Report on the Deliberation Results

March 4, 2015

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau

Ministry of Health, Labour and Welfare

[Brand name]	Pomalyst Capsules 1 mg, Pomalyst Capsules 2 mg, Pomalyst Capsules 3 mg, Pomalyst Capsules 4 mg
[Non-proprietary name]	Pomalidomide (JAN*)
[Applicant]	Celgene K.K.
[Date of application]	July 25, 2014

[Results of deliberation]

In the meeting held on February 26, 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 poisonous 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. Develop and appropriately implement a risk management plan;
2. Take strict and appropriate measures to ensure that the drug product is given only to eligible patients under the supervision of physicians with sufficient knowledge and experience, at medical institutions capable of providing sufficient emergency care, only after the efficacy and risks of the drug product have been explained to patients or their families in writing, and written consent has been obtained;
3. Conduct a post-marketing drug use-results survey, covering all patients treated with the product until data from a specific number of patients have been collected, in order to keep track of the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible and to ensure proper use of the product by taking necessary measures accordingly, because the number of patients included in the Japanese clinical studies was very small; and
4. Implement the measures for safety management (draft) appropriately.
   (Measures for safety management will be considered at the Subcommittee on Pharmaceutical Safety, Pharmaceutical Affairs and Food Sanitation Council.)

It was determined that specific conditions for approval concerning appropriate implementation of the measures for safety management (draft) should be left to the discretion of Committee Chair.

**Japanese Accepted Name (modified INN)*

Report on the Deliberation Results (2)

March 20, 2015

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau

Ministry of Health, Labour and Welfare

[Brand name]	Pomalyst Capsules 1 mg, Pomalyst Capsules 2 mg, Pomalyst Capsules 3 mg, Pomalyst Capsules 4 mg
[Non-proprietary name]	Pomalidomide (JAN*)
[Applicant]	Celgene K.K.
[Date of application]	July 25, 2014

[Results of deliberation]

The product may be approved with the following conditions.

[Conditions for approval]

The applicant is required to:

1. Properly comply with the "Proper management procedures for Revlimid and Pomalyst" in the processes including marketing, management, and use of the product, alterations of which need consent from the Ministry of Health, Labour and Welfare prior to making any changes to the procedures;
2. Develop and appropriately implement a risk management plan;
3. Take strict and appropriate measures to ensure that the drug product is given only to eligible patients under the supervision of physicians with sufficient knowledge and experience, at medical institutions capable of providing sufficient emergency care, only after the efficacy and risks of the drug product have been explained to patients or their families in writing, and written consent has been obtained; and
4. Conduct a post-marketing drug use-results survey, covering all patients treated with the product until data from a specific number of patients have been collected, in order to keep track of the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible and to ensure proper use of the product by taking necessary measures accordingly, because the number of patients included in the Japanese clinical studies was very small.

**Japanese Accepted Name (modified INN)*

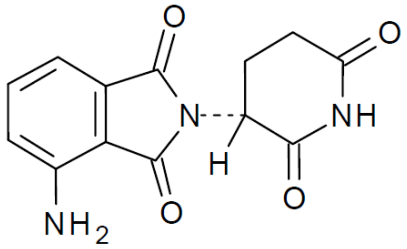
Review Report

February 16, 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]	Pomalyst Capsules 1 mg, Pomalyst Capsules 2 mg, Pomalyst Capsules 3 mg, Pomalyst Capsules 4 mg
[Non-proprietary name]	Pomalidomide
[Name of applicant]	Celgene K.K.
[Date of application]	July 25, 2014
[Dosage form/Strength]	A capsule containing 1 mg, 2 mg, 3 mg, or 4 mg of pomalidomide per capsule
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



and enantiomer

Molecular formula: $C_{13}H_{11}N_3O_4$

Molecular weight: 273.24

Chemical name: 4-Amino-2-[(3*RS*)-2,6-dioxopiperidin-3-yl]-2*H*-isoindole-1,3-dione

[Items warranting special mention]

Orphan drug (Drug Designation No. 342 of 2014 [*26 yaku*], dated June 11, 2014, PFSB/ELD Notification No. 0611-1, issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).

[Reviewing office] Office of New Drug V

Review Results

February 16, 2015

[Brand name] Pomalyst Capsules 1 mg,
Pomalyst Capsules 2 mg,
Pomalyst Capsules 3 mg,
Pomalyst Capsules 4 mg

[Non-proprietary name] Pomalidomide

[Name of applicant] Celgene K.K.

[Date of application] July 25, 2014

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of pomalidomide in the treatment of relapsed or refractory multiple myeloma has been demonstrated and its safety is acceptable in view of its observed benefits. Further investigation will be necessary through post-marketing surveillance for the following: teratogenicity, myelosuppression, peripheral neuropathy, thromboembolism, infections, arrhythmia, cardiac failure, acute renal failure, interstitial lung disease, tumor lysis syndrome, somnolence, depressed level of consciousness, confusion, fatigue, dizziness/vertigo, and hypersensitivity.

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.

The method for safety management of pomalidomide will be considered separately by the Ministry of Health, Labour and Welfare (MHLW).

[Indication]

Relapsed or refractory multiple myeloma

[Dosage and administration]

In combination with dexamethasone, the usual adult dosage is 4 mg as pomalidomide given orally once daily on a 21-day on/7-day off schedule. The dose may be reduced according to the patient's condition.

[Conditions for approval]

The applicant is required to:

1. Develop and appropriately implement a risk management plan;

2. Take strict and appropriate measures to ensure that the drug product is given only to eligible patients under the supervision of physicians with sufficient knowledge and experience, at medical institutions capable of providing sufficient emergency care, only after the efficacy

and risks of the drug product have been explained to patients or their families in writing, and written consent has been obtained;

3. Conduct a post-marketing drug use-results survey, covering all patients treated with the product until data from a specific number of patients have been collected, in order to keep track of the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible and to ensure proper use of the product by taking necessary measures accordingly, because the number of patients included in the Japanese clinical studies was very small; and

The condition for approval concerning the appropriate implementation of the measures for safety management of pomalidomide will be considered separately by the MHLW.

4. Implement the measures for safety management (draft) appropriately.

Review Report (1)

December 26, 2014

I. Product Submitted for Registration

[Brand name]	Pomalyst Capsules 1 mg, Pomalyst Capsules 2 mg, Pomalyst Capsules 3 mg, Pomalyst Capsules 4 mg
[Non-proprietary name]	Pomalidomide
[Name of applicant]	Celgene K.K.
[Date of application]	July 25, 2014
[Dosage form/Strength]	A capsule containing 1 mg, 2 mg, 3 mg, or 4 mg of pomalidomide per capsule
[Proposed indication]	Relapsed or refractory multiple myeloma
[Proposed dosage and administration]	In combination with dexamethasone, the usual adult dosage is 4 mg as pomalidomide given orally once daily on a 21-day on/7-day off schedule. The dose may be reduced according to the patient's condition.

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

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

(1) Summary of the product submitted for registration

Pomalidomide, a thalidomide analogue, is a low molecular weight compound discovered by Celgene Corporation in the US. Thalidomide is known to be teratogenic in humans (thalidomide embryopathy: limb malformation including amelia, phocomelia, and peromelia; heart disease; internal disorders such as obstruction in the digestive system). Toxicity studies of pomalidomide in rats and rabbits have indicated that pomalidomide may also be teratogenic. Based on the chemical structure and the results of nonclinical studies, pomalidomide treatment during pregnancy may cause serious fetal malformation, abortion, or stillbirth in humans.

As with thalidomide, pomalidomide is believed to inhibit the proliferation of myeloma cells by inducing apoptosis, suppressing the production of cytokines such as tumor necrosis factor (TNF)-α, activating T lymphocytes and natural killer cells, inhibiting angiogenesis, and other actions.

(2) Development history, etc.

Phase I studies, Studies CC-4047-1398/132 and CC-4047-MM-001, were conducted overseas in healthy adults and patients with relapsed multiple myeloma (MM) by Celgene Corporation, starting in [redacted] 19[redacted] and [redacted] 20[redacted], respectively. A phase I/II study (Study CC-4047-MM-002) in patients with relapsed or refractory MM who had received prior treatment including lenalidomide and bortezomib was initiated in December 2009. A phase III study (Study CC-4047-MM-003) was conducted in patients with the same conditions, starting in March 2011.

The applications for marketing approval of pomalidomide were submitted in the US in April 2012 with data from Study CC-4047-MM-002, and in the EU in May 2012 with data from Study CC-4047-MM-003, as the pivotal study results. Pomalidomide was approved in the US in February 2013 with the indication stating that "POMALYST is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy," and approved in the EU in August 2013 with the indication stating that "Imnovid in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy."

As of November 2014, pomalidomide has been approved in 36 countries and regions with indications for the treatment of MM.

In Japan, a phase I study (Study CC-4047-MM-004) and a phase II study (Study CC-4047-MM-011) in patients with relapsed or refractory MM were initiated by the applicant in April 2012 and December 2013, respectively. The studies are ongoing.

In July 2014, the application for the approval of pomalidomide was filed with the data from Study CC-4047-MM-003 as the pivotal study results.

Pomalidomide was designated as an orphan drug in June 2014 with the intended indication of "relapsed or refractory MM" (Drug Designation No.342 of 2014 [*26 yaku*]).

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 yellow powder, and its description, solubility, hygroscopicity, optical rotation, melting point, acid dissociation constant, partition coefficient, and particle size distribution have been determined.

The chemical structure of the drug substance has been elucidated by elemental analysis, nuclear magnetic resonance spectroscopy (^{1}H-, ^{13}C-NMR), single-crystal X-ray diffraction, mass spectrometry, ultraviolet-visible spectroscopy (UV/VIS), and infrared spectroscopy (IR). The drug substance is a racemic mixture of enantiomers containing a chiral center in the molecule.

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

[redacted]

The Quality by Design (QbD) approach has been used to determine the following issues:

- Identification of particle size and crystalline polymorphism as critical quality attributes;
- Selection of critical process parameters through quality risk assessment.

[redacted]

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

The proposed specifications for the drug substance include content, description, identification (IR), purity (Related Substance A [high-performance liquid chromatography, HPLC], and other related substances [HPLC]; residual solvents [gas chromatography]), water content, residue on ignition, particle size distribution, and assay (HPLC).

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

The table below shows the conditions for the stability studies of the drug substance. The results of the photostability studies indicated that the drug substance is photostable.

Stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 production-scale batches	25°C	60%RH	Low Density Polyethylene bags (double layer) + high density polyethylene container	24 months
Accelerated	3 production-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 2 layers of low-density polyethylene bags placed inside a high-density polyethylene container, in accordance with the "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, dated June 3, 2003, hereinafter referred to as "ICH Q1E Guidelines"). The long-term study will be continued for up to [redacted] months.

2.A.(2) Drug product

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

The drug product is an immediate-release hard capsule, each containing 1 mg, 2 mg, 3 mg, or 4 mg of pomalidomide. The drug product contains D-mannitol, partly pregelatinized starch, and sodium stearyl fumarate as excipients.

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

The drug product is produced through the manufacturing process comprising the following steps: mixing, encapsulation, packaging, and visual inspection. [redacted]

The QbD approach has been used to determine the following issues:

- Robustness of process parameters based on the design of experiments;
- Risk analysis of the manufacturing process

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

The proposed specifications for the drug product consist of content, description, identification (UV/VIS and HPLC), purity (related substances [HPLC]), uniformity of dosage units (content uniformity test [HPLC]), microbial limit, dissolution (HPLC), and assay (HPLC).

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

The table below shows the conditions for the stability studies of the drug product. The results of the photostability studies indicated that the drug product is photostable.

Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 production-scale batches	25°C	60%RH	PTP sheet	24 months
Accelerated	3 production-scale batches	40°C	75%RH	PTP sheet	6 months

Based on the above, a shelf life of 36 months has been proposed for the drug product when stored at room temperature in a push-through pack (PTP) (polyvinyl chloride/polychlorotrifluoroethylene laminated film/aluminum foil), in accordance with the ICH Q1E Guidelines. The long-term study will be continued for up to [redacted] months.

2.B Outline of the review by PMDA

Based on the submitted data and the following reviews, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

Control of optical purity

PMDA asked the applicant to explain how the optical purity of the drug substance is controlled since the drug substance is described as the racemic mixture of enantiomers.

The applicant responded as follows:

[redacted]

PMDA accepted the applicant's response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

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

3.(i).A.(1).1) Action on cereblon (Report DM2528)

Pomalidomide is a thalidomide analogue. Thalidomide inhibits ubiquitin ligase activity by binding to cereblon (CRBN), a component of the ubiquitin E3 ligase complex (*Science.* 2010;327:1345-50); thus, the following studies were conducted focusing on the binding of pomalidomide to CRBN:

- The binding property of pomalidomide to the protein complex of CRBN and DNA-damage binding protein-1 (DDB1) was studied using a fluorescence-based thermal shift assay. The results showed an IC_{50} of approximately 3 μmol/L for pomalidomide.
- To evaluate the binding of pomalidomide to endogenous CRBN, competitive inhibition by pomalidomide or lenalidomide of the binding between pomalidomide immobilized on beads and CRBN in cell lysate was studied using immunoblot analysis. The results showed that the IC_{50} was 2.1 μmol/L for pomalidomide and 2.3 μmol/L for lenalidomide (n = 2 for each agent).
- The relationship between the level of CRBN expression and the inhibitory effect of pomalidomide on cell proliferation was studied in U266, a human MM cell line, with CRBN expression knocked down using small interfering RNA (siRNA). The results showed that a decrease in the level of CRBN expression resulted in a reduction in the activity of pomalidomide to inhibit cell proliferation.
- The level of CRBN expression was studied using a reverse transcription-polymerase chain reaction (RT-PCR) assay in H929, a human MM cell line, rendered treatment-resistant by culturing in the presence of lenalidomide. The results showed that the level of CRBN expression was lower in the lenalidomide-resistant H929 cell line than in the parent H929 cell line. In addition, pomalidomide

was shown to have an inhibitory effect on the proliferation of the lenalidomide-resistant H929 cell line, albeit less inhibitory than that on the parent cell line, in terms of the number of viable cells.

3.(i).A.(1).2) Immunoregulatory activity (Report Nos.: PD365, PD408, 5043-152-5119-172, PD522, 5304-79, 5197-189-5226-016, 7596-09, 5422-8-CC-4047)

- Pomalidomide increased the anti-CD3 antibody-stimulated production of cytokines (interferon gamma [IFN-γ], interleukin [IL] -2, and regulated on activation, normal T cell expressed and secreted [RANTES]) in CD4 positive T cells that were isolated from human peripheral blood mononuclear cells (PBMCs), and inhibited the production of IL-10. T-cell activation with phytohemagglutinin (PHA) on T cells isolated from PBMCs was studied in terms of IL-2 production. The results showed enhanced T cell activity by pomalidomide.
- The B cell activation stimulated by immunoglobulin M (IgM) and anti-CD40 antibody was studied by flow cytometry with CD69 and Toll-like receptor 9 (TLR9) as indicators using B cells collected from healthy adults. The results indicated B cell activation by pomalidomide.
- The effect of pomalidomide on the production of IL-2 by concanavalin A (ConA) stimulation was studied using human peripheral blood. The results showed increased IL-2 production by pomalidomide.
- The effect of pomalidomide on the anti-CD3 antibody-stimulated production of Th1 cytokines (granulocyte macrophage colony-stimulating factor [GM-CSF], IFN-γ, tumor necrosis factor [TNF]-α, and IL-2) and Th2 cytokines (IL-4, IL-5, IL-10, and IL-13) was studied using human peripheral blood. The results showed that pomalidomide stimulated production of GM-CSF, IFN-γ, TNF-α, IL-2, IL-4, IL-5, and IL-13, and inhibited that of IL-10. Further, the levels of expression of T-bet and GATA-3, transcription factors that regulate the induction of differentiation of CD4 positive T cells into Th1 and Th2, respectively, were studied to evaluate the effect of pomalidomide on induction of differentiation. The results showed that the level of T-bet protein expression increased and the level of GATA-3 expression decreased.
- The antibody-dependent cell-mediated cytotoxicity (ADCC) activity when pomalidomide was used concomitantly with antibodies (trastuzumab [genetical recombination], cetuximab [genetical recombination], and rituximab [genetical recombination]) was studied using human non-Hodgkin lymphoma cell lines (NHLs), Farage, Raji, and Namalwa, human breast cancer cell lines SK-BR-3 and MCF-7, and human colorectal cancer cell lines HCT-116 and HT-29. The results showed that, in all cell lines, pomalidomide enhanced the ADCC activity of natural killer (NK) cells that were isolated from human peripheral blood treated with cytokines (IL-2 or IL-12).

3.(i).A.(1).3) Cell cycle arrest effects etc. (Report No.: 1110-038)

The potential of pomalidomide to arrest the cell cycle and induce apoptosis was studied using human MM cell lines Arp-1, U266, Norway U266, UUN, ARK, CAG, DF-15, H929, RPMI-8226, ANBL-6, W182, and MM-1S. The results showed the potential of pomalidomide to arrest the cell cycle at the G1 phase and induce apoptosis in DF-15, H929, and MM-1S cell lines.

3.(i).A.(1).4) Inhibition of angiogenesis (Report Nos.: 5071-180, 5127-132, 5239-92-5239-188, SRI-P10.0101)

- The effect of pomalidomide on lumen formation was studied using human umbilical vein endothelial cells (HUVECs). The results showed that pomalidomide inhibited lumen formation.
- The effect of pomalidomide on angioblast formation was studied using ring preparations of human umbilical arteries. The results showed an inhibitory effect of pomalidomide on angioblast formation.
- The effect of pomalidomide on endothelial cell invasion was studied using HUVECs. The results showed the inhibitory effects of pomalidomide on endothelial cell invasion.
- The effect of pomalidomide on angiogenesis induced by vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) was studied by administering pomalidomide to mice and using immunohistochemical (IHC) staining of CD31 antibody. The results showed the inhibitory effects of pomalidomide on angiogenesis.

3.(i).A.(1).5) Inhibitory effects on cytokine production etc. (Report Nos.: 5374-10, PD365, 5196-175, 5127-53, 5197-130, 5116-86)

- The effects of pomalidomide on the production of pro-inflammatory cytokines and chemokines in lipopolysaccharide (LPS)-stimulated PBMC were studied. The results showed that pomalidomide inhibited the production of IL-12, IL-1β, IL-6, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, TNF-α, GM-CSF, and granulocyte-colony stimulating factor (G-CSF), and increased the production of IL-10, an anti-inflammatory cytokine.
- Pomalidomide inhibited COX-2 expression and PGE2 production in LPS-stimulated PBMC.

3.(i).A.(1).6) Inhibitory effect on the proliferation of malignant tumor cell lines

i) *In vitro* studies

(a) MM cell lines (Report Nos.: 5286-186, 5710-048)

Given that the t(4;14) translocation is present in 15% of MM patients, and that the overexpression of fibroblast growth factor receptor (FGFR) due to this translocation is implicated in the proliferation of MM cells (*Leukemia.* 2009;23:2210-21, *Nat Genet.* 1997;16:260-4, *Blood.* 1998;92:3025-34), the inhibitory effect of pomalidomide on the proliferation of human MM cell lines with various FGFR3 genotypes was evaluated in terms of ^{3}H-thymidine incorporation levels. The results for IC_{50} are shown in the table below. The treatment time required for pomalidomide to inhibit the proliferation of the H929 cell line was also measured in the same system, and the results showed that a minimum of 48 hours was required for inhibition.

Inhibitory effect of pomalidomide on the proliferation of MM cell lines

Cell line	FGFR3	IC_{50} (μmol/L)
H929	Wild type	0.02
RPMI-8226	—	1.4
OPM-2	K650E	3.4
LP-1	F384L	0.05

n = 1, "—" indicates no FGFR3 expression.

(b) Non-MM tumor cell lines (Report Nos.: SF-ALM-0012, PD385, 5286-14, 5232-59-76)

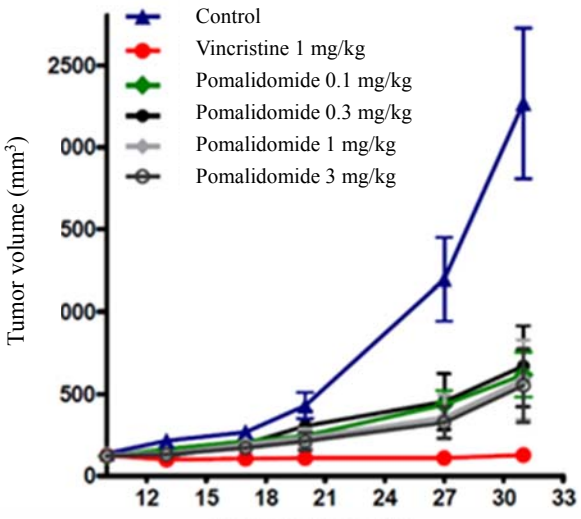
Human acute myeloid leukaemia (AML) cell lines HNT-34, HL-60, KASUMI-3, KG-1a, MOLM-13, OCI-AML3, and THP-1, and myelodysplastic syndrome (MDS) cell line MDS-L were cultured in the presence of pomalidomide. The results showed the cytocidal activity of pomalidomide against HL-60, KG-1a, OCI-AML3, and MDS-L cell lines.

The inhibitory effect of pomalidomide on cell proliferation was studied using human breast cancer cell lines SKBR3, ZR-75-1, MDA-MB-231, MDA-MB-468, MCF-7, and BT-474, and human non-small cell lung cancer (NSCLC) cell lines NCI-H460 and A549. The results showed the inhibitory effect of pomalidomide against MDA-MB-468 and MCF-7 cell lines.

The inhibitory effect of pomalidomide on cell proliferation was studied using the Namalwa cell line, human AML cell lines KG-1 and UT-7, and human acute lymphocytic leukaemia (ALL) cell line MUTZ-5. The results showed the inhibitory effect of pomalidomide against Namalwa and KG-1 cell lines.

ii) *In vivo* studies (Report Nos.: AP3975/4416/4462/4479/4524, IMBCR-03162010)

The inhibitory effect of pomalidomide on tumor proliferation was studied using severe combined immunodeficiency (SCID) mice which were inoculated subcutaneously with the H929 cell line, with vincristine sulfate as a positive control. Ten days after inoculation (tumor volume, approximately 125 mm^3), pomalidomide was orally administered to mice once daily at a dose of 0.1, 0.3, 1, or 3 mg/kg for 20 days, and the tumor volume was calculated (the following figure). On Day 31 after tumor cell inoculation, the reduction of tumor volume was statistically significant in all pomalidomide-treated groups compared to the control group (vehicle: 0.5% carboxymethylcellulose, 0.25% Tween-80) ($P < 0.001$, Dunnett's test).



Inhibitory effect of pomalidomide on tumor proliferation

Mean ± standard error, n = 7 to 10

The inhibitory effect of pomalidomide on tumor proliferation was studied using SCID mice which were inoculated intramuscularly with human MM tumors LAGκ-1A, LAGκ-1B, and LAGλ-1. Pomalidomide was orally administered to mice once daily at a dose of 0.3, 1, 3 or 10 mg/kg for 8 weeks, and the tumor volume was calculated. None of the results in any of the pomalidomide-treated groups showed statistical significance compared to the vehicle group (0.5% carboxymethylcellulose) ($P \geq 0.05$ for all results, Student's t-test).

