adult dosage is 20 mg of panobinostat administered orally once daily 3 times a week for 2 weeks (Days 1, 3, 5, 8, 10, and 12), followed by a 9-day rest period (Days 13-21). The 3-week treatment cycle is repeated. The dose may be adjusted according to the condition of the patient.

[Conditions for approval]
The applicant is required to:
1. Establish and appropriately implement a risk management plan.

2. Conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered, to identify the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product, since only a limited number of Japanese patients participated in clinical studies of the product.

[Warnings]
1. Panobinostat should be administered only to patients who are considered eligible to receive the product, under the supervision of a physician with expertise in the treatment of hematologic malignancies and at a medical institution capable of emergency response. Prior to the start of the therapy, the patient or a family member of the patient should receive a thorough explanation on the benefits and risks of the therapy and provide consent to the therapy.

2. The patient should be hospitalized or placed in a similar condition to receive appropriate care during the early stage of treatment with panobinostat. The physician should read the package insert, etc. carefully.

[Precautions for Indications]
1. Panobinostat should be administered to patients who are non-responsive to at least one of the standard regimens or who had a relapse after such regimen.

2. Eligibility of the patient for the therapy should be determined based on a good understanding of the study results in the “Clinical Studies” section of the package insert, including prior regimens of patients enrolled in the clinical studies, and of the efficacy and safety of panobinostat.

[Precautions for dosage and administration]
1. The efficacy and safety of panobinostat monotherapy have not been established.

2. Concomitant bortezomib and dexamethasone should be administered by physicians with a good understanding of the “Clinical Studies” section. The package inserts of the concomitant drugs should be read carefully.

3. The efficacy and safety of panobinostat in combination with antineoplastic drugs other than bortezomib and dexamethasone have not been established.

4. The efficacy and safety of panobinostat administered for >16 cycles have not been established.

5. Increased blood panobinostat concentration was reported in patients with hepatic impairment. In these patients, dose reduction should be considered and the condition of the patients should be closely monitored for possible adverse events.

6. Before starting treatment with panobinostat, the following criteria should be read.

Criteria for the start of treatment

Platelet count	≥100,000/μL
Neutrophil count	≥1500/μL
QTc interval	<450 msec (panobinostat should not be administered if the mean QTc is prolonged to ≥450 msec on ECG performed after electrolyte abnormality is corrected.)
Blood electrolytes[*1]	If patients had electrolyte abnormality, the electrolyte level should be corrected as needed.

[*1] Blood potassium, magnesium, and phosphate

7. The interruption, dose reduction, or discontinuation of panobinostat due to adverse drug reactions should be decided based on the following criteria according to the symptoms, grade,[*2] etc. of the adverse drug reactions. The 3-week treatment cycles should be maintained even after dose reduction. The dose may be reduced according to the patient's condition, by 5 mg/ but not to <10 mg/day.
[*2] NCI-CTCAE v.4.0

Criteria for the interruption, dose reduction, and discontinuation of panobinostat due to adverse drug reactions

	Criteria for treatment interruption and dose reduction	Dose adjustment
Platelet count	<25,000/μL or <50,000/μL with hemorrhage	Interrupt treatment until platelet count increases to ≥50,000/μL. Reduce the current dosing level by 5 mg/dose when resuming treatment. Reduce the dose again by 5 mg/dose (to 10 mg/dose) when decreased platelet count recurs during resumed treatment. Discontinue treatment if the adverse drug reaction recurs at 10 mg/dose. If frequent platelet transfusion is required, consider discontinuing treatment.
Neutrophil count	≥500/μL and <1000/μL	Interrupt treatment until neutrophil count increases to ≥1000/μL. Resume treatment at the starting dose.
	<500/μL	Interrupt treatment until neutrophil count increases to ≥1000/μL. Reduce the current dosing level by 5 mg/dose when resuming treatment. Reduce the dose again by 5 mg/dose (to 10 mg/dose) when decreased neutrophil count recurs during resumed treatment. Discontinue treatment if the adverse drug reaction recurs at 10 mg/dose.
	Febrile neutropenia (<1000/μL with pyrexia of ≥38.5°C)	Interrupt treatment until pyrexia has resolved and neutrophil count increases to ≥1000/μL. Reduce the current dosing level by 5 mg/dose when resuming treatment. Reduce the dose again by 5 mg/dose (to 10 mg/dose) when decreased neutrophil count recurs during resumed treatment. Discontinue treatment if the adverse drug reaction recurs at 10 mg/dose.
Diarrhea that persists despite the use of antidiarrheal drugs	Grade 2	Interrupt treatment until diarrhea improves to Grade ≤1. Resume treatment at the starting dose.
	Grade 3	Interrupt treatment until diarrhea improves to Grade ≤1. Reduce the current dosing level by 5 mg/dose when resuming treatment. Reduce the dose again by 5 mg/dose (to 10 mg/dose) when diarrhea recurs during resumed treatment. Discontinue treatment if the adverse drug reaction recurs at 10 mg/dose.
	Grade 4	Discontinue treatment.

	Criteria for treatment interruption and dose reduction	Dose adjustment
Nausea or vomiting that persists despite the use of antiemetics	Grade ≥3	Interrupt treatment until nausea or vomiting improves to Grade ≤1. Reduce the current dosing level by 5 mg/dose when resuming treatment. Reduce the dose again by 5 mg/dose (to 10 mg/dose) when nausea or vomiting recurs during resumed treatment. Discontinue treatment if the adverse drug reaction recurs at 10 mg/dose.
QTc interval	Prolongation to 480-500 msec or Prolongation of >60 msec from baseline	Interrupt treatment. Discontinue treatment if prolonged QTc interval does not resolve within 7 days. If symptom resolves within 7 days, resume treatment at the starting dose. If prolonged QTc interval recurs during resumed treatment but resolves within 7 days, reduce the dose by 5 mg/dose. If prolonged QTc interval recurs thereafter, reduce the dose again by 5 mg/dose (to 10 mg/dose). Discontinue treatment if the adverse drug reaction recurs at 10 mg per/dose.
	Prolongation to >500 msec	Discontinue treatment.
Other adverse drug reactions	Grade ≥3 adverse drug reactions or relapse of Grade 2 adverse drug reactions	Interrupt treatment until symptom improves to Grade ≤1. Reduce the current dosing level by 5 mg/dose when resuming treatment. Reduce the dose again by 5 mg/dose (to 10 mg/dose) when the symptom recurs during resumed treatment. Discontinue treatment if the adverse drug reaction recurs at 10 mg/dose.