3.(i).A.(1).7) Inhibitory effect on proliferation of lenalidomide-resistant MM cell lines (Report Nos.: 1785-4047, 7596-01, AP3975/4416/4462/4479/4524)

The H929 cell line was cultured in the presence of lenalidomide for 5 months or more to prepare lenalidomide-resistant cell lines H929-1051, H929-1052, H929-1053, and H929-1054, and these were used to study the inhibitory effect of pomalidomide on the proliferation of these cells. The results showed the inhibitory effect of pomalidomide on cell proliferation in all cell lines.

The H929 cell line and human MM cell line KMS-12-BM were cultured in the presence of lenalidomide or pomalidomide for 3 to 4 months, and time required to acquire resistance ($IC_{50} > 100$ μmol/L) to each drug was studied in terms of monthly IC_{50}. The results showed that time required to acquire pomalidomide-resistance is longer than that for lenalidomide-resistance in all cell lines.

The inhibitory effect of pomalidomide (1 or 3 mg/kg) in combination with dexamethasone (DEX) (5 mg/kg) on tumor proliferation was studied using SCID mice which were inoculated subcutaneously with the H929-1051 cell line. The results showed an enhanced inhibitory effect on tumor proliferation in the group concomitantly treated with pomalidomide (3 mg/kg) and DEX, compared to that with pomalidomide alone or DEX alone ($P < 0.01$, Bonferroni method).

3.(i).A.(1).8) Other effects (Report Nos.: CGN-04, CLG-10, 1110-028, 7600-025, 1200-066, UEN11162010JD, UEN07052012JD, 2231-24, 1270RC35.001, PD444, 5572-001, 5448-74)

The inhibitory effect of pomalidomide on proliferation was studied using normal human bone marrow-derived cells after induction of differentiation. The results showed the inhibitory effect of pomalidomide on the proliferation of human erythroid progenitor cells, erythroid colony forming cells, and megakaryocyte colony forming cells.

The effect of pomalidomide on the induction of differentiation of CD34-positive cells into dendritic cells was studied. The results showed that pomalidomide inhibited differentiation into dendritic cells.

The inhibitory effects of the metabolites of pomalidomide (CC-17372, M16 [CC-17369], M17 [CC-17368], M19 [CC-12074], M10 [CC-15262], M11 [CC-8017], and M18 [CC-4067]) on cell proliferation were studied using OPM-2, H929, and U266 cell lines. The results showed that IC_{50} values were >10 μmol/L for all metabolites.

3.(i).A.(2) Safety pharmacology

3.(i).A.(2).1) Effects on the central nervous system (Report No.: CC-4047-TOX-011)

A single oral dose of pomalidomide (250, 1000, or 2000 mg/kg) was administered to rats (n = 20/group) to study the effect on general symptoms, appearance, autonomic nervous function, grip strength, body weight, and body temperature. The results showed that pomalidomide administration had no effect on these parameters.

3.(i).A.(2).2) Effects on cardiovascular system

i) Effects on hERG current (Report No.: CC-4047-TOX-009)

The effect of pomalidomide on human ether-à-go-go gene (hERG) potassium channels was studied using the hERG-expressing human embryonic kidney 293 (HEK293) cell line. Pomalidomide inhibited the hERG potassium channels by 0.8 ± 0.4% at 7.9 μmol/L (n = 3) and by 0.9 ± 0.3% at 87.5 μmol/L (n = 4).

ii) Effects on blood pressure and electrocardiogram (Report Nos.: 1398/110-D6146, CC-4047-TOX-012)

Pomalidomide (2.5, 10, and 25 mg/kg) was intravenously administered to dogs (n = 4) in a dose-escalating manner at intervals of ≥30 minutes to study the effects on arterial pressure (systolic blood pressure, diastolic blood pressure, and mean blood pressure), heart rate, left ventricular pressure, maximum upstroke velocity, femoral arterial blood flow, maximum and mean values for femoral artery resistance, and electrocardiogram (ECG) parameters (RR interval, ST segment, QRS width, PR interval, QT interval, corrected QT interval [QT_C], and amplitudes of the R wave, P wave, and T wave). The results showed that pomalidomide administration had no effect on the above parameters.

A single oral dose of pomalidomide (0.2, 2, or 10 mg/kg) was administered to cynomolgus monkeys (n = 4/group) to study the effects on ECG parameters (PR interval, QRS width, QT interval, and QT_C), blood pressure, heart rate, survival, body weight, body temperature, food intake, and general symptoms. The results showed that pomalidomide administration had no effect on the above parameters.

3.(i).A.(2).3) Effects on respiratory system (Report Nos.: CC-4047-TOX-014, 1398/110-D6146)

A single oral dose of pomalidomide (250, 1000, or 2000 mg/kg) was administered to rats (n = 8/group) to study the effects on respiratory rate, tidal volume, and minute ventilation volume. The results showed that pomalidomide administration had no effect on the above parameters.

Pomalidomide (2.5, 10, and 25 mg/kg) was intravenously administered to dogs (n = 4/group) in a dose-escalating manner at intervals of ≥30 minutes to study the effect on maximum expiratory flow rate, maximum inspiratory flow rate, tidal volume, minute ventilation volume, and respiratory rate. The results showed that pomalidomide administration had no effect on the above parameters.

3.(i).A.(3) Pharmacodynamic drug interaction studies (Report Nos.: 7609-111, 1785-4047, DM2775-49, 7596-01, SALA-151008)

The inhibitory effect of the pomalidomide in combination with DEX (pomalidomide + DEX) on cell proliferation was studied using cell lines H929, KMS-12-BM, LP-1, and OPM-2, in terms of intracellular ATP concentration. The results showed enhanced anti-proliferative effects on H929, LP-1, and OPM-2 cell lines treated with pomalidomide + DEX, compared to DEX treatment alone. No enhanced effects of the combination of pomalidomide + DEX were observed in the KMS-12-BM cell line because it is insensitive to DEX.

Furthermore, the effects of pomalidomide on the inhibition of cell proliferation in the lenalidomide-resistant H929-1051 cell line, and apoptosis induction were studied using trypan blue staining and 7-aminoactinomycin D staining. The results showed enhanced anti-proliferative effects and apoptosis induction in the cell line treated with pomalidomide + DEX, compared to pomalidomide alone or DEX alone.

The inhibitory effects of pomalidomide + DEX on tumor proliferation were studied using SCID mice which were inoculated subcutaneously with the H929 cell line. From 12 days after inoculation (tumor volume: approximately 125 mm^3), pomalidomide (0.03 mg/kg) and DEX (5 mg/kg) were orally administered to mice once daily for 21 days, and the tumor volume was calculated. On Day 34 after inoculation, the reduction of tumor volume in the pomalidomide alone group, DEX alone group, and pomalidomide + DEX group (*P*-value for Dunnett's test, compared to the control [0.5% carboxymethylcellulose, Tween-80]) was 49% ($P < 0.01$), 44.9% ($P < 0.01$), and 64% ($P < 0.001$), respectively. The results showed enhanced anti-proliferative effects on tumor cells in the pomalidomide + DEX group, compared to treatment with pomalidomide alone or DEX alone.

The inhibitory effects of pomalidomide + DEX on tumor proliferation were studied using SCID mice which were inoculated subcutaneously with the MM.1S cell line. Starting from 4 to 6 weeks after inoculation (tumor volume, approximately 209 mm^3), pomalidomide (25 mg/kg) and DEX (1 mg/kg) were administered to mice once daily for 5 days, followed by a 2-day washout period. Although statistical evaluation of the results was not performed, approximately the same level of inhibitory effect on tumor proliferation was observed in the pomalidomide alone group and pomalidomide + DEX group.

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

Based on the submitted data and the following reviews, PMDA concluded that the efficacy of pomalidomide in the treatment of MM is expected.

3.(i).B.(1) Mechanism of action and efficacy of pomalidomide

The applicant explained as follows:

Although it is difficult to determine the mechanism of action of pomalidomide in relation to MM, several factors including immunoregulatory activity [see "3.(i).A.(1).2) Immunoregulatory activity"] are

considered involved, and the binding of pomalidomide and CRBN is implicated in part in the mechanism of action [see "3.(i).A.(1).1) Action on cereblon"].

PMDA asked the applicant to explain why the variation in susceptibility arose as a result of the variation in the inhibitory effects of pomalidomide on MM cell lines or tumor tissues [see "3.(i).A.(1).3) Cell cycle arrest effects and the like" and "3.(i).A.(1).6) Inhibitory effect on the proliferation of malignant tumor cell lines"].

The applicant responded as follows:
Because some patients with MM have high expression levels of elements that regulate endoplasmic reticulum stress (*Oncogene*. 2005;24:6936-44), differences in the intracellular environment, such as those in endoplasmic reticulum stress, may have affected the efficacy of pomalidomide. It is also possible that alteration or decreased expression level of CRBN may have affected the efficacy of pomalidomide, based on the fact that pomalidomide was not observed to have an anti-proliferative effect on cells with altered CRBN (*Nat Struct Mol Biol*. 2014;21:803-9) and that the susceptibility to pomalidomide decreased in cells for which the expression level of CRBN was suppressed [see "3.(i).A.(1).1) Action on cereblon"]. However, at this point of time, the mechanism that caused variation in susceptibility to pomalidomide has not been clearly elucidated.

PMDA considers as follows:
Although pomalidomide was shown to inhibit the proliferation of MM cell lines including those resistant to lenalidomide, the information available so far is not enough to explain the mechanism of its immunoregulatory and other effects at the molecular level. PMDA considers that it is necessary to collect information on the mechanism of action of pomalidomide and appropriately provide the information to healthcare professionals in clinical settings when new findings become available.

In addition, the applicant's explanation has limitations because the differences in susceptibility to pomalidomide were not analyzed in the cell lines or tumor tissues used in the pharmacology studies submitted in the application. Pomalidomide did not inhibit the proliferation of some of the MM cell lines and tumor tissues. The cause of such results may be important in predicting the efficacy and selecting eligible patients in the routine clinical use. Therefore, PMDA considers that it is necessary to collect relevant information and appropriately provide the information to the medical practice when new findings become available.

3.(ii) Summary of pharmacokinetic studies

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

The pharmacokinetics (PK) of pomalidomide in animals was studied in mice, rats, rabbits, and monkeys. A study on plasma protein binding, drug-metabolizing enzymes, and transporters of pomalidomide was performed using human or animal biomaterials.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose studies

A single dose of pomalidomide was administered intravenously (2.5 mg/kg) or orally (100 mg/kg) to male rats to study the plasma concentration of pomalidomide (see the table below). The clearance (CL) was less than one-tenth of rat hepatic blood flow, and the volume of distribution (V_d) was approximately 4 times the rat body fluid volume (*Toxicol Ind Health*. 1997;13:407-84, and *Pharm Res*. 1993;10:1093-5).

A single oral dose of 100 mg/kg of pomalidomide was administered to male monkeys, and following a washout interval, a single dose of 10 mg/kg of pomalidomide was administered intravenously to study the plasma concentration of pomalidomide (see the table below). The CL was less than one-tenth the monkey hepatic blood flow, and V_d was approximately 3 times the monkey body fluid volume (*Pharm Res.* 1993;10:1093-5).

Pharmacokinetic parameters of pomalidomide (male rats and monkeys, single intravenous or oral administration)

Animal species	Route of administration	Dose (mg/kg)	n	C_{max} (ng/mL)	T_{max} (h)	AUC_t (ng·h/mL)	$T_{1/2}$ (h)	CL (mL/h/kg)	V_d (mL/kg)	F (%)
Rat*1	i.v.	2.5	3*2	3185.7	0.083*3	8703.4	6.2	285.5	2564.2	–
	p.o.	100	3*2	4896.7	4.0	45,127.6	5.5	–	–	13.0
Monkey	i.v.	10	4	6930.6	0.333*3	42,083.7	6.7	239.5	2283.3	–
	p.o.	100	4	3714.2	2.0	63,110.4	25.0	–	–	15.0

Arithmetic mean; *1, PK parameters were calculated based on the arithmetic mean of plasma pomalidomide concentrations at each time point because blood samples were drawn from different rats from one time point to another; *2, number of animals for the time point; *3, initial time point; F, oral bioavailability; —, not applicable

3.(ii).A.(1).2) Repeated dose studies

An oral dose of 50, 250, or 1000 mg/kg of pomalidomide was administered to male and female rats once daily (QD) for 6 months to study the plasma concentration of pomalidomide and its enantiomers (R-enantiomer of pomalidomide [R-enantiomer] and S-enantiomer of pomalidomide [S-enantiomer]). The table below shows the results for the PK parameters of pomalidomide. After initial and repeated administrations, C_{max} and AUC_t increased in a less than dose-proportional manner in both male and female rats. The applicant explained that the increased exposure in a less than dose-proportional manner may be attributed to the saturation of the absorption process and decreased solubility of pomalidomide as a result of the increase in the dose administered. Also, C_{max} and AUC_t in female rats tended to be higher than those in male rats. The applicant explained that the variation in exposure between the sexes may have been caused by the difference in cytochrome P450 (CYP) isozymes between sexes in rats (*Mol Pharmacol*. 2009;76:215-28, and *Drug Metab Rev.* 1998;30:441-98). Following repeated administration, accumulation of pomalidomide was observed in females but not in males. The geometric mean ratio of AUC_t (pomalidomide S-enantiomer/ pomalidomide R-enantiomer) on Day 92 in the 50, 250, and 1000 mg/kg groups was 0.47, 0.43, and 0.45 for males, and 0.55, 0.57, and 0.57 for females, respectively.

Pharmacokinetic parameters of pomalidomide (male and female rats, 6-month repeated oral administration)

Time point (Day)	Dose (mg/kg)	C_{max} (ng/mL)		AUC_t (ng·h/mL)		Rc*	
		Male	Female	Male	Female	Male	Female
1	50	1457	2043	21,710	30,260	–	–
	250	2045	2949	30,770	47,440	–	–
	1000	2887	4078	38,490	63,050	–	–
180	50	1566	3377	21,440	40,420	0.99	1.34
	250	2277	4322	31,120	70,170	1.01	1.48
	1000	3813	6776	42,530	98,010	1.10	1.55

PK parameters were calculated based on the arithmetic mean of plasma pomalidomide concentrations at each time point because blood samples were drawn from different rats from one time point to another; n = 3/time point; *, accumulation ratio (AUC_t on Day 180 of treatment divided by AUC_t on Day 1 of treatment); —, not applicable

An oral dose of 0.05, 0.1, or 1.0 mg/kg QD of pomalidomide was administered to male and female monkeys for 9 months to study the plasma concentration of pomalidomide (see the table below). After initial and repeated administrations, dose proportionality was not observed in C_{max} and AUC_t of pomalidomide. The applicant explained that the lack of dose proportionality in pomalidomide exposure may be attributable to the measurement of samples at concentrations around the detection limit (1 ng/mL). No clear difference was observed between the sexes in C_{max} and AUC_t of pomalidomide. In the 1.0 mg/kg group, accumulation of pomalidomide was observed in both males and females following repeated administration. On Day 28, the geometric mean ratios of AUC_t (pomalidomide S-enantiomer/pomalidomide R-enantiomer) following repeated administrations at 0.05, 0.1, and 1.0 mg/kg QD were 0.73, 0.82, and 1.07 for males, and 0.78, 0.76, and 0.89 for females, respectively.

Pharmacokinetic parameters of pomalidomide (male and female monkeys, repeated oral administration)

Measured date (Day)	Dose (mg/kg)	C_{max} (ng/mL)		AUC_t (ng·h/mL)		Rc*1	
		Male	Female	Male	Female	Male	Female
1	0.05	17.77 ± 5.725	25.32 ± 8.275	98.46 ± 30.84	215.1 ± 126.0	–	–
	0.1	31.07 ± 6.902	30.44 ± 5.085	242.4 ± 84.23	173.2 ± 46.60	–	–
	1.0	277.9 ± 46.32*2	224.2 ± 49.34*2	2892 ± 709.3*2	2653 ± 574.9*2	–	–
272	0.05	15.23 ± 3.400	16.94 ± 4.095	132.7 ± 80.59	169.9 ± 88.69	1.34 ± 0.69	0.81 ± 0.11
	0.1	29.64 ± 8.523	26.79 ± 8.077	227.3 ± 130.2	211.4 ± 130.7	0.89 ± 0.28	1.16 ± 0.50
	1.0	554.5 ± 89.77*3	751.8 ± 513.1*4	5640 ± 1840*3	6540 ± 6886*4	2.19 ± 0.51*3	2.12 ± 1.78*4

Arithmetic mean ± standard deviation; n = 6; *1, accumulation ratio (AUC_t on Day 272 of treatment divided by AUC_t on Day 1 of treatment); *2, n = 7; *3, n = 4; *4, n = 3; —, not applicable

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

The permeability of pomalidomide was studied using the Madin-Darby canine kidney (MDCK) cell line. The apparent permeability coefficients in the apical-to-basolateral direction ($P_{app\ A\rightarrow B}$) at concentrations of 1, 5, and 10 µmol/L were 3.68×10^{-6}, 7.12×10^{-6}, and 9.74×10^{-6} cm/sec, respectively. The $P_{app\ A\rightarrow B}$ coefficients of ^{14}C-labelled mannitol and ^{14}C-labelled caffeine, the negative and positive controls (5 µmol/L for both), respectively, were 3.92×10^{-6} and 26.7×10^{-6} cm/sec, respectively.

The applicant explained that pomalidomide is considered to exhibit a moderate level of membrane permeability based on the above findings.

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

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

A single dose of 100 mg/kg of ^{14}C-labelled pomalidomide (^{14}C-pomalidomide) was orally administered to pigmented male rats, and the tissue distribution of radioactivity was determined by quantitative whole-body autoradiography.

The applicant explained as follows:

Radioactivity concentrations peaked 3 hours after administration in the majority of tissues, and decreased to below the lower limit of quantification (0.42 μg eq/g) 12 hours after administration. Based on the results, it is considered unlikely that pomalidomide or its metabolites accumulate in specific tissues. The C_{max} of radioactivity was high in the cecum, bladder, small intestine, stomach, kidney cortex, and kidney medulla (197.58, 28.47, 14.49, 12.49, 5.64, and 5.48 μg eq/g, respectively). Three hours after administration, the radioactivity concentration ratio of the spinal cord to blood was 0.43 and that of the cerebrum to blood, 0.27. Radioactivity was detected in the melanin-containing tissues (pigmented skin and uvea); however, the radioactivity in these tissues decreased to below the lower limit of quantification 12 hours after administration. Therefore, binding of pomalidomide or its metabolites to melanin is considered to be weak.

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

The mouse, rat, rabbit, monkey, and human plasma was incubated with different concentrations of pomalidomide (30, 100, 300, and 1000 ng/mL), and plasma protein binding of S-enantiomers and R-enantiomers was studied by ultrafiltration. The plasma protein binding of S-enantiomers and R-enantiomers was generally consistent in all animal species independent of concentration. The plasma protein binding of S-enantiomers (mean of all concentrations studied) were 40.3, 16.8, 37.8, 55.2, and 42.2%, and those of R-enantiomers (mean of all concentrations studied) were 35.7, 40.2, 31.2, 17.3, and 15.8% in the mouse, rat, rabbit, monkey, and human, respectively. The plasma protein binding in human and monkey were higher for S-enantiomers compared to R-enantiomers. Although the reason for the difference in the plasma protein binding between S- and R-enantiomers is not clear, the pharmacokinetic parameters did not indicate a clear difference between S- and R-enantiomers following a single oral administration (2 mg) of ^{14}C-pomalidomide to healthy adults [see "4.(ii).A.(1).3) Foreign phase I study"]; therefore, the applicant considers that the difference in the plasma protein binding between S- and R-enantiomers is not likely to have any impact on the pharmacokinetics of pomalidomide.

A single oral dose of 10 mg/kg of ^{14}C-pomalidomide or a single intravenous dose of 1 mg/kg of ^{14}C-pomalidomide was administered to male monkeys to study distribution in blood cells. For both oral and intravenous administrations, the blood/plasma radioactivity concentration ratios calculated from data sampled within 10 hours of administration were 0.89 to 1.11. The blood/plasma radioactivity concentration ratios increased to 2.15 at 48 hours following oral administration, and to 1.52 at 24 hours following intravenous administration; however, no radioactivity was observed in blood or plasma 72 hours after administration or later.

The applicant interpreted the findings as suggesting that pomalidomide can distribute into blood cells.

3.(ii).A.(2).3) Distribution in central nervous system

A single dose of pomalidomide (10 or 50 mg/kg) was orally administered to male mice. At 2 hours after administration, the spinal cord/plasma pomalidomide concentration ratio was 0.34 for both the 10 and 50 mg/kg groups, and the brain/plasma pomalidomide concentration ratio was 0.49 and 0.46 for the 10 and 50 mg/kg groups, respectively.

The brain/blood concentration ratio of AUC_t for unbound pomalidomide was 0.39 following a single oral administration of 50 mg/kg to male rats.

The applicant interpreted the findings as suggesting that pomalidomide can distribute into the central nervous system.

3.(ii).A.(2).4) Placental transfer and maternal-fetal transfer

Pomalidomide was orally administered to pregnant rabbits at 5, 10, 100, or 250 mg/kg QD on gestation days 7 to 20, and the pomalidomide plasma concentrations in the dam and fetus were studied. The pomalidomide plasma concentration in the fetus was equivalent to 50 ± 14% of the C_{max} in the dam's plasma at 1.5 to 2 hours after administration on gestation day 20.

The applicant interpreted the findings as suggesting that pomalidomide can cross the placenta.

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

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

Following a 3-hour incubation of 10 μmol/L of pomalidomide with rabbit or human hepatocytes, 85.0% of pomalidomide remained unchanged in the absence of hepatocytes, and 24.0% and 81.4% in the presence of rabbit hepatocytes and human hepatocytes, respectively. The metabolism of pomalidomide was faster in rabbit hepatocytes than in human hepatocytes.

The metabolites of pomalidomide were studied by incubating 0.2 and 10 μmol/L of ^{14}C-pomalidomide with rabbit hepatocytes and human hepatocytes for 2 or 4 hours. In the presence of human hepatocytes, M11 (hydrolysis product), M17 (5-hydroxylated pomalidomide), M12 and M13 (both are glucuronide conjugates of M17) were detected. In the presence of rabbit hepatocytes, two more types of metabolites were detected in addition to the above.

To investigate CYP isozymes that are involved in the formation of the major pomalidomide metabolites in human plasma [see "4.(ii).A.(1).3) Foreign phase I study"], a hydrolysis product of pomalidomide (M11), and hydroxylated pomalidomide (M16 and M17), 1 μmol/L of ^{14}C-pomalidomide was incubated with recombinant human CYP isozymes (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5)

for 1 hour. The applicant explained that the metabolism of pomalidomide primarily involves CYP1A2 and CYP3A4, and partially CYP2C19 and CYP2D6, based on the following findings.

- Metabolite M11 was detected at 2.5% to 5.9% in all CYP isozyme expression incubations and at 5.5% in incubations performed in the absence of CYPs, suggesting that M11 is formed in the reaction which is not mediated by CYP.
- Metabolite M16 was not formed in any of the CYP isozyme expression incubations studied.
- Metabolite M17 was formed in incubations with CYP1A2, 2C19, 2D6, and 3A4, but was not formed in the absence of CYPs. Based on the proportion of each CYP isozyme present in the liver, the relative contributions of CYP1A2, 2C19, 2D6, and 3A4 to the formation of M17 were estimated to be 54%, 11%, 4%, and 30%, respectively.

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

Following a single oral dose of 10 mg/kg of ^{14}C-pomalidomide (n = 3/sex), or a single intravenous dose of 1 mg/kg of ^{14}C-pomalidomide (n = 3, male) to bile duct-cannulated and non-cannulated rats, metabolites in plasma, urine, feces, and bile were studied as follows:

- Major components detected in plasma were unchanged pomalidomide at all time points up to 24 hours after oral administration (unchanged pomalidomide accounted for 81.12% to 95.20%, and 85.81% to 93.94% to the total plasma radioactivity in males and females, respectively). The major metabolites detected in plasma and their percentage to the total plasma radioactivity were as follows: M16 (15.34%), M17 (2.53%), and M13 (1.77%) in male rats; and M16 (4.96%), M13 (3.75%), M17 (2.96%), M12 (2.50%), and M10 (hydrolysis product of pomalidomide) (1.25%) in female rats.
- Following oral administration to non-cannulated rats, the urinary and fecal excretion rates of unchanged pomalidomide up to 48 hours (hereinafter in this section, excretion rates [percentage to the administered radioactivity] are described in the same order) were 1.54% and 82.73% in male rats, and 1.84% and 79.66% in female rats, respectively. Following oral administration to bile duct-cannulated rats, the urinary, fecal, and bile excretion rates of unchanged pomalidomide up to 48 hours were 3.35%, 65.83%, and 0.13% in male rats, and 3.72%, 71.73%, and 0.10% in female rats, respectively. The applicant explained that following oral administration, the majority of the administered radioactivity was detected as unchanged pomalidomide in feces, regardless of whether the bile duct was cannulated or not, indicating that unabsorbed unchanged pomalidomide was excreted in feces. In non-cannulated rats, major metabolites detected in urine (percentage to the administered radioactivity, the same applies hereinafter) were as follows: M16 (3.03% and 0.28% in males and females, respectively; the same applies hereinafter, for the order of male and female results), M17 (1.54% and 1.46%), M11 (0.93% and 1.10%), and M13 (0.39% and 1.43%), and major metabolites detected in feces include M17 (2.98% and 3.29%). In bile duct-cannulated rats, major metabolites detected in urine include: M16 (6.18% and 0.76%), M17 (2.29% and 2.09%), M13 (1.93% and 3.83%), and M11 (1.53% and 2.33%); and major metabolites detected in bile included the following: M16 (3.00% and 0.38%) and M13 (2.73% and 3.87%). In addition, metabolites M17, M11, and M16 were detected in feces at trace levels (≤ 0.20%).

- The major component in plasma was unchanged pomalidomide from 0.25 to 12 hours after intravenous administration (unchanged pomalidomide accounted for 49.10% to 81.94% to the total plasma radioactivity). Metabolite M16 was detected in larger amounts than any other metabolite in plasma at all time points. Following intravenous administration to non-cannulated rats, the urinary and fecal excretion rates of unchanged pomalidomide up to 48 hours (percentage to the administered radioactivity) were 8.65% and 0.39%, respectively. Following intravenous administration to bile duct-cannulated rats, the urinary, fecal, and bile excretion rates of unchanged pomalidomide up to 48 hours were 12.85%, 1.60%, and 0.46%, respectively. Major metabolites detected in urine include (percentage to the administered radioactivity; the same applies hereinafter) M16 (20.14% and 16.20% in non-cannulated rats and bile duct-cannulated rats, respectively; the same applies hereinafter, for the order of the results for non-cannulated rats and bile duct-cannulated rats), M17 (9.52% and 7.45%), M10 (8.06% and 9.91%), M13 (4.03% and 6.69%), and M12 (1.62% and 3.00%). In non-cannulated rats, major metabolites detected in feces include M17 (21.49%), which was detected at trace amounts (1.10%) in bile duct-cannulated rats. Major metabolites detected in bile include M16, M13, and M12, at 11.97%, 8.25%, and 4.12%, respectively.

After administration of a single oral dose of 10 mg/kg of ^{14}C-pomalidomide, or a single intravenous dose of 1 mg/kg of ^{14}C-pomalidomide to male monkeys, metabolites in plasma, urine, and feces were studied.

Following oral administration, major components detected in plasma were unchanged pomalidomide at all time points up to 48 hours (unchanged pomalidomide accounted for 83.46% to 90.49% to the total plasma radioactivity). Major metabolites detected in plasma included the following: M11, M13, M16, M17, and M12, at trace amounts (these metabolites accounted for 5.47%, 3.98%, 3.35%, 3.25%, and 2.33%, respectively, to the total plasma radioactivity at maximum). The excretion rates (percentage to the administered radioactivity) of unchanged pomalidomide in urine and feces up to 48 hours after the administration were 6.08% and 2.80%, respectively, indicating that unchanged pomalidomide was excreted in urine or feces at trace levels. Major metabolites detected in urine include M11, M13, M12, M16, M17, M10, and M2 (16.69%, 13.38%, 10.58%, 6.61%, 5.66%, 2.96%, and 2.74%, respectively, to the total administered radioactivity); major metabolites detected in feces include M17, M11, M2, and M10 (4.04%, 0.50%, 0.41%, and 0.04%, respectively, to the total administered radioactivity). The applicant explained that the first-pass effect of pomalidomide is considered to be very low in monkeys because the metabolic profile of pomalidomide in plasma, urine, and feces for intravenous administration was approximately the same as the metabolic profile for oral administration.

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

3.(ii).A.(4).1) Excretion in urine, feces, and bile

After administration of a single oral dose of 10 mg/kg of ^{14}C-pomalidomide (n = 3/sex), or a single intravenous dose of 1 mg/kg of ^{14}C-pomalidomide (n = 3, male) to bile duct-cannulated and non-

cannulated rats, the excretion rates of radioactivity in urine, feces, and bile (excreted radioactivity/administered radioactivity [%]) were studied.

In non-cannulated rats, the radioactivity excretion rates in urine and feces up to 168 hours after oral administration were 9.12% and 87.71%, respectively, in male rats, and 8.02% and 85.03%, respectively, in female rats; and those after intravenous administration were 57.47% and 30.53%, respectively. In bile duct-cannulated rats, the excretion rates in urine, feces, and bile up to 72 hours after oral administration were 18.29%, 67.12%, and 8.01%, respectively, in male rats, and 17.06%, 73.27%, and 7.44%, respectively, in female rats; and those after intravenous administration were 59.52%, 3.58%, and 26.91%, respectively.

Based on the findings above, the applicant explained that the in the rat, pomalidomide is mainly excreted in feces after oral administration, and in urine after intravenous administration.

After administration of a single oral dose of 10 mg/kg of ^{14}C-pomalidomide, or a single intravenous dose of 1 mg/kg of ^{14}C-pomalidomide to male monkeys, the excretion rates of radioactivity in urine and feces (excreted radioactivity/administered radioactivity [%]) were studied. The radioactivity excretion rates in urine and feces up to 168 hours after oral administration were 72.86% and 13.09%, respectively, and those after intravenous administration were 71.56% and 11.63%, respectively.

Based on the above findings, the applicant explained that the major excretion pathway of pomalidomide in the monkey is considered to be via urine.

The applicant explained that interspecies variation in the major excretion pathway of pomalidomide in oral administration may be attributed to the difference in the absorption of pomalidomide among species when administered orally, which is indicated by the higher excretion rate of unchanged pomalidomide in feces following oral administration in rats compared to that in monkeys [see "3.(ii).A.(3).2) *In vivo* metabolism"].

3.(ii).A.(4).2) Excretion in breast milk

Following single oral dose administration of 10 mg/kg of pomalidomide to lactating female rats (approximately 14 days postpartum), breast milk/plasma concentration ratios 1 to 24 hours after the administration were 0.63 to 1.5.

The applicant explained that the results suggest that pomalidomide is excreted into breast milk.

3.(ii).A.(5) Pharmacokinetic interaction

3.(ii).A.(5).1) Inhibition of enzymes

In the presence of pomalidomide at 0.1 to 30 μmol/L, substrates for CYP isozymes (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5) were incubated with human hepatic microsome. The results

showed that at the maximum concentration studied, pomalidomide did not show a clear inhibitory effect on substrate metabolism of any CYP isozymes. In addition, pomalidomide showed no time-dependent inhibitory effects on CYP1A2, 2C9, 2C19, 2D6, or 3A4/5.

Based on the above, the applicant explained that pomalidomide is unlikely to induce pharmacokinetic interactions by inhibiting CYPs in clinical use.

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

Human hepatocytes were treated with pomalidomide (0.3, 1, and 3 μmol/L) for 3 days, and CYP enzyme activity (1A2, 2B6, 2C9, 2C19, and 3A4/5) was studied. The results showed that for any CYP isozymes studied, increase in enzyme activity induced by treatment with pomalidomide was ≤1.3-fold the vehicle control.

The applicant explained as follows:

Given that the C_{max} of pomalidomide was approximately 50 ng/mL (approximately 0.2 μmol/L) following multiple oral administration of 5 mg of pomalidomide to patients with MM [see "4.(ii).A.(2).1) Foreign phase I study"], pomalidomide is unlikely to cause pharmacokinetic interactions by inducing CYP isozymes in clinical use.

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

According to the explanation of the applicant, the following studies suggested that pomalidomide is a substrate of P-glycoprotein (P-gp).

- The P-gp-mediated transport of pomalidomide (5 μmol/L) was studied using a MDCK cell line expressing human P-gp (P-gp-expressing MDCK cell line). The efflux ratio of pomalidomide was 13.0 in the absence of P-gp inhibitors, but was reduced to 1.72 and 1.37 in the presence of P-gp inhibitors verapamil (250 μmol/L) and ketoconazole (25 μmol/L), respectively.
- The transport of pomalidomide (0.25 and 2.5 μmol/L) mediated by human organic anion-transporting polypeptides (OATP) 1B1 and 1B3 was studied using a human embryonic kidney cell line 293 (HEK293) expressing OATP1B1 or 1B3. The results showed that the cellular uptake of pomalidomide in either study was similar to that with the HEK293 cell line transfected with a control vector.

The applicant also explained that pomalidomide is unlikely to induce pharmacodynamic interaction by inhibiting P-gp, breast cancer-resistant protein (BCRP), organic anion transporters (OAT) 1 and 3, organic cation transporter (OCT) 2, and OATP1B1 and 1B3 in its clinical use, as indicated by the fact that the C_{max} was approximately 50 ng/mL (approximately 0.2 μmol/L) in MM patients receiving repeated 5-mg oral doses of pomalidomide [see "4.(ii).A.(2).1) Foreign phase I study"] in addition to the following study results.

- The inhibitory effect of pomalidomide (0.03-10 μmol/L) on P-gp-mediated transport of ^{3}H-labeled digoxin (^{3}H-digoxin) (100 nmol/L) was studied using the P-gp-expressing MDCK cell line. The results showed no concentration-dependent inhibition within the range of concentrations studied. The inhibitory effect of pomalidomide (0.1-30 μmol/L) on P-gp-mediated transport of ^{3}H-digoxin (10 μmol/L) was studied using a human colonic carcinoma Caco-2 cell line intrinsically expressing P-gp. The results showed no concentration-dependent inhibition within the range of concentrations studied.
- The inhibitory effect of pomalidomide (2 and 20 μmol/L) on transporter-mediated transport of the following substrates was studied using a porcine kidney LLC-PK1 cell line expressing human BCRP, a mouse kidney S2 cell line expressing human OCT2, and a HEK293 cell line expressing human OATP1B1 and 1B3: ^{3}H-labeled prazosin (10 nmol/L) for BCRP; ^{14}C-labeled metformin (10 μmol/L) for OCT2; and ^{3}H-labeled estradiol glucuronide (50 nmol/L) for OATP1B1 and 1B3. The results showed no obvious inhibition of BCRP, OCT2, or OATP1B1/1B3 at the highest concentration studied.
- The inhibitory effect of pomalidomide (2 and 20 μmol/L) on OAT1-/OAT3-mediated transport of the respective substrates, ^{3}H-labeled p-aminohippuric acid (^{3}H-p-aminohippuric acid, 1 μmol/L) and ^{3}H-labeled estrone sulfate (^{3}H-estrone sulfate, 50 nmol/L), was studied in an S2 cell line expressing OAT1/3. The results showed that no obvious inhibition of OAT1/3 was observed in the presence of 2 μmol/L of pomalidomide, but cellular uptake of ^{3}H-p-aminohippuric acid and ^{3}H-estrone sulfate was reduced by 25.9% and 30.2%, respectively, in the presence of 20 μmol/L of pomalidomide, as compared to in the absence of pomalidomide.

3.(ii).A.(6) Pharmacokinetics of enantiomers

3.(ii).A.(6).1) *In vitro*

The stability and isomerization of pomalidomide enantiomers were studied by incubating the R- and S-enantiomers (both at 200 ng/mL) in phosphate buffer, monkey plasma, or human plasma for 0.5 to 24 hours. The results showed that both R- and S-enantiomers degraded slowly in phosphate buffer ($t_{1/2}$, 24 hours), but their degradation was faster in monkey and human plasmas ($t_{1/2}$, approximately 3-4 hours) than in phosphate buffer.

3.(ii).A.(6).2) *In vivo*

A single dose of 0.5 mg/kg of R-enantiomer or 0.5 mg/kg of S-enantiomer was intravenously administered to male monkeys, and following a washout period of approximately 2 weeks, a single dose of 1 mg/kg of R-enantiomer or 1 mg/kg of S-enantiomer was orally administered. The results for the plasma concentrations of R- and S-enantiomers (the table below) showed that the conversion rates from S-enantiomer to R-enantiomer (AUC_{inf} for R-enantiomer/sum of AUC_{inf} for S- and R-enantiomers [%]) following the oral or intravenous administration of S-enantiomer were 26% and 32%, respectively; on the other hand, the conversion rates from R-enantiomer to S-enantiomer (AUC_{inf} for S-enantiomer/sum of AUC_{inf} for S- and R-enantiomers [%]) following the oral or intravenous administration of R-enantiomer were 18% for both.

Pharmacokinetic (PK) parameters of R-and S-enantiomers (male monkeys, single intravenous or oral administration)

Administration route	Compound administered	n	Substance measured	C_{max}*1 (ng/mL)	T_{max}*2 (h)	AUC_{inf} (ng·h/mL)	$T_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)	F (%)
I.V.	S-enantiomer	3	S-enantiomer	698 ± 13.6	–	1230 ± 390	4.1 ± 1.4	457 ± 147	1,140 ± 116	–
			R-enantiomer	25.4 ± 4.65	–	576 ± 200	3.8 ± 1.3	–	–	–
	R-enantiomer	3	S-enantiomer	15.3 ± 4.17	–	553 ± 162	3.3 ± 0.7	–	–	–
			R-enantiomer	703 ± 124	–	2470 ± 382	3.8 ± 0.4	203 ± 33.1	769 ± 57.6	–
Oral	S-enantiomer	3	S-enantiomer	910 ± 191	1.0 (0.5, 2.0)	3000 ± 406	3.5 ± 1.3	–	–	130
			R-enantiomer	132 ± 33.2	3.0 (2.0, 3.0)	1030 ± 501	4.1 ± 0.6	–	–	–
	R-enantiomer	3	S-enantiomer	97.9 ± 20.2	3.0 (2.0, 3.0)	898 ± 293	4.4 ± 0.8	–	–	111
			R-enantiomer	780 ± 47.1	2.0 (2.0, 3.0)	4120 ± 1020	3.9 ± 0.7	–	–	–

Arithmetic mean ± standard deviation except for *2; *1, when administered intravenously, plasma concentration 5 minutes after administration; *2, median (minimum, maximum); "—", not applicable

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

Based on the submitted data, PMDA concluded that the explanations provided by the applicant on the absorption, distribution, metabolism, excretion, pharmacokinetic interactions, and pharmacokinetics of enantiomers of pomalidomide are acceptable.

3.(iii) Summary of toxicology studies

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

In *in vivo* studies, pomalidomide was administered as a suspension in 1% aqueous carboxymethylcellulose solution (CMC) unless the vehicle is otherwise specified.

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

3.(iii).A.(1).1) Single oral dose or intravenous dose toxicity studies in mice

Following a single oral administration of 2000 mg/kg of pomalidomide to CD-1 mice (n = 5/sex), no deaths or findings related to the administration of pomalidomide were observed. Based on the results, the approximate lethal dose for oral administration was determined to be >2000 mg/kg.

Following a single intravenous administration of 80 mg/kg (vehicle, 20% intralipid solution of 20v/v% polyethylene glycol [PEG] 400) to CD-1 mice (n = 5/sex), no deaths were observed. While hyperpnea, lethargy, soiled urinary organ or genital organ, and hunchback position were observed, these resolved on the day of administration. Based on the results, the approximate lethal dose for intravenous administration was determined to be >80 mg/kg.

3.(iii).A.(1).2) Single oral dose or intravenous dose toxicity studies in rats

Following a single oral administration of 2000 mg/kg of pomalidomide to CDBR rats (n = 5/sex), no deaths or findings related to the administration of pomalidomide were observed. Based on the results, the approximate lethal dose for oral administration was determined to be >2000 mg/kg.

In a dose-finding study, following intravenous administration of a single dose of 0 (vehicle control), 10, 25, 50, or 80 mg/kg of pomalidomide (vehicle, 20% intralipid solution of 20v/v% PEG400) to CDBR rats (n = 1-2/sex/group), 3 of 4 animals died in the 80 mg/kg group, based on which the maximum tolerated dose was determined to be 50 mg/kg.

Following a single intravenous administration of 50 mg/kg of pomalidomide to CDBR rats (n = 5/sex/group), no deaths were observed. While decreased physical activity and respiration abnormalities were observed, these had resolved by 4 days post-dose. Based on the results, the approximate lethal dose for intravenous administration was determined to be >50 mg/kg.

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

3.(iii).A.(2).1) Thirteen-week repeated oral dose toxicity study in mice

CD-1 mice (n = 15/sex/group) were orally given 0 (vehicle control), 2.5, 25, or 250 mg/kg/day of pomalidomide for 13 weeks.

Although 1 of the 30 animals died in the 25 mg/kg/day group, no findings related to the administration of pomalidomide were observed; therefore, the death was determined to be unrelated to pomalidomide administration.

Urine discoloration, which was observed in the ≥25 mg/kg/day groups, was considered to be caused by excretion of the test substance or its metabolites in urine, and not determined as a toxicity finding.

Based on the above results, the no observed adverse effect level (NOAEL) for the study was determined to be 250 mg/kg/day.

3.(iii).A.(2).2) Twenty eight-day repeated oral dose toxicity study in rats

CDBR rats (n = 10/sex/group) were orally given 0 (vehicle control), 300, 800, or 2000 mg/kg/day of pomalidomide for 28 days.

No deaths or toxicity findings related to administration of pomalidomide were observed during the study period.

Based on the above results, the NOAEL for the study was determined to be 2000 mg/kg/day.

3.(iii).A.(2).3) Ninety-day repeated oral dose toxicity studies in rats

CDBR rats (n = 10/sex/group) were orally given 0 (vehicle control), 100, 500, or 1500 mg/kg/day of pomalidomide for 90 days.

No deaths were observed except for 3 deaths that were considered to be caused by administration error.

Body weight was decreased by approximately 8% to 9% in male rats in the 1500 mg/kg/day group, compared with the control group. The changes were slight decreases, therefore, this was not considered to be toxicologically significant.

Based on the above results, the NOAEL for the study was determined to be 1500 mg/kg/day.

3.(iii).A.(2).4) Six-month repeated oral dose toxicity study with one-month recovery period in rats

SD rats (n = 20/sex/group) were orally given 0 (vehicle control), 50, 250, or 1000 mg/kg/day of pomalidomide for 6 months. Five males and 5 females in each group underwent a 28-day recovery period to study the reversibility of toxicity.

Deaths or sacrificed moribund occurred in 2 of 40, 2 of 40, and 4 of 40 animals in the 50, 250, and 1000 mg/kg/day groups, respectively; however, none of them were considered to be related to the administration of pomalidomide.

Yellow digestion product or feces were observed in the small and large intestines in the ≥250 mg/kg/day groups; however, these findings were not considered toxicologically significant because no such findings were observed after the 28-day recovery period, and because the color of the test substance was yellow.

Based on the above results, the NOAEL for the study was determined to be 1000 mg/kg/day.

3.(iii).A.(2).5) The maximum tolerated dose (MTD) study in monkeys (Reference data, GLP study)

Cynomolgus monkeys (n = 2/sex) were given pomalidomide in the dose-escalating manner as follows: 100 mg/kg/day for 4 days, 300 mg/kg/day for 3 days, 600 mg/kg/day for 4 days, and 1200 mg/kg/day for 3 days. After administration, no clear toxicological findings were observed.

Based on the above results, the approximate lethal dose of pomalidomide was determined to be >1200 mg/kg.

With these results taken into consideration, cynomolgus monkeys were orally given 0 (vehicle control) or 50 mg/kg/day of pomalidomide for 7 days, or 300 or 1200 mg/kg/day for 14 days. After

administration, yellow discoloration of feces and urine, increased spleen weight, and enlarged spleen were observed in all pomalidomide treatment groups. In the ≥300 mg/kg/day groups, weight loss, decreases in red blood cell (RBC) count, hemoglobin (Hb), hematocrit (HCT), and white blood cell (WBC) count were observed in a dose-dependent manner. Decreased WBC count tended to be reversible in the 300 mg/kg/day group, but not in the 1200 mg/kg/day group.

Based on the above results, the MTD for the study was determined to be 300 mg/kg/day.

3.(iii).A.(2).6) Twenty eight-day repeated oral dose toxicity studies in monkeys

Cynomolgus monkeys (n = 3/sex/group) were given 0 (vehicle control), 30, 100, or 300 mg/kg/day of pomalidomide. The treatment duration was originally scheduled to be 28 days; however, from Day 15 to Day 18, deaths or sacrificed moribund due to the poor clinical conditions occurred in 6 of 18 animals (1 of 6, 2 of 6, and 3 of 6 animals in the 30, 100, and 300 mg/kg/day groups, respectively), administration was discontinued on Day 18, and necropsies and histopathological examinations were performed. Because of the discontinuation at an early stage, no ophthalmological examinations, ECG, or urinalysis was performed.

In all treatment groups, soft or watery feces, urine yellow discoloration, hunchback position, piloerection, sedation, tremor, facial swelling, limb swelling, gingival bleeding, enophthalmos, decreased food consumption, reduced body weight gain, and weight loss were observed. The findings from the hematological examinations included decreases in RBC count, Hb, HCT, and WBC count. The findings from blood biochemical examinations included increases in lactate dehydrogenase activity, glucose, urea, creatinine, and triglyceride, decreases in albumin and total protein. The findings from necropsies and histopathological examinations included increases in liver weight and spleen weight, thymic atrophy, atrophy of bone marrow, altered hematopoietic functions in the bone marrow, marrow hyperplasia, lymphocyte atrophy in the lymph nodes, spleen, thymus, and lymphoid tissues of ileum. Other secondary alterations included acinar cell degranulation in the pancreas related to malnutrition, hypertrophy of the adrenal cortex related to stress caused by poor clinical conditions, dermatitis and folliculitis caused by bacterial flora related to immunosuppression.

Based on the above results, the NOAEL for the study (for an 18-day treatment duration) was determined to be <30 mg/kg/day.

With these results taken into consideration, a 28-day repeated oral dose toxicity study with reduced doses was conducted.

Cynomolgus monkeys (n = 3/sex/group) were orally given 0 (vehicle control), 0.2, or 2 mg/kg/day of pomalidomide for 28 days.

On Day 26, 1 of 6 animals in the 2 mg/kg/day group was sacrificed moribund due to poor clinical conditions. A decrease in WBC count, and facial swelling accompanied by ulcers and necrosis inside of the upper lip were observed in this animal.

Among the surviving animals, soft or watery feces, and on Day 14 or later, decreased WBC count were observed in the 2 mg/kg/day group; decreased WBC count tended to resolve on Day 21 or later.

Based on the above results, the NOAEL for the study was determined to be 0.2 mg/kg/day.

3.(iii).A.(2).7) Thirteen-week repeated oral dose toxicity study in monkeys

Cynomolgus monkeys (n = 5/sex/group in the 0 and 10 mg/kg/day groups; and n = 3/sex/group in the 0.05, 0.2, and 2 mg/kg/day groups) were orally given 0 (vehicle control), 0.05, 0.2, 2, or 10 mg/kg/day of pomalidomide. The treatment duration was originally scheduled to be 13 weeks; however, pomalidomide administration was discontinued in the 10 mg/kg/day group at Week 5 because of poor clinical condition observed. Pomalidomide was continuously administered to the remaining groups for 13 weeks. In the 10 mg/kg/day group, 3 males and 3 females were sacrificed moribund at Week 6, and the remaining 2 males and 2 females at Week 13.

In the 2 mg/kg/day group the following were observed: watery feces, low albumin, increases in band neutrophils, decreases in B lymphocytes (CD20 positive), NK cells (CD3 negative, CD16 positive), and monocyte count, thymic atrophy, increased bone marrow cellularity, immature myeloid cells, decreased megakaryocytes, lymphoid depletion or lymphoid hyperplasia in the spleen, and localized lymphoid depletion in the thymus. In the 10 mg/kg/day group, at Week 5 or 6, the following were observed: weight loss, watery feces, increased fibrinogen level which was determined to be a secondary effect of an inflammatory reaction, decreases in albumin and total protein, appearance of band neutrophils, an increase or decrease in neutrophils, appearance of Döhle bodies in neutrophils, decreases in B lymphocytes (CD20 positive), NK cells (CD3 negative, CD16 positive), and monocyte count, decreases in total T lymphocyte count (CD3 positive), helper T lymphocytes (CD3 positive, CD4 positive), cytotoxic T lymphocytes, and suppressor T lymphocytes (CD3 positive, CD8 positive), decreases in RBC count, Hb, and HCT, increased reticulocytes, decreased glucose levels, increased alkaline phosphatase (ALP), thymic atrophy, lymphoid depletion in the thymus, increased bone marrow cellularity, immature myeloid cells, decreased megakaryocytes, and lymphoid depletion or lymphoid hyperplasia in the spleen. Except for lymphoid hyperplasia in the spleen, all the above findings had either resolved or tended to resolve by the end of the recovery period at Week 13 of the study.

Based on the above results, the NOAEL for the study was determined to be 0.2 mg/kg/day.

3.(iii).A.(2).8) Nine-month repeated oral dose toxicity study with 8-week recovery period in monkeys

Cynomolgus monkeys (n = 6/sex/group) were orally given 0 (vehicle control), 0.05, 0.1, or 1 mg/kg/day of pomalidomide for 39 weeks. Two males and 2 females in each group underwent an 8-week recovery period to study the reversibility of toxicity.

In the 1 mg/kg/day group, 1 animal died prematurely on Day 40 and 1 was sacrificed moribund on Day 44. In the animal that died (n = 1), vomiting and pulmonary edema, conditions unrelated to pomalidomide administration, were observed; and in the sacrificed animal (n = 1), staphylococcal infection in the spine, which was associated with pomalidomide administration, was observed. Following the addition of 1 male and 1 female to the 1 mg/kg/day group, pomalidomide-related poor clinical condition was observed in 6 animals, and thus, the animals were sacrificed moribund on Days 139 to 253. The poor clinical conditions in the animals which were sacrificed moribund was determined to be related to immunomodulatory and immunosuppressive activities of pomalidomide (i.e., decreased peripheral lymphocytes, lymphoid depletion in the lymphoid organs, and decreased bone marrow cellularity), and secondary alterations observed included staphylococcal infection, chronic inflammation of the colon, and villus atrophy in the small intestine. Further, 1 female monkey exhibited acute myelogenous leukaemia (AML) -like symptoms (abnormal increase in the WBC count, infiltration of multiple organs, and infiltration of myeloblasts), which were determined to be related to immunosuppressive activity of pomalidomide for the following reasons:

- The genotoxicity studies of pomalidomide did not indicate genotoxicity;
- Immunosuppression is reported to be a critical factor in the onset of AML in human (*Leukemia.* 2012;26:422-3), and immunosuppression activities are observed in pomalidomide.

Although lymphoid depletion in the spleen was observed in the 0.05 and 0.1 mg/kg/day groups, it was not determined to be a toxicological finding for the following reasons: frequency of occurrence was low (2 of 8 animals in the 0.05 mg/kg/day group, 1 of 8 animals in the 0.1 mg/kg/day group); the degree of lymphoid depletion was slight to mild; and the animals did not exhibit pathological findings in the whole body, such as decreased peripheral lymphocytes or bacterial infections.

Major toxicological findings observed in the surviving animals in the 1 mg/kg/day group include: watery feces, decreased food consumption, increases in ALP and γ-glutamyltransferase, decreases in peripheral lymphocytes, bone marrow lymphocytes, lymphocytes in the lymphoid tissues, and lymphocytes in the gut-associated lymphatic tissue (GALT), thymic atrophy, lymphoid depletion in the mandibular lymph nodes, mesenteric lymph nodes, Peyer's patch, thymus, and the spleen, chronic diffuse inflammation in the colon, and bile duct proliferation of the liver. After the completion of the 8-week recovery period, all the findings except for bile duct proliferation of the liver showed signs of recovery.

Based on the above results, the NOAEL for the study was determined to be 0.1 mg/kg/day. The $AUC_{0\text{-}24h}$ (211-227 ng·h/mL) in the 0.1 mg/kg/day group was approximately 0.3-fold the clinical exposure level.*

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

As genotoxicity studies, a bacterial reverse mutation assay, a chromosomal aberration assay in human peripheral lymphocytes, and micronucleus assay in rat bone marrow were performed. As a result of all the studies, pomalidomide was determined to be non-genotoxic. In the first experiment in the mouse lymphoma TK assay, a mild increase in the mutation frequency was observed only at a concentration of 150 μg/mL in the presence of S9 mix. However, no statistically significant increases in mutation frequency were observed at 300 and 600 μg/mL in the first experiment, and there were no statistically significant increases in mutation frequency at any concentration in the second experiment (18.75-600 μg/mL); therefore, pomalidomide was found to be non-mutagenic in this assay.

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

No carcinogenicity study has been performed because pomalidomide is an antineoplastic drug intended for the treatment of patients with advanced cancer.

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

No study of effects on pre- and postnatal development, including maternal function has been conducted because pomalidomide is an antineoplastic drug intended for the treatment of patients with advanced cancer.

3.(iii).A.(5).1) Study of fertility and early embryonic development

To investigate the effects of pomalidomide on male and female fertility, SD rats (n = 25/sex/group) were orally given 0 (vehicle control), 25, 250, or 1000 mg/kg/day of pomalidomide in the following manner: from 14 days prior to mating to gestation day 7 in females; and from 28 days prior to mating to after mating for 100 days in males. Males that had received pomalidomide and non-treated females (n = 25/group) were also mated to investigate the effects on male fertility.

When treated females and treated males were mated, in the pregnancy following the first mating, a decrease in the number of viable embryos, and increases in resorption of embryos and postimplantation loss were observed in the ≥25 mg/kg/day groups. In maternal animals, low body weight during pregnancy was noted; however, this was attributable to the small number of viable embryos, and thus was not considered to be a finding suggesting a toxic effect on maternal animals.

Based on the above results, the NOAEL in terms of fertility in this study was determined to be <25 mg/kg/day. When treated male rats and non-treated female rats were mated, no effects on fertility

* The mean AUC_{24h} on Day 10 of administration was 713.8 ng·h/mL following multiple oral administration of 4 mg of pomalidomide to patients with MM in the Japanese phase I study (Study CC-4047-MM-004).

were observed. Accordingly, it was determined that effects on the fertility observed in the study are not attributable to pomalidomide administered to male rats.

3.(iii).A.(5).2) Rat embryo-fetal development study

Pregnant SD rats (n = 22/group) were orally given 0 (vehicle control), 25, 250, or 1000 mg/kg/day of pomalidomide from gestation day 6 to gestation day 17.

Effects on maternal animals include low body weight and reduced body weight gain in late pregnancy in the ≥25 mg/kg/day groups. However, when body weight gain during the period from gestation day 0 to gestation day 20 was adjusted by subtracting the gravid uterus weight, the adjusted body weight gain was not significantly different from that in the control group; therefore, it was determined to be attributable to the increase in postimplantation loss.

Effects on embryo-fetal development in the ≥25 mg/kg/day groups included increases in postimplantation loss and resorption of embryos, decreases in the number of viable fetuses and number of pups per litter, decreased fetal weight, visceral abnormality in fetuses (lack of bladder and lack of thyroid gland), and skeletal abnormalities (fused, or abnormal arrangement of lumbar vertebrae and thoracic vertebrae), internal organ variations (vacuolation of the kidney, underdeveloped papilla renalis, and ureteral dilatation), and ossification variations (shortened ribs, unossified sternebra). Effects found in the ≥250 mg/kg/day groups included lack of the 13th rib; and in the 1000 mg/kg/day group, increased frequency of the occurrence of brachiocephalic artery agenesis.

Based on the above results, the NOAELs in terms of general toxicity in maternal animals and embryo-fetal development in this study were determined to be <1000 mg/kg/day and <25 mg/kg/day, respectively.

3.(iii).A.(5).3) Rabbit embryo-fetal development study

Pregnant NZW rabbits (n = 20/group) were orally given 0 (vehicle control), 10, 100, or 250 mg/kg/day of pomalidomide from gestation days 7 to 19. NZW rabbits (n = 5) in the positive control group were orally given 180 mg/kg/day of thalidomide.

Effects on maternal animals included reduced body weight gain, decreases in triglyceride levels and spleen weight in the ≥100 mg/kg/day groups; and decreases in RBC count, Hb, and HCT, and increases in calcium and inorganic phosphorus in the 250 mg/kg/day group.

Effects on embryo-fetal development in the ≥10 mg/kg/day groups included an increasing trend in the frequent occurrence of dysplasia of the heart (significantly increased in the 250 mg/kg/day group); effects in the ≥100 mg/kg/day groups included increased postimplantation loss, decreased fetal weight, and rotating limbs and shortened tail in 1 fetus; effects in the 250 mg/kg/day group included abnormalities in the fetal limbs (rotation or bending of the forelimbs or hind limbs, missing fingers, and

unconnected fingers) and associated skeletal abnormalities (unossified metacarpals, abnormal arrangement of phalanges and metacarpals, missing fingers and unossified phalanges, shortened, unossified, or bent cervical spine), moderate dilatation of the lateral cerebral ventricles, abnormal position of the right subclavian artery, missing middle lobe of the lung, kidney at lower position, abnormal liver morphology, retarded ossification of or unossified pelvis, supernumerary rib, and reduced ossification of the tarsal bone. These effects on fetuses were considered to be very similar to the findings observed in the thalidomide treatment group (rotation or bending of the forelimbs or hind limbs, missing fingers, and unconnected fingers).

Based on the above results, the NOAELs for maternal animals and embryo-fetal development in this study were determined to be 10 mg/kg/day, and <10 mg/kg/day, respectively. The AUC_{24h} at 10 mg/kg/day on gestation day 19 (418 ng·h/mL) was approximately 0.6-fold the clinical exposure level.*

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

3.(iii).A.(6).1) Twenty-eight day repeated oral administration immunotoxicity study with 30-day recovery period in monkeys

Cynomolgus monkeys (n = 6/sex/group) were orally given 0 (vehicle control), or 2 mg/kg/day of pomalidomide for 28 days, and 2 males and 2 females of each group underwent a 30-day recovery period to study the reversibility of toxicity. The following parameters were also examined: NK cell activity, functions of granulocytes and monocytes and keyhole limpet hemocyanin (KLH)-specific IgM and IgG production after administration of KLH on Day 12.

One of 12 animals in the 2 mg/kg/day group was sacrificed moribund on Day 22 after exhibiting decreased food consumption, watery feces, and weight loss. In this sacrificed animal, decreases in the number and functions of CD3 negative/CD16 positive NK cells, and an increase in the number of CD3 negative/CD14 positive monocytes were observed, and the poor clinical conditions of the animal were possibly related to the immunological effects of pomalidomide administration. In addition, lymphoid depletion was observed in the germinal center, cortex, medulla, and paracortex of the lymphoid tissues, and decreases in associated peripheral blood lymphocytes and thymic atrophy were observed.

Immunotoxicity findings related to the administration of pomalidomide observed in the animals which survived until the end of the treatment period included primary and secondary humoral immune responses (decreased KLH-specific IgM and IgG production following the administration of KLH), decreases in peripheral blood lymphocytes (CD20 positive B lymphocytes, CD3 positive T lymphocytes, CD3 positive/CD4 positive helper T lymphocytes, CD3 positive/CD8 positive cytotoxic T lymphocytes, CD3 negative/CD16 positive NK cells and CD3 negative/CD14 positive monocytes), decreased

* The mean AUC_{24h} on Day 10 of administration was 713.8 ng·h/mL following multiple oral administration of 4 mg of pomalidomide to patients with MM in the Japanese phase I study (Study CC-4047-MM-004).

cellularity of bone marrow lymphocytes, decreased thymus weight, increased spleen weight, thymic atrophy, lymphoid depletion in the spleen, lympholysis, increased red pulp cells, lymphoid depletion in the mandibular lymph nodes and mesenteric lymph nodes, and swelling in the paracortical area. However, no findings related to the administration of pomalidomide were observed for granulocytes, monocytes, and NK cell functions.

Other findings related to pomalidomide administration include: watery feces, gastric ulcer, and mucosa hemorrhage.

In the recovery group, the decreased CD20 positive B lymphocytes partially resolved, and other findings resolved except for the reduction in thymus weight, swelling of the paracortex of the mandibular lymph node, and lymphoid depletion in the germinal center of the mesenteric lymph nodes.

Based on the above results, it was determined that administration of 2 mg/kg/day of pomalidomide does not affect the natural immune system (functions of granulocytes, monocytes, and NK cells), but does affect the adaptive immune system (T-cell dependent immune response and decreased lymphocytes).

3.(iii).A.(6).2) Phototoxicity

The results of the initial phototoxicity evaluation of pomalidomide indicated that the molar absorption coefficient at absorption peak (λ = 392 nm) was 5462, which exceeded the standard of 1000. However, no cytotoxic photoreaction product was formed in the photostability study. The risk of pomalidomide administration causing phototoxic responses was considered to be low based on the following observations: after administration, pomalidomide was locally observed in the tissues including skin and eyes, however, the concentrations were below the detection limit after 12 hours; and half-lives in the tissues were 0.5 to 8.0 hours [see "3.(ii).A.(2).1) Tissue distribution"]. In addition, no phototoxicity-related events following pomalidomide administration were reported in the safety data and post-marketing surveillance data (n = 1577) compiled in the safety database of Celgene Corporation in the US (data cutoff on [redacted], 20[redacted]).

Based on the above, the phototoxicity risks of pomalidomide were considered to be low, and therefore, a phototoxicity study was not considered to be necessary.

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

Like thalidomide, pomalidomide has teratogenic potential, and it has been suggested that there is a risk of teratogenicity even at the exposure seen at the proposed clinical dosage. Therefore PMDA considers that utmost caution must be exercised in its clinical use. Otherwise, except for teratogenicity, PMDA concluded, based on the submitted data and the following reviews, that the assessment of non-clinical toxicity has not identified any specific problems associated with the clinical use of pomalidomide.

3.(iii).B.(1) Species differences in the toxicity profile of pomalidomide observed in toxicity studies

PMDA asked the applicant to explain the possible causes for the marked species differences in the general toxicity of pomalidomide observed in repeated oral dose toxicity studies in rodents (mice and rats) and monkeys.

The applicant responded as follows:

The species differences in the amino acid sequence of CRBN, the molecular target of pomalidomide, is attributable to the species variation in the activities of thalidomide analogues, including pomalidomide (*Nat Struct Mol Biol.* 2014;21:803-9). In particular, ^{380}His (histidine)* and ^{382}Trp (tryptophan)* are essential for binding of the thalidomide analog-binding domain of CRBN to the glutarimide ring of thalidomide analogues (*Nature.* 2014;512:49-53). The amino acid immediately preceding ^{380}His is valine in mice and rats, while such amino acid is glutamate in humans, monkeys, and rabbits. When measured in terms of antiproliferative effects and the degradation of Ikaros family zinc finger proteins 1 and 3 (IKZF1/3), mouse CRBN was shown to be unresponsive to pomalidomide because of this difference in the amino acid residue (*Nat Struct Mol Biol.* 2014;21:803-9). Given the impact of these effects on the important pharmacological action of pomalidomide, the response of CRBN to this agent is considered to be entirely different between humans and mice.

From the above discussion, the differences in the toxicity profile between mice/rats and monkeys observed in repeated oral dose toxicity studies are considered to be mainly attributable to species differences in CRBN, the molecular target of pomalidomide. Because of these species differences found in CRBN, it is considered difficult to extrapolate the results of the toxicity studies in mice and rats to humans. However, the toxicity of pomalidomide is considered to be reasonably assessable from the results of the repeated oral dose toxicity studies in monkeys and the reproductive and developmental toxicity study in rabbits.

PMDA accepted the applicant's explanation.

3.(iii).B.(2) AML-like symptoms in monkeys

PMDA asked the applicant to explain the cause of AML-like symptoms observed in the 9-month repeated oral dose toxicity study in monkeys and the risk of carcinogenesis, including AML, in clinical practice.

The applicant responded as follows:

Pomalidomide induces either immunosuppression mediated by cytokine production or enhancement of NK cell-mediated immunity. It has been reported that pomalidomide-induced immunosuppression

* Residue numbers differ between species; these numbers are based on the amino acid sequence of chicken CRBN.

mediated by cytokine production is related to cancer-inducing changes in the microenvironment around tumor cells, and is actually an important factor in the pathogenesis of AML in human (*Leukemia.* 2012;26:422-3). Therefore, the development of AML-like symptoms in cynomolgus monkeys is considered to be attributable to pomalidomide-induced immunosuppression.

In addition, the risk of carcinogenesis, including AML, cannot be ruled out when pomalidomide is used in clinical settings for the following reasons:

- The mean AUC_{24h} (6540 ng·h/mL) in female monkeys in the 1.0 mg/kg/day group, in which 1 animal had exhibited AML-like symptoms on Day 272, was approximately 9.2-fold the clinical exposure level.* The AUC_{24h} at 0.1 mg/kg/day, the NOAEL of AML-like symptoms, on Day 272 (211 ng·h/mL and 227 ng·h/mL in females and males, respectively) was approximately 0.3-fold the clinical exposure level.*
- Immunosuppression, which is considered to have induced AML-like symptoms in monkeys, is the main pharmacological action of pomalidomide.
- Malignant tumors, such as basal cell carcinoma, have been reported in the clinical studies of pomalidomide.

PMDA accepted the applicant's response. The risk of second primary malignancy in the clinical use of pomalidomide will be further discussed in "4.(iii).D.(3).12).(c) Second primary malignancy."

4. Clinical data

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

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

The following formulations were mainly used in clinical studies of pomalidomide: 1 mg and 5 mg capsules of Formulation 1; 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg capsules of Formulation 3; and 2 mg capsules of Formulation 4. [redacted]

Among clinical studies of pomalidomide in patients with multiple myeloma (MM), capsules of Formulation 1 were used in a foreign phase I study (Study CC-4047-MM-001), while capsules of Formulation 3 were used in later studies, including a foreign phase I/II study (Study CC-4047-MM-002), a foreign phase III study (Study CC-4047-MM-003), a Japanese phase I study (Study CC-4047-

* The mean AUC_{24h} on Day 10 of administration was 713.8 ng·h/mL following multiple oral administration of 4 mg of pomalidomide to patients with MM in the Japanese phase I study (Study CC-4047-MM-004).

MM-004), and a Japanese phase II study (CC-4047-MM-011). The proposed commercial formulations are 1 mg, 2 mg, 3 mg, and 4 mg capsules of Formulation 3, among which bioequivalence was shown by comparison of dissolution between 1 mg and 2 mg capsules and between 3 mg and 4 mg capsules.

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

The pomalidomide concentrations in human plasma, urine, and semen were measured by liquid chromatography/tandem mass spectrometry (LC/MS/MS). The lower limits of quantification in human plasma were 0.2 ng/mL (Study CC-4047-1398/132), 0.25 ng/mL (Studies CC-4047-CP-005, CC-4047-CP-006, CC-4047-CP-007, CC-4047-MM-003, and CC-4047-MM-004), 0.4 ng/mL (Study CC-4047-MM-001), and 0.5 ng/mL (Study CC-4047-MM-002). The lower limits of quantification in human urine and semen were 20 ng/mL and 0.5 ng/mL, respectively.

4.(i).A.(2) Foreign phase I study (5.3.1.1.1, Study CC-4047-CP-005 [to 20])

A crossover study was conducted in 28 healthy adult subjects to assess the following: (a) the bioequivalence (BE) between the 2 mg capsules of Formulations 3 and 4 by administering a single oral dose of 2 mg (a 2 mg capsule of Formulation 3 or 4) in the fasted state (at least 10 hours before administration); and (b) the effect of food on the pharmacokinetics (PK) of pomalidomide by administering a single oral dose of 2 mg (a 2 mg capsule of Formulation 4) to subjects in the fasted state or after a high-fat meal (800-1000 kcal total, approximately 50% from fat).

The applicant explained as follows:

The results for (a) showed that the geometric mean ratios of $AUC_{0\text{-}t}$, and AUC_{inf} (Formulation 4/Formulation 3) [90% confidence interval (CI)] were both 0.96 [0.92, 1.01]. In contrast, the geometric mean ratio of C_{max} (Formulation 4/Formulation 3) [90% CI] was 0.73 [0.70, 0.76], indicating that C_{max} did not meet the BE criteria (0.80-1.25) at 90% confidence. Therefore, 2 mg capsules of Formulation 4 were not used in clinical studies that were conducted after this study.

With regard to the results for (b), the PK parameters of pomalidomide after administration of a 2 mg capsule of Formulation 4 in the fasted state or after a high-fat meal were as shown in the table below. No clear differences were observed in $t_{1/2}$, CL/F, or V_z/F between the groups; however, T_{max} was delayed in the fed group compared to the fasted group. The geometric mean ratios of $AUC_{0\text{-}t}$, AUC_{inf}, and C_{max} (fed group/fasted group) [90% CI] were 0.92 [0.88, 0.95], 0.92 [0.89, 0.95], and 0.76 [0.72, 0.80], respectively, indicating that C_{max} was lower in the fed group than the fasted group. A decrease in the rate of gastric emptying due to food intake may be involved in the mechanism of action responsible for lowered C_{max} and delayed T_{max} observed in the fed group.

PK parameters of pomalidomide (a 2 mg capsule of Formulation 4) under fasted or fed condition

Condition	n	C_{max} (ng/mL)	AUC_{0-t} (ng•h/mL)	AUC_{inf} (ng•h/mL)	T_{max}* (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Fasted	28	22.8 (17.6)	262 (22.3)	267 (22.4)	3.00 (2.50, 6.00)	7.01 (14.2)	7.5 (22.4)	75.8 (17.4)
Fed	26	17.4 (14.9)	245 (21.6)	250 (21.3)	6.00 (4.00, 8.00)	7.4 (13.7)	7.99 (21.3)	85.3 (16.2)

Geometric mean (coefficient of variation, %); *, median (minimum, maximum)

4.(i).A.(3) Foreign phase I study (5.3.1.2.1, Study CC-4047-CP-007 [[redacted] 20[redacted]])

A crossover BE study was conducted in healthy adult subjects (n = 72) in the fasted state by administering a single oral dose of Formulation 3 capsules to compare the following: (a) BE of one 4 mg capsule and two 2 mg capsules; and (b) BE of one 3 mg capsule and one 2 mg capsule plus one 1 mg capsule.

The applicant explained as follows:

The results for (a) showed that the geometric mean ratios of AUC_{0-t}, AUC_{inf}, and C_{max} (one 4 mg capsule/two 2 mg capsules) [90% CI] were 1.05 [1.01, 1.08], 1.05 [1.01, 1.08], and 1.04 [0.99, 1.09], respectively, indicating that the 90% CIs of all the 3 parameters were within the criteria for BE (0.80-1.25).

With regard to the results for (b), the geometric mean ratios of AUC_{0-t}, AUC_{inf}, and C_{max} (one 3 mg capsule/one 2 mg capsule plus one 1 mg capsule) [90% CI] were 1.03 [1.00, 1.06], 1.03 [1.00, 1.06], and 1.03 [0.99, 1.07], respectively, indicating that the 90% CIs of all the 3 parameters were within the criteria for BE (0.80-1.25).

The above results showed that for Formulation 3, one 4 mg capsule was bioequivalent to two 2 mg capsules; and one 3 mg capsule was bioequivalent to one 2 mg capsule plus one 1 mg capsule.

4.(i).A.(4) Applicant's discussion on the effects of gastric pH on PK of pomalidomide

The solubilities of pomalidomide in buffers of pH 1.2, 4.5, and 6.8 were 15.04, 14.64, and 13.15 µg/mL, respectively, indicating constant solubility over the pH range tested. Further, a dissolution test of pomalidomide was conducted using 0.1 mol/L of hydrochloric acid and buffers of pH 4.5 and 6.8, and the results indicated that the dissolution characteristics of pomalidomide was constant over the pH range tested.

Because the above results indicate no clear pH dependence of the solubility or dissolution of pomalidomide, variations in gastric pH are unlikely to affect the PK of pomalidomide.

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

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

PMDA asked the applicant to explain the food effect on the PK of pomalidomide after administration of its proposed commercial formulation because food effect had been studied using 2 mg capsules of

Formulation 4, instead of the proposed commercial formulation (Formulation 3) in the data submitted for registration [see "4.(i).A.(2) Foreign phase I study"].

The applicant responded as follows:
The results have recently been obtained from a foreign phase I study (Study CC-4047-CP-011), a clinical study that was examining the food effect on the PK of pomalidomide to be administered in the proposed commercial formulation when the application was submitted. The outline of the study results is as follows.

A crossover study was conducted in 28 healthy adult subjects to assess the food effect on the PK of pomalidomide by administering a single oral dose of 4 mg of pomalidomide (Formulation 3) in the fasted state or after a high-fat meal (800-1000 kcal total, approximately 50% from fat). The table below shows the PK parameters of pomalidomide after administration of a 4 mg capsule of pomalidomide (Formulation 3) in the fasted state or after a high-fat meal. No clear differences were observed in $t_{1/2}$, CL/F, or V_z/F between the groups; however, T_{max} was delayed in the fed group compared to the fasted group. No clear difference was observed between the fasted group and fed group. The geometric mean ratios of $AUC_{0\text{-}t}$, AUC_{inf}, and C_{max} (fed group/fasted group) [90% CI] were 0.92 [0.90, 0.94], 0.92 [0.90, 0.94], and 0.73 [0.69, 0.78], respectively.

PK parameters of pomalidomide (a 4 mg capsule of Formulation 3) under fasted or fed condition

Condition	n	C_{max} (ng/mL)	$AUC_{0\text{-}t}$ (ng•h/mL)	AUC_{inf} (ng•h/mL)	T_{max}* (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Fasted	27	73.4 (19.5)	734 (22.1)	744 (22.1)	2.02 (0.5, 6.0)	7.29 (15.2)	5.38 (22.1)	56.5 (16.7)
Fed	25	53.8 (17.2)	667 (20.9)	675 (20.9)	5.98 (3.0, 6.0)	7.01 (14.0)	5.92 (20.9)	59.9 (15.9)

Geometric mean (coefficient of variation, %); *, median (minimum, maximum)

The above results showed that the AUC of pomalidomide when using the proposed commercial formulation was approximately the same in the fed group and fasted group, and the C_{max} tended to be lower in the fed group compared to the fasted group. The results were similar to those obtained in Study CC-4047-CP-005 [see "4.(i).A.(2) Foreign phase I study"]. However, because no clear relationship was observed between the C_{max} and efficacy and safety [see "4.(ii).A.(6) Relationship of pomalidomide exposure to efficacy and safety"], variations in the C_{max} seen in the study were not considered to be clinically important. Additionally, the efficacy and safety of pomalidomide in patients with relapsed or refractory MM were demonstrated in a foreign phase III study (Study CC-4047-MM-003) and Japanese phase II study (Study CC-4047-MM-011), in which no food intake conditions were specified in the dosage regimen. Therefore, it is considered that no strong need exists to specify food intake conditions in the Dosage and Administration of pomalidomide.

PMDA accepted the applicant's explanation.

4.(ii) Summary of clinical pharmacology studies

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

The PK of pomalidomide was studied in healthy adult subjects and patients with MM receiving pomalidomide alone, or in combination with dexamethasone (DEX), bortezomib, ketoconazole, fluvoxamine maleate (fluvoxamine), or carbamazepine.

4.(ii).A.(1) Studies in healthy adult subjects

4.(ii).A.(1).1) Foreign phase I study (5.3.3.1.1, Study CC-4047-1398/132 [[redacted] to [redacted] 19[redacted]])

A randomized, single-blind study was conducted in 30 healthy adult subjects (pomalidomide, 20; placebo, 10) to investigate the pharmacokinetics etc., of pomalidomide. Subjects received a single oral dose of 1, 5, 10, 25, or 50 mg in the fasted state, and concentrations in plasma and urine were measured (the table below).

The $AUC_{0\text{-}t}$ and AUC_{inf} were approximately dose-proportional over the dose levels studied, while C_{max} increased in a less than dose-proportional manner. The applicant attributed this less than dose-proportional increase in C_{max} to the low solubility of pomalidomide, which may have decreased the absorption rate with the increasing dose. The $t_{1/2}$ and CL/F were generally stable regardless of dose.

The fractions of pomalidomide excreted in urine (Fe) within 48 hours post-dose were as low as <3% at all dose levels studied. The renal clearance (CL_R) was approximately the same at doses of 10 to 50 mg; however, CL_R tended to be lower in the 5 mg group than in the 10 to 50 mg groups. The applicant explained this low CL_R in the 5 mg group was attributable to the following: the concentrations of pomalidomide in urine were measurable up to 48 hours post-dose at doses of 25 and 50 mg, and up to 24 hours post-dose at 10 mg; while in the 5 mg group, urine pomalidomide concentrations decreased to below the lower limit of quantification in all subjects no later than 16 hours post-dose; as a result, the number of time points at which urine pomalidomide concentrations were measurable differed among dose levels.

PK parameters of pomalidomide in plasma and urine following single administration

Dose (mg)	n	In plasma							In urine	
		C_{max} (ng/mL)	$AUC_{0\text{-}t}$ (ng•h/mL)	AUC_{inf} (ng•h/mL)	T_{max}* (h)	$t_{1/2}$ (h)	CL/F (mL/min)	V_z/F (L)	Fe (%)	CL_R (mL/min)
1	4	11.2 (18.1)	118 (17.7)	122 (17.3)	3.00 (0.50, 4.00)	8.65 (14.6)	137 (17.3)	102 (21.8)	—	—
5	4	51.8 (12.2)	516 (21.3)	529 (21.5)	2.50 (1.50, 3.00)	10.1 (14.2)	158 (21.5)	138 (29.9)	1.37 (30.8)	6.66 (12.2)
10	4	80.8 (11.3)	911 (13.5)	930 (14.0)	3.25 (2.00, 6.00)	8.17 (33.7)	179 (14.0)	127 (32.0)	2.41 (22.1)	13.3 (13.3)
25	4	176 (19.7)	2647 (20.6)	2778 (21.1)	3.25 (2.00, 6.00)	10.8 (23.7)	150 (21.1)	140 (31.9)	2.66 (30.2)	12.3 (33.0)
50	4	288 (30.9)	4730 (30.4)	5001 (31.5)	6.00 (3.00, 8.00)	9.69 (42.9)	167 (31.5)	140 (50.5)	2.84 (23.4)	14.4 (17.8)

Geometric mean (coefficient of variation, %); *, median (minimum, maximum); "—", not calculated

4.(ii).A.(1). 2) Foreign phase I study (5.3.3.1.2, Study CC-4047-CP-006 [September to November 2011])

A double-blind, randomized study was conducted in 33 healthy adults (pomalidomide, 24; placebo, 9) to investigate the pharmacokinetics of pomalidomide. Subjects received multiple oral doses of 0.5, 1, or 2 mg once daily (QD), and the concentration of pomalidomide in plasma was measured (the table below). Additionally, the concentration of pomalidomide in semen was measured in the 2 mg group. Semen specimens were collected before administration of pomalidomide on Day 1, and 4 hours after administration of pomalidomide on Day 4.

The decrease in the plasma pomalidomide concentration followed a multiphasic pattern, and on Day 5 (the last administration), the plasma pomalidomide concentration decreased to below the detection limit (0.25 ng/mL) by 36 hours post-dose at 0.5 and 1 mg, and by 48 hours post-dose at 2 mg. The C_{max} and AUC_{inf} were generally dose-proportional over the dose levels studied on Days 1 and 5. Compared to Day 1, the C_{max} and AUC_{0-24} on Day 5 were higher. The plasma trough concentration of pomalidomide nearly reached steady state by Day 3. The CL/F and V_z/F were almost constant and independent of dose over the dose levels studied.

The geometric mean of the semen pomalidomide concentrations 4 hours post-dose on Day 4 was 16.4 ng/mL, corresponding to approximately 67% of the mean plasma pomalidomide concentration (24.5 ng/mL) measured 4 hours post-dose on Day 5.

PK parameters of pomalidomide in plasma following multiple administration

Dose (mg)	Time point (Day)	n	C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	AUC_{0-t} (ng•h/mL)	AUC_{inf} (ng•h/mL)	T_{max}* (h)	$t_{1/2}$ (h)	CL/F (mL/min)	V_z/F (L)
0.5	1	8	6.73 (17.8)	58.6 (24.5)	–	–	1.75 (1.00, 3.00)	–	–	–
	5		7.69 (20.8)	66.5 (24.0)	68.8 (28.2)	73.7 (27.7)	2.00 (1.00, 4.00)	6.96 (22.2)	113 (27.6)	68.1 (12.7)
1	1	8	13.1 (18.0)	95.0 (35.4)	–	–	1.76 (1.00, 3.00)	–	–	–
	5		13.6 (18.2)	103 (39.4)	106 (46.7)	110 (45.3)	1.50 (1.50, 3.10)	5.67 (34.2)	152 (45.3)	74.3 (14.2)
2	1	8	28.5 (18.6)	232 (24.5)	–	–	2.25 (1.50, 4.00)	–	–	–
	5		30.6 (26.2)	242 (25.0)	254 (28.0)	259 (26.7)	2.25 (1.50, 4.00)	6.33 (16.5)	129 (26.8)	70.5 (16.0)

Geometric mean (coefficient of variation, %); *, median (minimum, maximum); "—", not applicable

4.(ii).A.(1).3) Foreign phase I study (5.3.3.1.3, Study CC-4047-CP-004 [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 8 healthy adult subjects to evaluate the mass balance and metabolic profile of pomalidomide. Subjects received a single oral dose of 2 mg of ^{14}C-pomalidomide (racemic mixture [see "2.B. Control of optical purity"]) in the fasted state, and the concentration of radioactivity in whole blood and plasma, as well as the plasma concentrations of the S- and R-

enantiomers were studied (the table below). The plasma concentration of pomalidomide represents the total of the plasma concentration of S-enantiomers and R-enantiomers.

The ration of radioactivity in whole blood to that in plasma ranged from 74.88% to 111.5% during the first 48 hours after administration, based on which the applicant considered that radioactivity distributed into RBCs. The percentages of C_{max} and AUC_{0-t} for S-enantiomers to the unchanged pomalidomide were 52% and 49%, respectively, and those for R-enantiomers to the unchanged pomalidomide were 49% and 50%, respectively. The results indicated that S- and R-enantiomers were present in plasma at a ratio of approximately 1:1.

The AUC_{0-t} for radioactivity of unchanged pomalidomide in plasma accounted for 69.6% of the radioactivity in plasma, suggesting that unchanged pomalidomide represented the majority of whole blood radioactivity. Major metabolites in plasma included M2 (3-aminophthalic acid), M11 (hydrolysis product), M12, and M13 (both glucuronide conjugates of M17 [hydroxylated pomalidomide]), M16 (hydroxylated pomalidomide), and M17, and the percentage of AUC_{0-t} of radioactivity in each metabolite to AUC_{0-t} of plasma radioactivity was <10% for all metabolites.

The ratio of radioactivity excreted in urine by 72 hours post-dose to radioactivity administered was 72.1% and the corresponding ratio (hereinafter referred to as excretion rate [%]) for feces by 96 hours post-dose was 15.3%. Radioactivity was excreted primarily in urine, and only a very small amount of unchanged pomalidomide was excreted in urine (urinary excretion rate, 2.17%). Metabolites primarily found in urine up to 72 hours post-dose include M11, M12, and M13 (urinary excretion rates, 23.3%, 17.1%, and 12.4%, respectively). The fecal excretion rate of unchanged pomalidomide was 7.72% by 96 hours post-dose. Metabolites primarily found in feces up to 96 hours post-dose included M10, M11, M17, and M18, all of which were excreted in small amounts (≤2.78%). The applicant explained that, based on the above results, the predominant metabolic pathways of pomalidomide in humans were assumed to be hydrolysis, hydroxylation, and glucuronidation of the hydroxylated pomalidomide.

PK parameters of pomalidomide, S-enantiomers, R-enantiomers, and radioactive concentrations

Measurement target		n	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	AUC_{inf} (ng·h/mL)	T_{max}*5 (h)	$t_{1/2}$ (h)	CL/F (mL/min)	V_z/F (L)
Pomalidomide	Plasma	8	12.95 ± 3.93	136.65 ± 67.23	189.05 ± 51.81*6	3.00 (2.00, 6.00)	8.90 ± 3.40*6	9.85 ± 2.72*6	116.49 ± 14.13*6
S-enantiomer	Plasma	8	6.78 ± 1.99	66.88 ± 34.08	84.27 ± 28.77*6	3.00 (1.00, 6.00)	8.21 ± 3.34*6	22.84 ± 9.02*6	247.53 ± 73.41*6
R-enantiomer	Plasma	8	6.36 ± 2.08	67.68 ± 33.84	116.61 ± 11.55*7	3.00 (2.50, 6.00)	12.01 ± 1.75*7	15.82 ± 3.27*7	268.74 ± 16.68*7
Radioactivity	Plasma	8	15.14 ± 2.68*1	224.75 ± 98.95*3	260.20 ± 101.99*3	2.50 (1.00, 4.00)	10.21 ± 1.93	7.96 ± 2.43	112.69 ± 26.20
	Whole blood	8	12.10 ± 2.19*2	188.58 ± 88.23*4	225.09 ± 94.14*4	3.25 (1.00, 4.00)	11.21 ± 2.52	–	–

Arithmetic mean ± standard deviation; *1, ngEq/mL; *2, ngEq/g; *3, ngEq·h/mL; *4, ngEq·h/g;
*5, median (minimum, maximum); *6, n = 4; *7, n = 3; "—", not applicable

4.(ii).A.(2) Studies in patients with cancer

4.(ii).A.(2).1) Foreign phase I study (5.3.3.2.1 and 5.3.3.2.2, Study CC-4047-MM-001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in patients with MM (n = 45; of these, 28 subjects included in PK analysis) and pharmacokinetics of pomalidomide was investigated. The study consisted of 2 cohorts of subjects: subjects in Cohort 1 received multiple oral doses of 1, 2, 5, or 10 mg QD of pomalidomide; and subjects in Cohort 2 received multiple oral doses of 1, 2, 5, or 10 mg of pomalidomide on alternate days (QOD). The plasma pomalidomide concentrations were evaluated in Cohort 1 and only at 5 mg in Cohort 2 (the table below).

The $AUC_{0-\tau}$, AUC_{0-t}, and AUC_{inf} of pomalidomide increased generally in a dose-proportional manner on Day 1 over the dose levels studied, and C_{max} increased in a less than dose-proportional manner. At 1 and 2 mg QD, the C_{max} and $AUC_{0-\tau}$ on Day 28 were higher than those on Day 1, indicating accumulation of pomalidomide as a result of multiple administration. The applicant explained that, at 5 mg QD, no clear differences in C_{max} and $AUC_{0-\tau}$ were observed between Day 1 and Day 28. Because the number of subjects in whom PK was analyzed on Day 28 was small, the lack of a clear difference in C_{max} and $AUC_{0-\tau}$ was possibly attributable to a random event caused by inter individual variability. The $t_{1/2}$ of pomalidomide was generally constant, and independent of dose levels or time point.

PK parameters of pomalidomide

	Dosage/administration	n	Time point (Day)	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng•h/mL)	AUC_{inf} (ng•h/mL)	T_{max}*1 (h)	$t_{1/2}$ (h)	CL/F (mL/min)	V_z/F (L)
Cohort 1	1 mg QD	6	1	14.6 (25.8)	132 (21.0)	149 (25.3)	2.75 (0.750, 8.00)	6.76 (46.5)	112 (25.3)	65.3 (38.9)
		5	28	22.2 (34.2)	256*3 (42.4)	–	3.00 (2.00, 6.00)	6.45*2 (5.23)	65.1*3 (42.4)	42.4*2 (28.6)
	2 mg QD	8	1	24.5 (34.6)	205 (39.3)	232 (43.3)	2.50 (0.750, 4.00)	7.21 (18.1)	144 (43.3)	89.7 (36.4)
		7	28	31.9 (40.6)	306*4 (55.4)	–	2.92 (0.500, 4.00)	7.87*4 (25.2)	109*4 (55.4)	74.2*4 (28.9)
	5 mg QD	6	1	45.2 (20.9)	493 (39.3)	598 (51.4)	2.50 (2.00, 6.00)	7.95 (45.5)	139 (51.4)	95.9 (22.5)
		3	28	48.1 (95.1)	502 (93.2)	–	4.00 (3.00, 8.00)	6.99 (64.0)	166 (93.2)	101 (24.0)
	10 mg QD	3	1	95.0 (11.1)	849 (22.5)	1009 (24.3)	1.50 (0.750, 2.50)	6.79 (7.12)	165 (24.3)	97.1 (23.3)
		0	28	–	–	–	–	–	–	–
Cohort 2	5 mg QOD	4	1	45.8*2 (52.8)	470*2 (93.0)	590*2 (126)	3.00*2 (1.50, 8.17)	8.92*2 (34.8)	141*2 (126)	109*2 (70.9)
		4	28	62.9*2 (62.1)	662*2 (123)	–	2.50*2 (1.58, 4.00)	8.43*2 (58.4)	126*2 (123)	91.8*2 (44.7)

Geometric mean (coefficient of variation, %); *1, median (minimum, maximum); *2, n = 3; *3, n = 4; *4, n = 6; "–", not applicable

4.(ii).A.(2).2) Foreign phase I/II study (5.3.5.2.3, Study CC-4047-MM-002 [started in June 2008, ongoing; data cut-off on April 1, 2011])

A randomized, open-label study was conducted to evaluate the safety and other aspects of administration of pomalidomide alone, and in combination with DEX (pomalidomide + DEX) in patients with MM (n

= 259; of these subjects, the PK was analyzed in 14 subjects in the phase II part of the study). The study consisted of the phase I part (pomalidomide monotherapy) and phase II part (pomalidomide monotherapy or pomalidomide + DEX). In the phase II part of study, subjects in the pomalidomide group received multiple oral doses of pomalidomide at 4 mg QD, the maximum tolerated dose determined in the phase I part of study, on Days 1 to 21 of each 28-day cycle. In the pomalidomide + DEX group, subjects received oral doses of DEX 40 mg at a time (DEX 20 mg at a time for subjects older than 75 years) additionally on Days 1, 8, 15, and 22 of each 28-day cycle. The plasma pomalidomide concentrations on Days 1 and 8 of the first cycle were studied (the table below).

The C_{max} and AUC_{0-t} of pomalidomide were similarly high on Day 8 compared to Day 1 with or without co-administration of DEX. The applicant stated that co-administration of DEX is not likely to influence the PK of pomalidomide because no clear difference was observed in C_{max} and AUC_{0-t} of pomalidomide between the pomalidomide alone group and pomalidomide + DEX group on Days 1 and 8.

PK parameters of pomalidomide after administration of pomalidomide alone or pomalidomide + DEX (measured on Days 1 and 8 of the first cycle)

	n	Time point (Day)	C_{max} (ng/mL)	T_{max}*1 (h)	AUC_{0-t} (ng•h/mL)
Pomalidomide alone	7	1	64.6 (39.2)	2.00 (1.00, 4.00)	314 (43.9)
	5	8	78.8 (27.7)	2.00 (1.00, 3.00)	411 (28.2)
Pomalidomide + DEX*2	7	1	62.4 (28.1)	2.00 (1.00, 3.00)	300 (39.9)
	7	8	73.2 (35.3)	3.00 (2.00, 6.00)	382 (55.5)

Geometric mean (geometric mean of coefficient of variation, %) except for*1
*1, median (minimum, maximum); *2, including 1 patient who received 20 mg of DEX

4.(ii).A.(2).3) Foreign phase III study (5.3.5.1.1, Study CC-4047-MM-003 [started in March 2011, ongoing; data cut-off on March 1, 2013])

A randomized, open-label controlled study was conducted in patients with MM (n = 455) to investigate the efficacy and safety of pomalidomide + DEX therapy and high-dose DEX monotherapy. In the pomalidomide + DEX group, subjects received multiple oral doses of 4 mg QD of pomalidomide on Days 1 to 21 on a 28-day cycle, and oral doses of DEX 40 mg at a time (DEX 20 mg at a time for subjects older than 75 years) on Days 1, 8, 15, and 22 of each 28-day cycle. The plasma pomalidomide concentrations were determined before and 2 hours after administration on Days 1, 8, 15, and 22 of the first cycle.

The plasma pomalidomide concentrations (arithmetic means) before administration on Days 8, 15, and 22 were 14.56, 12.48, and 10.03 ng/mL, respectively. The plasma pomalidomide concentrations (arithmetic means) 2 hours after administration (near T_{max}) on Days 1, 8, and 15 were 44.28, 47.37, and 51.03 ng/mL, respectively, indicating similar concentrations between time points.

4.(ii).A.(2).4) Japanese phase I study (5.3.5.2.2, Study CC-4047-MM-004 [started in April 2012, ongoing; data cut-off on November 19, 2013])

An open-label study was conducted in patients with MM (n = 12; 12 patients included in PK analysis) to investigate PK and other aspects of pomalidomide. The study consisted of 2 stages, maximum tolerated dose (MTD) determination stage (pomalidomide monotherapy) and treatment stage (pomalidomide + DEX). A study to ascertain the plasma pomalidomide concentration was performed in the MTD determination stage [for information on the treatment stage, see "4.(iii).B.(2).1) Japanese phase I study"]. In the MTD determination stage, patients received a single oral dose of 0.5 mg of pomalidomide 7 days prior to the first 28-day treatment cycle. Patients received multiple oral doses of 2 or 4 mg QD of pomalidomide on Days 1 to 21 (except Day 2 in the first cycle) on a 28-day cycle (the table below).

The C_{max}, AUC_{24}, and AUC_{inf} of pomalidomide were generally dose proportional on Day 1 of the first cycle and the following 8 days of multiple administration, and no clear difference in C_{max} or AUC_{24} was observed between Day 1 and Day 10 of the first cycle. The $t_{1/2}$, CL/F, and V_z/F of pomalidomide were generally constant and independent of dose levels or time point.

PK parameters of pomalidomide

Dose (mg)	Time point (Day)	n	C_{max} (ng/mL)	AUC_{24} (ng•h/mL)	AUC_{inf} (ng•h/mL)	T_{max}*1 (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
0.5	1	6	9.1 (18.8)	84.9 (14.9)	92.6 (14.6)	2.0 (0.9, 4.0)	6.4 (12.4)	5.4 (14.6)	50 (18.5)
2	1	6	35.6 (15.9)	364.4 (20.3)	411.0 (26.4)	3.0 (2.0. 6.0)	6.9 (20.7)	4.9 (26.4)	48.2 (15.9)
	10*2		37.6 (20.9)	411.5 (17.7)	463.6 (19.4)	3.0 (1.0, 4.0)	7.3 (8.8)	4.9 (17.7)	45.6 (15.4)
4	1	6	70.2 (49.7)	685.7 (43.1)	750.1 (44.8)	3.0 (1.0, 5.8)	6.0 (21.1)	5.3 (44.8)	46 (37.4)
	10*2		71.2 (40.6)	713.8 (40.1)	764.3 (40.8)	4.0 (2.0, 4.0)	5.5 (24.4)	5.6 (40.1)	41.6 (42.0)

Geometric mean (coefficient of variation, %), *1, median (minimum, maximum); *2, following the 8-day multiple administration (no administration on Day 2 in the first cycle)

4.(ii).A.(3) Study of drug interactions with ketoconazole, fluvoxamine, and carbamazepine (5.3.3.1.4, Study CC-4047-CP-008 [September to November, 2012])

An open-label study was conducted in healthy adult subjects (n = 32; 32 subjects included in PK analysis) to investigate the effects of ketoconazole (CYP3A4 and P-gp inhibitor), fluvoxamine (CYP1A2 inhibitor), and carbamazepine (CYP3A4 inducer) on the PK of pomalidomide. The study consisted of Parts 1 and 2. In Part 1, subjects received 3 different dosage regimens: (i) pomalidomide monotherapy (a single oral dose of 4 mg of pomalidomide); (ii) pomalidomide/ketoconazole combination therapy (oral doses of 200 mg of ketoconazole twice daily on Days 1-7, and a single oral dose of 4 mg of pomalidomide on Day 5); and (iii) pomalidomide/ketoconazole/fluvoxamine combination therapy (multiple oral doses of 200 mg of ketoconazole and oral doses of 50 mg of fluvoxamine twice daily on Days 1-7, and a single oral dose of 4 mg of pomalidomide on Day 5). In Part 2, subjects received 2 different dosage regimens: (i) pomalidomide monotherapy (a single oral dose of 4 mg of pomalidomide); and (ii) pomalidomide/carbamazepine combination therapy (multiple oral

doses of 100 mg of carbamazepine once daily on Day 1, twice daily on Days 2 and 3, and multiple oral doses of 200 mg of carbamazepine twice daily on Days 4-11, and a single oral dose of 4 mg of pomalidomide on Day 10).

With regard to the results for Part 1, the geometric mean ratios of C_{max} and AUC_{inf} (pomalidomide + ketoconazole/pomalidomide alone) [90% CI] were 1.07 [1.01, 1.14] and 1.19 [1.10, 1.28], respectively. The geometric mean ratios of C_{max} and AUC_{inf} (pomalidomide + ketoconazole + fluvoxamine/pomalidomide alone) [90% CI] were 1.21 [1.14, 1.30] and 2.46 [2.26, 2.67]. The $t_{1/2}$ of pomalidomide when administered alone, in combination with ketoconazole, and in combination with ketoconazole and fluvoxamine were 6.07, 6.77, and 12.37 hours, respectively. The above results showed that the AUC_{inf} and $t_{1/2}$ of pomalidomide increased approximately 2.5-fold and 2-fold, respectively, as a result of combined administration with ketoconazole and fluvoxamine.

With regard to the results for Part 2, the geometric mean ratios of C_{max} and AUC_{inf} (pomalidomide + carbamazepine/pomalidomide alone) [90% CI] were 0.75 [0.68, 0.83], and 0.80 [0.73, 0.87], respectively. The $t_{1/2}$ of pomalidomide when administered alone and in combination with carbamazepine were 6.05 and 5.85 hours, respectively. The above results showed that the C_{max} and AUC_{inf} of pomalidomide decreased slightly when administered in combination with carbamazepine compared to when administered alone, but with no clear difference.

4.(ii).A.(4) Study on the relationship between exposure levels and variation in QT/QTc interval (5.3.4.1.1, Study CC-4047-CP-010 [October to December, 2013])

A randomized, double-blind, crossover study was conducted in healthy adult subjects (n = 72) to investigate the effect of pomalidomide on QT intervals by Fridericia's method (QTcF) using placebo and moxifloxacin hydrochloride (moxifloxacin) as controls. A single oral dose of 4 or 20 mg of pomalidomide, placebo, or a single oral dose of 400 mg of moxifloxacin was administered in the fasted state.

The placebo-adjusted least-squares mean change from baseline in QTcF interval was calculated for administration of 4 or 20 mg of pomalidomide. The upper limit of the two-sided 90% CI for the calculated least squares mean change was <10 msec at every time point. Two to 4 hours after administration of moxifloxacin, the positive control, the lower limit of the two-sided 90% CI for the placebo-adjusted least-squares mean change from baseline in QTcF was >5 msec. At dose levels of 4 and 20 mg of pomalidomide, no subject had a mean QTcF at 3 consecutive time points of >450 msec, or a QTcF change from baseline of >30 msec. Furthermore, no clear relationship was observed between plasma pomalidomide concentration and QTcF interval.

The applicant stated that based on the above results, pomalidomide is unlikely to have a clinically significant effect on prolonging the QTcF interval.

4.(ii).A.(5) Population pharmacokinetic (PPK) analysis

A population pharmacokinetic (PPK) analysis was conducted by a nonlinear mixed-effect modeling program (NONMEM Ver. 7.2) using a 2-compartment model with first-order absorption, on the PK parameter data (236 subjects, 3909 time points) obtained from foreign phase I studies in healthy adults (Studies CC-4047-CP-006 and CC-4047-CP-007) and foreign studies in patients with MM, including phase I studies (Studies CC-4047-MM-001 and CC-4047-MM-005), a phase I/II study (Study CC-4047-MM-002), and a phase III study (Study CC-4047-MM-003). The following covariates were tested for their effect on CL/F and V_2/F of pomalidomide: age, sex, body weight, ethnicity, race, albumin, total bilirubin, total protein, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and creatinine clearance (CLcr). The applicant provided the following explanation of the obtained results:

- Sex was identified as a significant covariate on CL/F; body weight and total protein were identified as significant covariates on V_2/F. However, the inter-individual variability of CL/F was 44.1% in the base model, and 42.77% in the final model (adjusted for sex); the inter-individual variability of V_2/F was 22.3% in the base model, and 18.9% in the final model (adjusted for body weight and total protein), indicating that there were no obvious differences between the models for both covariates. Therefore, these covariates are considered to be of little clinical significance with limited effects on the inter-individual variability of CL/F and V_2/F.
- The estimated PK parameters of pomalidomide in healthy adults (men) and patients with MM (79 men and 61 women) were as follows: CL/F was 8.52 and 7.78 L/h, respectively, V_2/F was 58.3 and 69.9 L, respectively, V_3/F was 8.45 and 71.5 L, respectively, and the apparent inter-compartmental clearance was 1.0 and 3.75 L/h, respectively. Thus, healthy subjects and patients with MM had similar CL/F and V_2/F; in contrast, V_3/F and the apparent inter-compartmental clearance were higher in MM patients than in healthy adults. The differences in V_3/F and the apparent inter-compartmental clearance are considered to be attributable to the distribution of pomalidomide in the tumors of MM patients.

4.(ii).A.(6) Relationship between pomalidomide exposure and efficacy and safety

The relationships between steady-state C_{max} and AUC_{24} of pomalidomide and the efficacy and safety following multiple administration of 4 mg of pomalidomide were studied based on the results of the following studies in patients with MM: foreign phase I/II study (Study CC-4047-MM-002), and phase III study (Study CC-4047-MM-003). The steady state C_{max} and AUC_{24} of pomalidomide were estimated using the PPK model described in the previous section [see "4.(ii).A.(5) Population pharmacokinetic (PPK) analysis"]).

4.(ii).A.(6).1) Relationship between pomalidomide exposure and efficacy

The steady-state C_{max} and AUC_{24} of pomalidomide were analyzed to evaluate their relationships to objective tumor response according to the International Myeloma Working Group (IMWG) criteria. The geometric means of C_{max} of pomalidomide in patients who achieved very good partial response (VGPR; n = 3), stable disease (SD; n = 37), progressive disease (PD; n = 9), partial response (PR; n = 13), not

evaluable (NE; n = 2), and evaluable* (n = 7) were 51.4, 41.6, 47.5, 48.5, 47.2, and 49 ng/mL, respectively; and geometric means of AUC_{24} of pomalidomide in the respective patient groups were 574.1, 602, 510.5, 517.3, 615, and 450.7 ng·h/mL. The results indicated that there was no clear relationship between steady-state C_{max} and AUC_{24} of pomalidomide and objective tumor response based on the IMWG criteria.

Further, the relationships between steady-state C_{max} and AUC_{24} of pomalidomide and the maximum percent changes from baseline in serum and urine M-protein, serum immunoglobulins 1, 2, and 3, serum free light chains 1 and 2, and β2-microglobulin were studied; and no clear relationships were found in any of them.

4.(ii).A.(6).2) Relationship between pomalidomide exposure and safety

The relationships between any dose adjustment or dose interruption of pomalidomide and the steady-state C_{max} and AUC_{24} of pomalidomide during the first cycle (the first 28 days of administration) were analyzed. The results showed no obvious relationships between dose adjustment and the steady-state C_{max} and AUC_{24} of pomalidomide: in the 71 patients who did not have their doses adjusted and 19 patients who had their doses adjusted at least once during the first cycle, the geometric mean C_{max} was 44.8 and 50.7 ng/mL, respectively, and the geometric mean AUC_{24} was 537.5 and 646.1 ng·h/mL, respectively. On the other hand, the steady-state C_{max} and AUC_{24} of pomalidomide were significantly higher in the 25 patients whose treatment was interrupted during the first cycle than in the 65 patients whose treatment was not interrupted: the geometric mean C_{max} was 54.9 and 43.0 ng/mL, respectively, and the geometric mean AUC_{24} was 673.9 and 520 ng·h/mL, respectively.

The relationships between the steady-state C_{max} and AUC_{24} of pomalidomide and the maximum percent changes from baseline in neutrophil count, platelet count, and hemoglobin level were analyzed, but no clear relationships were found in any of them.

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

4.(ii).B.(1) Differences in pharmacokinetic parameters of pomalidomide between Japanese and non-Japanese patients

The applicant explained the differences in the PK parameters of pomalidomide between Japanese and non-Japanese patients as follows:

Differences in the PK parameters of pomalidomide between Japanese and non-Japanese patients were studied in those with MM using data from the following studies (the table below): a foreign phase I study (Study CC-4047-MM-008) in which pomalidomide and low-dose DEX were administered in

* This category includes patients who had their pre-treatment clinical laboratory test data (e.g., M protein) collected, but did not have their clinical laboratory test data collected after administration of pomalidomide for efficacy evaluation.

combination* to investigate the effect of renal impairment on the PK of pomalidomide (only PK data of MM patients with normal renal function [CLcr ≥ 60 mL/min] were used); and a Japanese phase I study (Study CC-4047-MM-004) in which pomalidomide alone was administered [see "4.(ii).A.(2).4) Japanese phase I study"]. The results indicated that levels of AUC_{24} following multiple oral administration of 4 mg QD of pomalidomide tended to be lower in Japanese patients with MM than in non-Japanese patients with MM. However, the difference was not statistically significant, and may be attributable to a large inter-individual variability; therefore, it is considered that there were no clear differences in PK parameters between Japanese and non-Japanese patients. Further, the PK parameters of pomalidomide from Studies CC-4047-MM-008 and CC-4047-MM-004 were assumed to be comparable, based on the results of Study CC-4047-MM-002 [see "4.(ii).A.(2).2) Foreign phase I/II study"]), which indicated no clear effects of DEX on pomalidomide PK parameters, even though the drugs administered differed between the two studies above.

PK parameters of pomalidomide in Japanese and non-Japanese patients

	Study	Time point (Day)	n	C_{max} (ng/mL)	AUC_{24} (ng•h/mL)	T_{max}*1 (h)	$T_{1/2}$ (h)	CL/F (mL/min)	V_z/F (L)
Japanese	CC-4047-MM-004	1	6	70.2 (49.7)	685.7 (43.1)	3.0 (1.0, 5.8)	6.0 (21.1)	88.3 (44.8)	46 (37.4)
Non-Japanese	CC-4047-MM-008	1	8	59.4 (41.3)	638.1 (43.0)	2 (1, 3.9)	7.3 (27.5)	90.0 (49.6)	56.9 (33.0)
Japanese	CC-4047-MM-004	10*2	6	71.2 (40.6)	713.8 (40.1)	4.0 (2.0, 4.0)	5.5 (24.4)	93.3 (40.1)	41.6 (42.0)
Non-Japanese	CC-4047-MM-008	21	7	79.3 (25.1)	997.9 (27.4)	3 (1, 4)	8.7 (11.5)	66.67 (27.4)	50.6 (24.6)

Geometric mean (coefficient of variation, %); *1, median (minimum, maximum); *2, after multiple administration for 8 days (no administration on Day 2 in the first cycle)

In addition, the results of the PPK analysis showed that race had no significant influence on any PK parameters of pomalidomide [see "4.(ii).A.(5) Population pharmacokinetic (PPK) analysis"]; therefore, it is considered that no clear differences in the PK of pomalidomide exist between Japanese and non-Japanese patients.

PMDA accepted the applicant's explanation.

4.(ii).B.(2) Effect of renal impairment on the PK of pomalidomide

The applicant explained the effect of renal impairment on the PK of pomalidomide as follows:

Renal impairment is unlikely to affect the PK of pomalidomide noticeably for the following reasons.

- Pomalidomide has been shown to be metabolized almost completely, with 2.17% of the administered dose being excreted unchanged in urine [see "4.(ii).A.(1).3) Foreign phase I study"];

* In the combination treatment, patients received multiple oral doses of 4 mg QD of pomalidomide on Days 1 to 21, and oral doses of DEX 40 mg at a time (DEX 20 mg at a time for patients older than 75 years) on Days 1, 8, 15, and 22 on a 28-day cycle, except in the first cycle, in which DEX was administered on Days 2, 8, 15, and 22.

- CLcr, with the median being 100.4 mL/min (range, 20.8-188.2 mL/min), was not identified in the PPK analysis as a significant covariate of the PK of pomalidomide.

Currently a foreign phase I study (Study CC-4047-MM-008) is underway to assess the effect of renal impairment on the PK of pomalidomide used in combination with low-dose DEX in MM patients with normal renal function (CLcr ≥ 60 mL/min) and those with severe renal impairment (CLcr < 30 mL/min).

PMDA considers as follows:
The effect of renal impairment on the PK of pomalidomide is difficult to assess conclusively for the following reasons: (a) the results of a foreign phase I study (Study CC-4047-CP-004) suggest that pomalidomide and its metabolites are mainly excreted in urine [see "4.(ii).A.(1).3) Foreign phase I study"]; (b) patients with CLcr of <45 mL/min were excluded from clinical studies of pomalidomide; and (c) the results of clinical studies in patients with renal impairment are as yet unavailable. Therefore, it is necessary to advise careful administration of pomalidomide in patients with renal impairment in the package insert and other relevant documents. Upon completion of Study CC-4047-MM-008 with results becoming available, relevant information and findings should be provided to healthcare professionals in clinical settings.

4.(ii).B.(3) Effect of hepatic impairment on PK of pomalidomide
The applicant explained the effect of hepatic impairment on the PK of pomalidomide as follows:

Hepatic impairment is unlikely to affect the PK of pomalidomide noticeably because albumin, total bilirubin, and AST were not identified in the PPK analysis as being significant covariates of the PK of pomalidomide [see "4.(ii).A.(5) Population pharmacokinetic (PPK) analysis"].

A foreign phase I study (Study CC-4047-CP-009) in patients with hepatic impairment is ongoing.

PMDA considers as follows:
The effect of hepatic impairment on the PK of pomalidomide is difficult to assess conclusively for the following reasons: (a) the results of a foreign phase I study (Study CC-4047-CP-004) suggest that the majority of pomalidomide is metabolized [see "4.(ii).A.(1).3) Foreign phase I study"]; (b) patients with hepatic transaminases of > 3-fold the upper limit of normal were excluded from clinical studies of pomalidomide; and (c) the results of the clinical study to assess the effect of hepatic impairment on the PK of pomalidomide are as yet unavailable. Therefore, it is necessary to advise careful administration of pomalidomide in patients with hepatic impairment in the package insert and other relevant documents. Upon completion of Study CC-4047-CP-009 with results becoming available, relevant information and findings should be provided to healthcare professionals in clinical setting.

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

The applicant explained the effect of the CYP3A4 inhibitor, CYP1A2 inhibitor, CYP3A4 inducer on the PK of pomalidomide as follows:

- Compared to pomalidomide monotherapy, the C_{max} and AUC_{inf} of pomalidomide in combination with ketoconazole and fluvoxamine increased by 21% and 146%, respectively [see "4.(ii).A.(3) Study of drug interactions with ketoconazole, fluvoxamine, and carbamazepine"]. Therefore, it is necessary to advise careful administration of pomalidomide in combination with CYP3A4 inhibitor and CYP1A2 inhibitor in the package insert and other relevant documents.
- Compared to pomalidomide monotherapy, the C_{max} and AUC_{inf} of pomalidomide increased by 7% and 19%, respectively, in combination with ketoconazole and decreased by 25% and 20%, respectively, in combination with carbamazepine [see "4.(ii).A.(3) Study of drug interactions with ketoconazole, fluvoxamine, and carbamazepine"]. However, given the inter-individual variability in the PK parameters of pomalidomide, the variations in C_{max} and AUC_{inf} are not considered clinically relevant; therefore, it would appear unnecessary to advise careful administration of pomalidomide in combination with a CYP3A4 inhibitor or with a CYP3A4 inducer.
- Compared to co-administration of pomalidomide and ketoconazole, both the C_{max} and AUC_{inf} of pomalidomide in combination with ketoconazole and fluvoxamine were markedly high. The results cannot rule out the possibility that pharmacokinetic interactions between pomalidomide and a CYP1A2 inhibitor may occur in coadministration. Meanwhile, a foreign phase I study (Study CC-4047-CP-012) to assess the effects of a CYP1A2 inhibitor (fluvoxamine) on the PK of pomalidomide is scheduled to start in the fourth quarter of 2014.

PMDA accepted the applicant's explanation. As soon as the result of scheduled Study CC-4047-CP-012 become available, relevant information and findings should be provided to healthcare professionals in clinical settings.

4.(iii) Summary of clinical efficacy and safety

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

As the efficacy and safety evaluation data, the results from 1 Japanese phase I study, 1 Japanese phase II study, 8 foreign phase I studies, 1 foreign phase I/II study, and 1 foreign phase III study were submitted. The results from 1 foreign phase II study and 1 global phase III study were also submitted as reference data.

List of clinical studies on efficacy and safety

Data type	Study region	Study number	Phase	Target	Number of patients	Dosage and administration	Primary endpoints
Evaluation	Japan	CC-4047-MM-004	I	Relapsed or refractory MM	12	Oral doses of 2 or 4 mg QD of pomalidomide alone, or in combination with DEX were administered on Days 1 to 21 on a 28-day cycle.	Safety Efficacy PK
		CC-4047-MM-011	II	Relapsed MM	36	Oral doses of 4 mg QD of pomalidomide were administered in combination with DEX on Days 1 to 21 on a 28-day cycle.	Efficacy Safety
	Foreign	CC-4047-CP-005	I	Healthy adults	28	A single oral dose of 2 mg of pomalidomide (test formulation or control formulation) was administered in the fasted state or after a meal.	PK Safety
		CC-4047-CP-007	I	Healthy adults	72	A single oral dose of pomalidomide (one 4 mg capsule or two 2 mg capsules; one 3 mg capsule or one 2 mg plus one 1 mg capsule) was administered in the fasted state.	PK Safety
		CC-4047-1398/132	I	Healthy adults	30	A single oral dose of 1, 5, 10, 25, or 50 mg of pomalidomide, or placebo was administered in the fasted state.	PK PD Safety
		CC-4047-CP-006	I	Healthy adults	33	Oral doses of 0.5, 1, or 2 mg QD of pomalidomide were administered for 5 days.	PK Safety
		CC-4047-CP-004	I	Healthy adults	8	A single oral dose of 2 mg of ^{14}C-pomalidomide was administered.	PK Safety
		CC-4047-CP-008	I	Healthy adults	32	Oral doses of pomalidomide (4 mg QD), ketoconazole, fluvoxamine, or carbamazepine were administered.	PK Safety
		CC-4047-CP-010	I	Healthy adults	72	A single oral dose of pomalidomide (4 or 20 mg), placebo, or moxifloxacin was administered.	PK Safety
		CC-4047-MM-001	I	Relapsed MM	45	Multiple oral doses of 1, 2, 5, or 10 mg of pomalidomide were administered for 4 weeks (daily or on alternate days).	Safety Efficacy PK
		CC-4047-MM-002	I/II	Relapsed MM	38	Phase I part of study: oral doses of 2, 3, 4, or 5 mg QD of pomalidomide were administered on Days 1 to 21 on a 28-day cycle.	Efficacy Safety PK
					119 (a) 107 (b) 112	Phase II part of study: (a) Oral doses of 4 mg QD of pomalidomide were administered on Days 1 to 21 on a 28-day cycle. (b) Oral doses of 4 mg QD of pomalidomide were administered on Days 1 to 21 on a 28-day cycle in combination with DEX (oral doses of DEX 40 mg* at a time on Days 1, 8, 15, and 22).	
		CC-4047-MM-003	III	Relapsed or refractory MM	450 (a) 300 (b) 150	(a) Oral doses of 4 mg QD of pomalidomide were administered on Days 1 to 21 on a 28-day cycle in combination with DEX (oral doses of DEX 40 mg* at a time on Days 1, 8, 15, and 22). (b) Oral doses of 40 mg* of DEX at a time were given on Days 1 through 4, 9 through 12, and 17 through 20 on a 28-day cycle.	Efficacy Safety PK
Reference	Foreign	IFM 2009-02	II	Relapsed MM	84 (a) 43 (b) 41	(a) Oral doses of 4 mg QD of pomalidomide were administered on Days 1 to 21 on a28-day cycle in combination with DEX (oral doses of DEX 40 mg at a time on Days 1, 8, 15, and 22). (b) Oral doses of 4 mg QD of pomalidomide were administered on Days 1 to 28on a 28-day cycle in combination with DEX (oral doses of DEX 40 mg at a time on Days 1, 8, 15, and 22).	Efficacy Safety
	Global	CC-4047-MF-002	III	Myelofibrosis	250 (a) 167 (b) 83	(a) Oral doses of 0.5 mg QD of pomalidomide were administered. (b) Placebo QD was orally administered.	Efficacy Safety PK

MM, multiple myeloma; QD, once daily; DEX, dexamethasone; *, 20 mg at a time for patients older than 75 years

The outlines of the clinical studies are described in the following sections.

Major adverse events observed in the studies except for deaths are described in "4.(iv) Adverse events and other findings observed in clinical studies," and study results related to PK in "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies."

4.(iii).B Evaluation data

4.(iii).B.(1) Clinical pharmacology studies

The following studies were submitted as clinical pharmacology studies [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. No deaths occurred during the study periods in the following 7 studies which were conducted in healthy adults.

4.(iii).B.(1).1) Foreign phase I study (5.3.1.1.1, Study CC-4047-CP-005 [[redacted] to [redacted] 20[redacted]])

4.(iii).B.(1).2) Foreign phase I study (5.3.1.2.1, Study CC-4047-CP-007 [[redacted] 20[redacted]])

4.(iii).B.(1).3) Foreign phase I study (5.3.3.1.1, Study CC-4047-1398/132 [[redacted] to [redacted] 19[redacted]])

4.(iii).B.(1).4) Foreign phase I study (5.3.3.1.2, Study CC-4047-CP-006 [September to November 2011]

4.(iii).B.(1).5) Foreign phase I study (5.3.3.1.3, Study CC-4047-CP-004 [[redacted] to [redacted] 20[redacted]])

4.(iii).B.(1).6) Foreign phase I study (5.3.3.1.4, Study CC-4047-CP-008 [September to November 2012])

4.(iii).B.(1).7) Foreign phase I study (5.3.4.1.1, Study CC-4047-CP-010 [October to December 2013])

4.(iii).B.(2) Japanese clinical studies

4.(iii).B.(2).1) Japanese phase I study (5.3.5.2.2, Study CC-4047-MM-004 [started in April 2012, ongoing; data cut-off on November 19, 2013])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory* MM (target sample size of 12) at 7 institutions in Japan to study the safety and tolerability of pomalidomide.

The study consisted of 2 stages, the maximum tolerated dose (MTD) determination stage (administration of pomalidomide alone), and the treatment stage (administration of pomalidomide in combination with DEX). In the MTD determination stage, patients received a single oral dose of 0.5 mg of pomalidomide 7 days prior to a 28-day treatment cycle, and patients received multiple oral doses of 2 or 4 mg QD of pomalidomide on Days 1 to 21 (no dose on Day 2 in the first cycle) of the first cycle; in the treatment stage, patients received oral doses of 2 or 4 mg QD of pomalidomide on Days 1 to 21 on a 28-day cycle, in combination with DEX 40 mg at a time (DEX 20 mg at a time for patients older than 75 years) on Days 1, 8, 15, and 22.

* "refractory" was defined as cases in which prior treatment(s) resulted in responses no better than progressive disease (PD).

All 12 patients enrolled in the study received pomalidomide, and were included in the safety analysis population.

Dose-limiting toxicity (DLT) was evaluated during the first cycle, and tolerability was evaluated. Dose-limiting toxicity was observed in 1 patient at 2 mg who exhibited neutrophil count decreased (Grade 4) continuously for 7 days or more, and no DLT was observed in the 4 mg group. The results showed that 4 mg of pomalidomide is tolerated by Japanese patients with MM.

No deaths occurred during the treatment period or within 30 days after the last administration of pomalidomide.

4.(iii).B.(2).2) Japanese phase II study (5.3.5.2.1, Study CC-4047-MM-011 [started in December 2013, ongoing; data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in patients with relapsed MM (target sample size of 37) at 14 institutions in Japan to study the efficacy and safety of pomalidomide.

Patients received oral doses of 4 mg QD of pomalidomide, on Days 1 to 21 on a 28-day cycle, in combination with oral doses of DEX 40 mg at a time (DEX 20 mg at a time for patients older than 75 years) on Days 1, 8, 15, and 22.

All 36 patients enrolled in the study received pomalidomide, and were included in the safety analysis population. All of them received pomalidomide at least once and had efficacy evaluations at baseline and after receiving at least one dose of pomalidomide. All the 36 patients were included in the efficacy analysis population.

The table below outlines the objective tumor response based on the IMWG criteria (*Leukemia*. 2006;20:1467-73), which is the primary endpoint.

Objective tumor response (determined by the investigators; efficacy analysis population, n = 36; data cut-off on [redacted], 20[redacted])

	Number of patients (%)
Best overall response[*1]	
Stringent complete response (sCR)	0
Complete response (CR)	1 (2.8)
Very good partial response (VGPR)	0
Partial response (PR)	8 (22.2)
Stable disease (SD)	22 (61.1)
Progressive disease (PD)	5 (13.9)
Not evaluable (NE)[*2]	0
Number of responses (sCR, CR, VGPR, or PR) (percentage of responses [95% CI (%)])	9[*3] (25.0 [10.9, 39.1[*4]])

*1, The following IMWG criteria were used to determine objective tumor response:

- sCR: CR as defined below plus normal free light chain (FLC) ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.
- CR: negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow
- VGPR: serum and urine M-protein detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein, plus urine M-protein level < 100 mg/24 h
- PR: ≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90%, or reduction to <200 mg/24 h. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum FLC assay is not also measurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
- SD: not meeting criteria for sCR, CR, VGPR, PR, or PD
- PD: at least one of the following test results needs to increase by 25%:
  (1) serum M-protein (the absolute increase must be ≥0.5 g/dL); (2) urine M-protein (the absolute increase must be ≥200 mg/24 h); (3) only in patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (the absolute increase must be >10 mg/dL); (4) bone marrow plasma cell percentage (the absolute % must be ≥10%); (5) definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of existing bone lesions or soft tissue plasmacytomas; (6) development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or > 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.
- Response categories of sCR, CR, VGPR, and PR require two consecutive assessments before determination.

*2, the category includes patients who had their pre-treatment clinical laboratory test data (e.g., M-protein) collected, but did not have their clinical laboratory test data after administration collected for efficacy evaluation [for a case in which the data were used for evaluation, see "4.(ii).A.(6).1) Relationship of pomalidomide exposure to efficacy"].

*3, for all patients, the effect of response has been confirmed 4 weeks after the response was initially determined.

*4, after the application were submitted, an analysis was performed as the main analysis of the study [see "4.(iii).D.(2).4) Efficacy of pomalidomide in Japanese patients"].

Safety results showed that 3 of 36 patients died during the treatment period or within 28 days after the last administration of pomalidomide. The causes of death were pneumonia plus asthma, multi-organ failure, and hypoxia (1 patient each). For pneumonia and asthma, a causal relationship to the study drug could not be ruled out.

4.(iii).B.(3) Foreign clinical studies

4.(iii).B.(3).1) Foreign phase I study (5.3.3.2.2, Study CC-4047-MM-001/CDC-407-00-001 [[redacted] 20[redacted] to [redacted] 20[redacted]]

An open-label, uncontrolled study was conducted in patients with relapsed MM (target sample size, depending on the occurrence of DLT) at 1 institution outside Japan to evaluate the tolerability and safety of pomalidomide.

Multiple oral doses of 1, 2, 5, or 10 mg QD of pomalidomide were administered in Cohort 1, and on alternate days in Cohort 2 for 4 weeks.

All 45 enrolled patients (24 and 21 patients in Cohorts 1 and 2, respectively) received pomalidomide, and were included in the safety analysis population. Dose-limiting toxicity was observed in 1 of 6 patients (Grade 3 deep vein thrombosis) in the 1 mg group, 2 of 9 patients (Grade 4 neutropenia) in the 2 mg group, 1 of 6 patients (Grade 4 neutropenia) in the 5 mg group, 2 of 3 patients (Grade 4 neutropenia) in the 10 mg group. Based on the results, the MTD of pomalidomide when administered once daily was determined to be 2 mg. In Cohort 2, DLT was observed in 0 of 4 patients in the 1 mg group, 1 of 4 patients (infection with Grade 3 neutropenia) in the 2 mg group, 1 of 10 patients (infection with Grade 3 neutropenia) in the 5 mg group, and 3 of 3 patients (Grade 3 neutropenia [1 patient] and Grade 4 neutropenia [2 patient]) in the 10 mg group. Based on the results, the MTD of pomalidomide when administered on alternate days was determined to be 5 mg.

Safety results showed that no deaths occurred during the treatment period or within 30 days after the last administration of pomalidomide.

4.(iii).B.(3).2) Foreign phase I/II study (5.3.3.2.3 and 5.3.5.2.3; Study CC-4047-MM-002 [started in June 2008, ongoing; data cut-off on April 1, 2011])

An open label, uncontrolled study was conducted in patients with relapsed MM (target sample size, 60 and 192 patients in the phase I and II parts of the study, respectively) at 18 institutions outside Japan to evaluate tolerability, efficacy, and safety.

In the phase I part of the study, patients received oral doses of 2, 3, 4, 5, 6, 8, 10, or 12 mg QD of pomalidomide on Days 1 to 21 on a 28-day cycle. If patients had exhibited PD or their urine M-protein had not decreased by ≥50% at some point after completion of the first cycle, the patients were allowed to receive, in addition to pomalidomide, oral doses of 40 mg of DEX on Days 1, 8, 15, and 22 on a 28-cycle.

All 38 patients enrolled in the phase I part of study were included in the ITT population and were analyzed for safety and efficacy. DLT occurred in 1 of 6 patients (Grade 3 fatigue) in the 2 mg group, 1 of 8 patients (Grade 4 neutropenia) in the 3 mg group, 2 of 14 patients (Grade 4 neutropenia) in the 4 mg group, and 4 of 10 patients (Grade 4 neutropenia) in the 5 mg group. Based on the results, the MTD of pomalidomide was determined to be 4 mg (when administered on Days 1-21 on a 28-day cycle).

In the phase II part of study, patients in the pomalidomide group received oral doses of 4 mg QD of pomalidomide alone on Days 1 to 21 on a 28-day cycle. Patients in the pomalidomide + DEX group received oral doses of 4 mg QD of pomalidomide on Days 1 to 21 on a 28-day cycle, and oral doses of DEX 40 mg at a time (DEX 20 mg at a time for patients older than 75 years) on Days 1, 8, 15, and 22.

All 221 patients enrolled in the phase II part of the study were included as the ITT population (113 and 108 patients in the pomalidomide + DEX group and pomalidomide group, respectively) and were analyzed for efficacy. Of these, 219 patients (112 and 107 patients in the pomalidomide + DEX group and pomalidomide group, respectively) received pomalidomide, and were included in the safety analysis population.

The primary endpoint of efficacy was progression free survival (PFS) assessed by an Independent Response Adjudication Committee (IRAC) according to the criteria of the European Group for Blood and Marrow Transplant (EBMT) (*Br J Haematol*. 1998;102:1115-23).

The table below shows the results of the final analysis for PFS (data cut-off on April 1, 2011). The results showed a prolonged PFS in the pomalidomide + DEX group compared to the pomalidomide group.

Results of the final analysis for PFS (assessed by IRAC; ITT population; data cut-off on April 1, 2011)

	Pomalidomide + DEX group	Pomalidomide group
Number of patients	113	108
Censored	27 (23.9%)	27 (25.0%)
Number of events	86 (76.1%)	81 (75.0%)
Median [95% CI] (week)	16.6 [14.1, 21.1]	10.7 [8.3, 16.1]
Hazard ratio*1 [95% CI]	0.73 [0.54, 0.99]	
P-value (two-sided)*2	0.037	

*1, calculated using Cox proportional hazard model; *2, log-rank test

In the phase I part of the study, 3 of 38 patients (7.9%) died during the treatment period or within 30 days after administration of the last dose. The incidences of the deaths were 1 of 8 patients (12.5%) in the 3 mg group, and 2 of 14 patients (14.3%) in the 4 mg group. The causes of these deaths were as follows: gastrointestinal haemorrhage in the 3 mg group, and meningitis bacterial, and lung infection pseudomonal in the 4 mg group. In the phase II part of the study, 32 of 219 patients (14.6%) died during the treatment period or within 30 days after administration of the last dose. The incidences of the deaths were 16 of 112 patients (14.3%) in the pomalidomide + DEX group, and 16 of 107 patients (15.0%) in the pomalidomide group. Among these, the causes of deaths other than PD (8 patients each in the pomalidomide + DEX and pomalidomide groups) were pneumonia and respiratory failure (2 patients each), bronchopneumonia, cerebral haemorrhage, cardiac failure congestive, cardio-respiratory distress, completed suicide, and subarachnoid haemorrhage (1 patient each) in the pomalidomide + DEX group; and pneumonia (3 patients), sepsis (2 patients), bronchopneumonia, lobar pneumonia, cerebral haemorrhage, staphylococcal sepsis, and cardio-respiratory arrest (1 patient each) (including duplicates). A causal relationship to the study drug could not be ruled out for pneumonia and respiratory failure in 1

patient each in the pomalidomide + DEX group, pneumonia in 2 patients, and sepsis and staphylococcal sepsis in 1 patient each in the pomalidomide group.

4.(iii).B.(3).3) Foreign phase III study (5.3.5.1.1; Study CC-4047-MM-003 [started in March 2011, ongoing; data cut-off date on March 1, 2013])

An open-label, controlled study was conducted in patients with relapsed or refractory MM (target sample size of 426) at 93 institutions outside Japan to investigate the efficacy and safety of pomalidomide in comparison with high-dose DEX monotherapy.

Patients in the pomalidomide + DEX group received oral doses of 4 mg QD of pomalidomide on Days 1 to 21 on a 28-day cycle, and oral doses of 40 mg of DEX at a time (DEX 20 mg at a time for patients older than 75 years) on Days 1, 8, 15, and 22 in a cycle. Patients in the high-dose DEX group received oral doses of DEX 40 mg QD (DEX 20 mg QD for patients older than 75 years) alone on Days 1 to 4, 9 to 12, and 17 to 20 of each cycle.

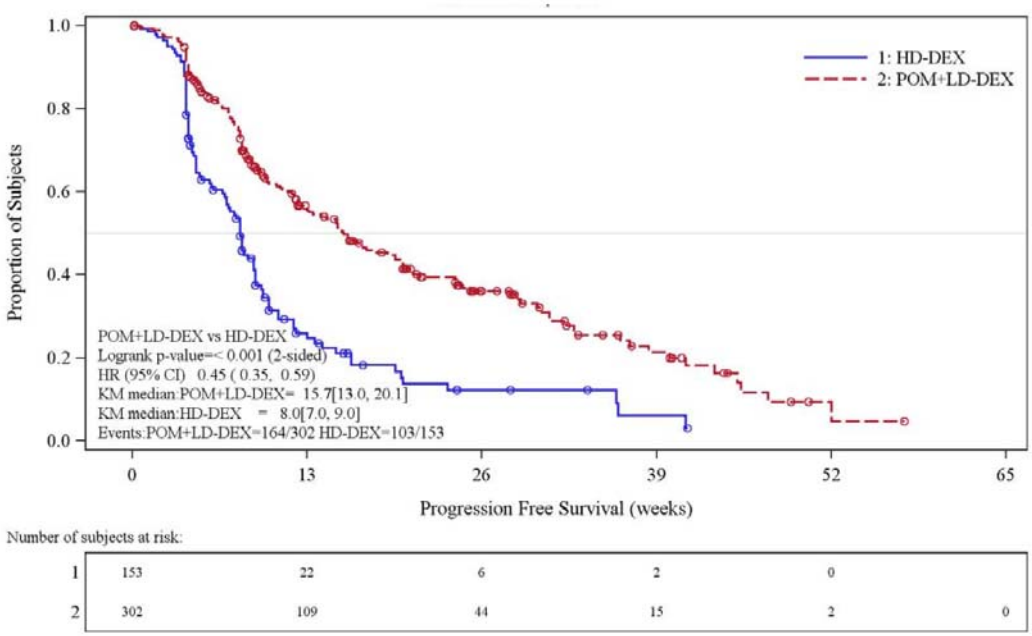
The patients enrolled in the study were 455 (302 and 153 patients in the pomalidomide + DEX group and DEX group, respectively), and all the patients were included in the ITT population for efficacy analysis. Of these patients, 450 patients who received pomalidomide or DEX (300 and 150 patients in the pomalidomide + DEX group and DEX group, respectively) were included in the safety analysis population.

The primary endpoint of efficacy was PFS assessed by IRAC according to the IMWG criteria. The table and figure below show the results of the final analysis for PFS (data cut-off on September 7, 2012). The results demonstrated the superiority of the pomalidomide + DEX group over the DEX alone group.

Results of the final analysis for PFS (assessed by IRAC; ITT population; data cut-off on September 7, 2012)

	Pomalidomide + DEX group	DEX group
Number of patients	302	153
Censored	138 (45.7%)	50 (32.7%)
Number of events	164 (54.3%)	103 (67.3%)
Median [95% CI] (week)	15.7 [13.0, 20.1]	8.0 [7.0, 9.0]
Hazard ratio*1 [95% CI]	0.45 [0.35, 0.59]	
P-value (two-sided)*2	<0.001	

*1, calculated using a Cox proportional hazard model adjusted for stratification-factors (age, prior treatment response, number of anti-myeloma treatment regimens)
*2, stratified log-rank test (stratification as in the Cox model); two-sided significance level of 0.05



Kaplan-Meier curve for PFS (ITT population; data cut-off on September 7, 2012)

A total of 65 of 450 patients (14.4%) died during the treatment period or within 30 days after the last administration. The incidences of deaths were 44 of 300 patients (14.7%) in the pomalidomide + DEX group and 21 of 150 patients (14.0%) in the DEX group. The causes of deaths were as follows: in the pomalidomide + DEX group, general physical health deterioration (17 patients), pneumonia and acute renal failure (3 patients each), multi-organ failure and sepsis (2 patients each), sudden death, bronchopneumonia, Klebsiella sepsis, lower respiratory tract infection, lung infection, pneumonia pneumococcal, septic shock, urinary retention, cardiac amyloidosis, cardiac arrest, cardio-respiratory arrest, cerebral haemorrhage, ischaemic cerebral infarction, subarachnoid haemorrhage, pelvic fracture, subdural haematoma, chronic obstructive pulmonary disease, respiratory failure, and cachexia (1 patient each) (including duplicates); in the high-dose DEX alone group, general physical health deterioration (6 patients), septic shock (5 patients), pneumonia (3 patients), sepsis and lower respiratory tract infection (2 patients each), lung infection pseudomonal, cardiac arrest, and gastrointestinal haemorrhage (1 patient each). Of these deaths in the pomalidomide + DEX group, a causal relationship to the study drug could not be ruled out for pneumonia (3 patients), multi-organ failure, lung infection, Klebsiella sepsis, pneumonia pneumococcal, lower respiratory tract infection, sudden death, ischaemic cerebral infarction, and septic shock (1 patient each).

4.(iii). C Reference data

4.(iii).C.(1) Foreign clinical studies

Foreign phase II study (5.3.5.2.4, Study IFM 2009-02 [started in January 2009, ongoing; data cut-off on March 1, 2011])

An open-label, uncontrolled study was conducted in patients with relapsed MM (target sample size of 84) at 22 institutions outside Japan to evaluate the efficacy and safety of a combination of pomalidomide and DEX.

The following 2 different 28-day cycle dosage regimens were studied: (i) in the 21-day treatment group, patients received oral doses of 4 mg QD of pomalidomide on Days 1 to 21, and oral doses of 40 mg of DEX at a time on Days 1, 8, 15, and 22; (ii) in the 28-day treatment group, patients received oral doses of 4 mg QD of pomalidomide on Days 1 to 28, and oral doses of 40 mg of DEX at a time on Days 1, 8, 15, and 22.

Eighty-four patients enrolled in the study (43 and 41 patients in the 21-day treatment group and 28-day treatment group, respectively) were included in the ITT population and were analyzed for efficacy and safety.

The response rate [95% CI] based on the IMWG criteria, the primary endpoint of efficacy, was 34.9% [21.0, 50.9] (15 of 43 patients) in the 21-day treatment group, and 34.1% [20.1, 50.6] (14 of 41 patients) in the 28-day treatment group.

A total of 21 patients died during the treatment period or within 30 days after the last administration. The incidences of deaths were 11 of 43 patients (25.6%) in the 21-day treatment group and 10 of 41 patients (24.4%) in the 28-day treatment group. The causes of deaths were as follows: in the 21-day treatment group, general physical health deterioration and pneumonia (2 patients each), haemorrhagic stroke, periorbital cellulitis, quadriparesis, renal failure, lung infection, respiratory failure, and death (1 patient each); and in the 28-day treatment group, pneumonia (2 patients), aplasia, respiratory distress, cerebral haemorrhage, staphylococcal sepsis, pulmonary oedema, renal failure, epistaxis, dyspnoea, and general physical health deterioration (1 patient each) (including duplicates). A causal relationship to the study drug could not be ruled out for respiratory distress (1 patient) in the 28-day treatment group.

4.(iii).C.(2) Global study

Global phase III study (5.3.5.4.1, Study CC-4047-MF-002 [September 2010 to January 2013])

A randomized, double-blind, controlled study was conducted in patients with myelofibrosis (target sample size: 140 in the pomalidomide group; 70 in the placebo group; 210 in total) at 72 institutions outside Japan to investigate the efficacy, safety, and the PK of pomalidomide.

Patients were to receive oral doses of 0.5 mg QD of pomalidomide or placebo QD every day.

A total of 252 patients enrolled in the study (168 and 84 patients in the pomalidomide group and placebo group, respectively) were included in the ITT population, and were analyzed for efficacy. Of these patients, 250 patients who received pomalidomide or placebo (167 and 83 patients in the respective groups) were included in the safety analysis population. Seventeen of 167 patients (10.2%) in the pomalidomide group and 10 of 83 patients (12.0%) in the placebo group died during the treatment period or within 28 days after the last administration. The causes of deaths other than PD (3 patients each in both groups) were as follows: in the pomalidomide group, cardiac arrest and pneumonia (2 patients

each), septic shock, anaemia, pancytopenia, multi-organ failure, renal failure, pneumonitis, cardiac failure, cardiac failure congestive, interstitial lung disease, respiratory failure, generalised oedema, and subdural haemorrhage (1 patient each) (including duplicates); and in the placebo group, multi-organ failure (2 patients), cholecystitis, sudden cardiac death, sudden death, subdural haematoma, and acute renal failure (1 patient each). Of these deaths, a causal relationship to the study drug could not be ruled out for cardiac failure (1 patient) in the pomalidomide group, and subdural haematoma, and multi-organ failure (1 patient each) in the placebo group.

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

4.(iii).D.(1) Review policy

PMDA considers that, among the submitted data, Study CC-4047-MM-003 (Study MM-003), a foreign phase III study in patients with relapsed or refractory MM, is the most important study in the evaluation of the efficacy and safety of pomalidomide, and has decided to review the present application with a focus on this study.

PMDA has also decided to evaluate the efficacy and safety of pomalidomide in Japanese patients with a focus on Study CC-4047-MM-011 (Study MM-011), a Japanese phase II study in patients with relapsed MM.

4.(iii).D.(2) Efficacy

PMDA concluded that the efficacy of pomalidomide in the treatment of relapsed or refractory MM was demonstrated by the following review results:

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

PMDA asked the applicant to explain the reason why high-dose DEX monotherapy was selected as the control group of Study MM-003. The applicant responded as follows:

DEX was listed with the following clinical descriptions in diagnostic guidelines and textbooks on blood diseases at the time when Study MM-003 was planned.

- The National Comprehensive Cancer Network (NCCN) *Clinical Practice Guidelines in Oncology for Multiple Myeloma* (version 3, 2010): DEX monotherapy, bortezomib monotherapy, and a combination of lenalidomide and DEX were recommended as salvage therapy for relapsed or refractory MM. This document also stated that high-dose DEX monotherapy was used as the control group in a phase III clinical study that served as the rationale for recommending a combination of lenalidomide and DEX.
- *Wintrobe's Clinical Hematology, Twelfth Edition* (Lippincott Williams & Wilkins, 2009, USA): this document stated that high-dose DEX monotherapy achieved a response rate of 25% in patients with relapsed or refractory MM.

- *Cecil Medicine, 23rd Edition* (Saunders Elsevier, 2008, USA): this document listed high-dose DEX monotherapy as a treatment for relapsed or refractory MM, with the typical dosage being 40 mg QD on Days 1 to 4, 9 to 12, and 17 to 20.

According to guidelines such as the NCCN Guidelines at the time when Study MM-003 was planned, DEX monotherapy was being recommended as a treatment option for relapsed or refractory MM. Textbooks on blood diseases at that time also listed DEX monotherapy as a treatment for MM, showing that it was used extensively. In addition, Study MM-003 was aimed at treating relapsed or refractory MM that had responded poorly to bortezomib and lenalidomide, and when it was planned, no treatment with strong evidence was available. Therefore, given the circumstances at the time when Study MM-003 was planned, it appeared reasonable to use high-dose DEX monotherapy as a comparator.

PMDA accepted the applicant's explanation.

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

The applicant justified the selection of PFS, assessed by central review, as the primary endpoint for Study MM-003as follows:

Treatments for patients with relapsed or refractory MM, the target population of Study MM-003, are initiated to extend the lives of patients; therefore, extension of survival is of great importance. However, for patients with relapsed or refractory MM, PFS has been considered as a surrogate marker for overall survival (OS), and using PFS as the endpoint is recommended when presenting clinical trial results (*Leukemia*. 2006;20:1467-73). Therefore, using PFS as the primary endpoint for Study MM-003 to investigate patients with relapsed or refractory MM is considered appropriate.

PMDA considers that, the applicant's explanation is reasonable, nevertheless OS is also an important endpoint when assessing the efficacy of treatments for patients with relapsed or refractory MM for which standard treatments have not been established. Therefore, PMDA determined that the efficacy of pomalidomide was to be evaluated based primarily on PFS and that the results of OS were also to be taken into account.

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

In the pomalidomide + DEX group, the results for PFS (assessed by IRAC according to IMWG criteria), the primary endpoint of Study MM-003, were superior to those in the DEX group [see "4.(iii).B.(3).3). Foreign phase III study"]. The table and figure below show the results of the interim analysis (primary analysis)[*1] and the Kaplan-Meier curve for OS, one of the secondary endpoints. The results of the final

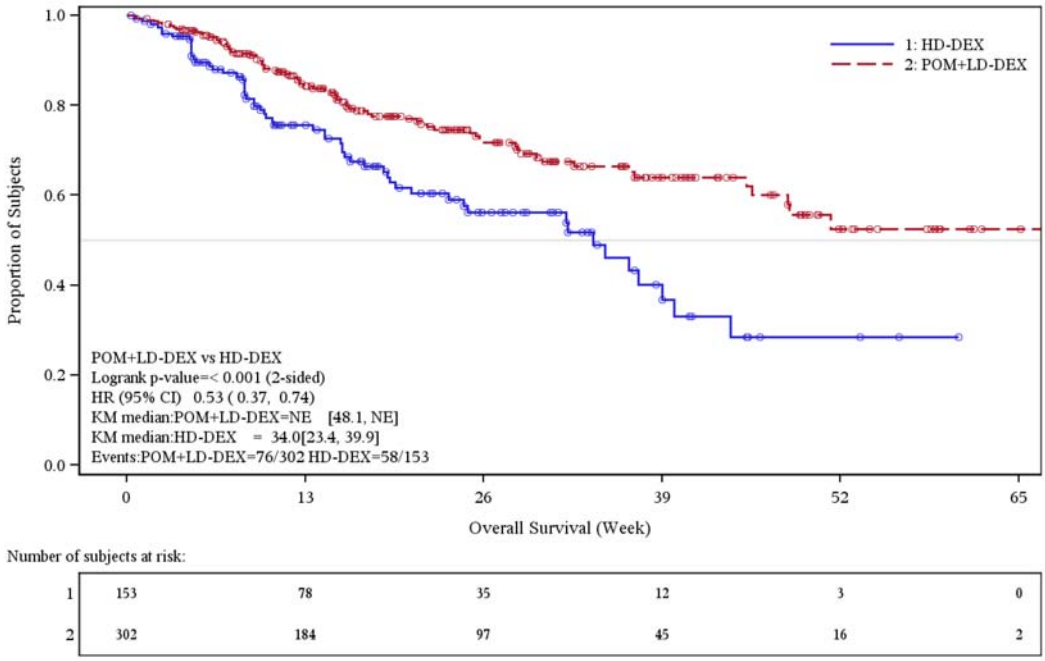
[*1] The analysis was to be performed at the same time as the final analysis for PFS (provided PFS was found to be statistically significant), or at the time when 50% of OS information were collected (at the time when 106 patients in total have died), whichever was later. The two-sided significance level for the interim OS analysis (primary analysis) based on the Lan-DeMets α-spending function of the O'Brien-Fleming type was 0.0031.

analysis (additional analysis)[*2] for OS showed that the number of OS events was 147 in 302 patients (48.7%) in the pomalidomide + DEX group, and 86 in 153 patients (56.2%) in the DEX group. The median [95% CI] values for OS were 54.0 [45.3, 66.4] weeks in the pomalidomide + DEX group, and 34.9 [29.9, 39.1] weeks in the DEX group (data cut-off on March 1, 2013).

Results of interim analysis for OS (ITT population; data cut-off on September 7, 2012)

	Pomalidomide + DEX group	DEX group
Number of patients	302	153
Censored	226 (74.8%)	95 (62.1%)
Number of events	76 (25.2%)	58 (37.9%)
Median [95% CI] (week)	NE [48.1, NE]	34.0 [23.4, 39.9]
Hazard ratio[*1] [95% CI]	0.53 [0.37, 0.74]	
P-value (two-sided)[*2]	<0.001	

NE, not evaluable; *1, calculated using Cox proportional hazard model; *2, unstratified long-rank test



Kaplan-Meier curve for OS (ITT population; data cut-off on September 7, 2012)

PMDA concluded that the efficacy of pomalidomide in the target patients of Study MM-003 has been demonstrated for the following reasons:

- The results for PFS (assessed by central review), the primary endpoint of Study MM-003, verified the superiority of the pomalidomide + DEX group over the DEX group;
- The results of the interim analysis for OS (primary analysis; data cut-off on September 7, 2012) indicated that OS was prolonged in the pomalidomide + DEX group compared with that in the DEX group.

[*2] The analysis was to be performed at the time when 212 patients in total had died

4.(iii).D.(2).4) Efficacy of pomalidomide in Japanese patients

The applicant explained the efficacy of pomalidomide in Japanese patients as follows:

Because Study MM-011 required a sample size of 33, assuming a threshold response rate of 10%, a true response rate of 25%, a two-sided significance level of 10% with a statistical power of 80%, and a dropout rate of 10%, the number of patients was set at 37. The primary analysis of the response rate was to be conducted after all patients finished the Week 24 evaluation according to the Study MM-011 protocol (dated [redacted], 20[redacted]). This timing of the primary analysis was selected because it was assumed possible to evaluate most of the patients for response, taking into account the following: of 302 patients in the pomalidomide + DEX group in Study MM-003, 71 patients (23.5%) responded, and the median (minimum, maximum) time from randomization to their response was 8.1 (4.0, 48.0) weeks; and in Study MM-011, the interval of efficacy evaluation was set at 4 weeks.

The efficacy endpoint of Study MM-011, the response rate according to the IMWG criteria, was 25.0% (9 of 36 patients) (data cut-off on [redacted], 20[redacted]) [see "4.(iii).B.(2).2) Japanese phase II study"]. This result was obtained when all patients finished the Week 4 evaluation, and it was defined that the number of responders in Study MM-011 would be at least 9 (25.0%) because the efficacy endpoint was the objective tumor response defined as the sum of best responses. From the above discussion, it was considered that the results (data cut-off on [redacted], 20[redacted]) from Study MM-011would allow evaluation of the efficacy of pomalidomide in Japanese patients; therefore, the analysis was conducted as the primary analysis of the study. The results obtained from Study MM-011 yielded a response rate [95% CI] of 25% [10.8%, 39.1%] with a two-sided *P* value of 0.0027 (by a binominal test using the normal approximation by the Wald test), which was higher than the threshold response rate (10%) predefined as the efficacy criterion. Therefore, pomalidomide is expected to be as effective in Japanese MM patients as in non-Japanese MM patients.

PMDA accepted the applicant's explanation, and also considers that the following information should be provided to healthcare professionals in clinical settings using suitable materials:

1. Patients with refractory MM were not enrolled in Study MM-011; and
2. The results of the follow-up analysis of Study MM-011, including the PFS and the duration of response (as soon as the results become available).

4.(iii).D.(3) Safety

The following characteristic adverse events associated with pomalidomide were identified in the reviews outlined in the subsequent sections: bone marrow depression, neuropathy peripheral, thromboembolism, infection, arrhythmia, cardiac failure, acute kidney failure, interstitial lung disease, tumour lysis syndrome, somnolence, depressed level of consciousness, confusion, fatigue, dizziness/vertigo, and second primary malignancy. PMDA considers special attention should be paid to the occurrence of these adverse events when using pomalidomide.

PMDA concluded that pomalidomide is tolerable given that appropriate measures including monitoring and control of adverse events, dose adjustment and other precautions such as dose-reduction, interruption or discontinuation of the drug are taken by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancy when pomalidomide is used. However, safety data on Japanese patients are extremely limited in the studies conducted so far; therefore, it is necessary to obtain further safety data through a post-marketing survey.

4.(iii).D.(3).1) Safety profile of pomalidomide and safety in Japanese patients

The table below summarizes the safety data obtained from foreign clinical studies (Studies MM-003 and CC-4047-MM-002 [Study MM-002]), and Japanese clinical studies (Studies CC-4047-MM-004 [Study MM-004] and Study MM-011), which were conducted in patients with relapsed or refractory MM.

Summary of safety

	Number of patients (%)					
	Study MM-003		Study MM-002		Study MM-004	Study MM-011
	Pomalidomide + DEX	DEX	Pomalidomide + DEX	Pomalidomide		
	300 patients	150 patients	112 patients	107 patients	12 patients	36 patients
All adverse events	297 (99.0)	149 (99.3)	112 (100)	106 (99.1)	12 (100)	33 (91.7)
Adverse events (Grade ≥3)	259 (86.3)	127 (84.7)	90 (88.4)	90 (84.1)	11 (91.7)	28 (77.8)
Death	44 (14.7)	22 (14.7)	20 (17.9)	21 (19.6)	0	3 (8.3)
Serious adverse events	183 (61.0)	80 (53.3)	69 (61.6)	50 (46.7)	5 (41.7)	11 (30.6)
Adverse events leading to treatment discontinuation	31 (10.3)	16 (10.7)	9 (8.0)	11 (10.3)	0	3 (8.3)
Adverse events leading to treatment interruption	206 (68.7)	73 (48.7)	74 (66.1)	51 (47.7)	7 (58.3)	12 (33.3)
Adverse events leading to dose reduction	113 (37.7)	47 (31.3)	44 (39.3)	27 (25.2)	5 (41.7)	14 (38.9)

The applicant explained the differences in the safety profiles of pomalidomide between Japanese and non-Japanese patients as follows:

A pooled analysis was performed using the results of clinical studies in patients with relapsed or refractory MM (Studies MM-003, MM-002, MM-004, and MM-011) by dividing data into Japanese and non-Japanese patients (412 non-Japanese patients in the pomalidomide + DEX group; 48 Japanese patients in the pomalidomide + DEX group and in the pomalidomide group in the first cycle of Study MM-004). Adverse events with an higher incidence in Japanese patients than in non-Japanese patients by ≥5% included leukopenia (58 non-Japanese patients [14.1%] and 13 Japanese patients [27.1%]), lymphopenia (30 non-Japanese patients [7.3%] and 13 Japanese patients [27.1%]), neutropenia (207 non-Japanese patients [50.2%] and 37 Japanese patients [77.1%]), thrombocytopenia (115 non-Japanese patients [27.9%] and 25 Japanese patients [52.1%]), dental caries (1 non-Japanese patient [0.2%] and 3 Japanese patients [6.3%]), malaise (14 non-Japanese patients [3.4%] and 8 Japanese patients [16.7%]), oedema peripheral (70 non-Japanese patients [17.0%] and 13 Japanese patients [27.1%]), hepatic

function abnormal (0 non-Japanese patients and 6 Japanese patients [12.5%]), nasopharyngitis (29 non-Japanese patients [7.0%] and 6 Japanese patients [12.5%]), alanine aminotransferase increased (11 non-Japanese patients [2.7%] and 4 Japanese patients [8.3%]), hypoalbuminaemia (17 non-Japanese patients [4.1%] and 6 Japanese patients [12.5%]), hypophosphataemia (11 non-Japanese patients [2.7%] and 4 Japanese patients [8.3%]), myalgia (16 non-Japanese patients [3.9%] and 5 Japanese patients [10.4%]), dysgeusia (14 non-Japanese patients [3.4%] and 6 Japanese patients [12.5%]), asthma (0 non-Japanese patients and 3 Japanese patients [6.3%]), hypoxia (6 non-Japanese patients [1.5%] and 4 Japanese patients [8.3%]), pleural effusion (8 non-Japanese patients [1.9%] and 4 Japanese patients [8.3%]), rash (41 non-Japanese patients [10.0%] and 9 Japanese patients [18.8%]), and rash maculo-papular (2 non-Japanese patients [0.5%] and 5 Japanese patients [10.4%]). Adverse events (Grade ≥3) with an incidence rate higher in Japanese patients than in non-Japanese patients by ≥3% included anaemia (121 non-Japanese patients [29.4%] and 17 Japanese patients [35.4%]), neutropenia (188 non-Japanese patients [45.6%] and 30 Japanese patients [62.5%]), lymphopenia (19 non-Japanese patients [4.6%] and 9 Japanese patients [18.8%]), leukopenia (38 non-Japanese patients [9.2%] and 6 Japanese patients [12.5%]), thrombocytopenia (87 non-Japanese patients [21.1%] and 13 Japanese patients [27.1%]), dental caries (0 non-Japanese patients and 2 Japanese patients [4.2%]), hepatic function abnormal (0 non-Japanese patients and 2 Japanese patients [4.2%]), decreased appetite (3 non-Japanese patients [0.7%] and 3 Japanese patients [6.3%]), hyponatraemia (13 non-Japanese patients [3.2%] and 3 Japanese patients [6.3%]), hypophosphataemia (6 non-Japanese patients [1.5%] and 4 Japanese patients [8.3%]), and cancer pain (2 non-Japanese patients [0.5%] and 2 Japanese patients [4.2%]). Serious adverse events with an incidence rate higher in Japanese patients than in non-Japanese patients by ≥3% included anaemia (12 non-Japanese patients [2.9%] and 4 Japanese patients [8.3%]) and cancer pain (0 non-Japanese patients and 2 Japanese patients [4.2%]).

Among adverse events observed only in Study MM-004, those that occurred in ≥2 patients were hepatic function abnormal (3 patients) and asthma (2 patients); adverse events of Grade ≥3 were ilium fracture and hepatic function abnormal (1 patient each) only; and a serious adverse event was ilium fracture (1 patient), for which any relationship to pomalidomide was ruled out.

Among adverse events observed only in Japanese patients in Study MM-011, those that occurred in ≥2 patients were hepatic function abnormal (3 patients), proctalgia, and blood fibrinogen decreased (2 patients each). Adverse events of Grade ≥3 were as follows: Grade 5, asthma (1 patient); Grade 4, antithrombin III decreased (1 patient); Grade 3, shock haemorrhagic, malnutrition, pneumocystis jirovecii pneumonia, localised oedema, supraventricular tachycardia, hepatic function abnormal, and blood fibrinogen decreased (1 patient each). Serious adverse events were asthma, shock haemorrhagic, hepatic function abnormal, and blood fibrinogen decreased (1 patient each). Of these, a causal relationship to pomalidomide could not be ruled out for asthma.

PMDA considers as follows:

The safety data obtained from the clinical studies (Studies MM-003, MM-002, MM-011, and MM-004) in which patients with relapsed or refractory MM were enrolled indicated no definite differences in terms of the types and frequency of adverse events between studies. However, there was a limitation of safety data for Japanese patients treated with a combination of pomalidomide and DEX, which may limit the comparative evaluation of safety profiles of pomalidomide between Japanese and non-Japanese patients. Therefore, special attention should be paid to adverse events that occurred at higher rates in Japanese patients than in non-Japanese patients in Studies MM-011 and MM-004, such as hepatic function abnormal and asthma.

4.(iii).D.(3).2) Safety of co-administration of pomalidomide and DEX

The applicant explained the safety of combined administration of pomalidomide and DEX as follows:

In Study MM-003, adverse events with a higher incidence in the pomalidomide + DEX group (300 patients) than in the DEX group (150 patients) by ≥5% included neutropenia (154 patients [51.3%] in the pomalidomide + DEX group and 30 patients [20.0%] in the DEX group; the same applies hereinafter in this section, for the order of the groups), cough (60 patients [20.0%] and 15 patients [10.0%]), leukopenia (38 patients [12.7%] and 8 patients [5.3%]), fatigue (101 patients [33.7%] and 40 patients [26.7%]), oedema peripheral (52 patients [17.3%] and 17 patients [11.3%]), upper respiratory tract infection (48 patients [16.0%] and 11 patients [7.3%]), constipation (65 patients [21.7%] and 22 patients [14.7%]), muscle spasms (46 patients [15.3%] and 11 patients [7.3%]), dyspnoea (59 patients [19.7%] and 22 patients [14.7%]), decreased appetite (38 patients [12.7%] and 11 patients [7.3%]), rash (23 patients [7.7%] and 1 patient [0.7%]), febrile neutropenia (28 patients [9.3%] and 0 patients), nasopharyngitis (25 patients [8.3%] and 1 patient [0.7%]), and peripheral sensory neuropathy (24 patients [8.0%] and 4 patients [2.7%]). Adverse events of ≥Grade 3 with an incidence rate higher in the pomalidomide + DEX group than in the DEX group by ≥3% include: neutropenia (145 patients [48.3%] and 23 patients [15.3%]), febrile neutropenia (28 patients [9.3%] and 0 patients), leukopenia (27 patients [9.0%] and 5 patients [3.3%]), pneumonia (38 patients [12.7%] and 12 patients [8.0%]), and neutrophil count decreased (14 patients [4.7%] and 1 patient [0.7%]). Serious adverse events with a higher incidence in the pomalidomide + DEX group than in the DEX group by ≥3% included pneumonia (39 patients [13.0%] and 13 patients [8.7%]), pyrexia (23 patients [7.7%] and 7 patients [4.7%]), and febrile neutropenia (17 patients [5.7%]and 0 patients).

PMDA considers as follows:

PMDA considers that the following information should be provided to healthcare professionals in clinical settings using a suitable method: (1) in Study MM-003, the incidence of serious adverse events, and the incidence of adverse events leading to treatment interruption tended to be higher in the pomalidomide + DEX group than in the DEX group (serious adverse events, 183 of 300 patients [61.0%] in the pomalidomide + DEX group and 80 of 150 patients [53.3%] in the DEX group; adverse events leading to treatment interruption, 206 of 300 patients [68.7%] and 73 of 150 patients [48.7%],

respectively); (2) as characteristic events of the findings in (1), the incidence of Grade ≥3 neutropenia, febrile neutropenia, and leukopenia in the pomalidomide + DEX group were ≥2-fold those in the DEX group.

In the following sections, PMDA reviewed the results of the pomalidomide + DEX groups in Studies MM-003 and MM-002, and the safety results of Studies MM-004 and MM-011, especially focusing on adverse events requiring special cautions, including adverse events leading to death, adverse events for which a causal relationship to pomalidomide could not be ruled out, and adverse events with a higher incidence in Japanese patients.

4.(iii).D.(3).3) Bone marrow depression

(a) Bone marrow depression

Adverse events categorized as the Standardised MedDRA Query (SMQ) "Haematopoietic cytopenias" and those as the MedDRA High Level Term (HLT) "Marrow depression and hypoplastic anaemias" were retrieved.

Bone marrow depression leading to death was not observed in Japanese patients.

Occurrence of bone marrow depression (with an incidence of ≥5% in any group)

Preferred Term	Number of patients (%)			
	MM-003	MM-002	MM-004	MM-011
	Pomalidomide/DEX	Pomalidomide/DEX		
	300 patients	112 patients	12 patients	36 patients
Anaemia	156 (52.0)	44 (39.3)	7 (58.3)	16 (44.4)
Neutropenia	154 (51.3)	53 (47.3)	12 (100)	25 (69.4)
Thrombocytopenia	89 (29.7)	26 (23.2)	8 (66.7)	17 (47.2)
Leukopenia	38 (12.7)	20 (17.9)	7 (58.3)	6 (16.7)
Febrile neutropenia	28 (9.3)	2 (1.8)	0	1 (2.8)
Lymphopenia	13 (4.3)	17 (15.2)	6 (50.0)	7 (19.4)
Neutrophil count decreased	15 (5.0)	8 (7.1)	0	0
White blood cell count decreased	8 (2.7)	8 (7.1)	0	0

Versions of MedDRA used in the studies: v14.0 (MM-003), v14.0 (MM-002), v14.1 (MM-004), and v16.1 (MM-011).

In the pomalidomide + DEX group of Study MM-003, bone marrow depression occurred in 236 of 300 patients (78.7%), and the events in 215 of 300 patients (71.7%) were Grade ≥3. Bone marrow depression for which a causal relationship to pomalidomide could not be ruled out occurred in 185 of 300 patients (61.7%), and the events in 168 of 300 patients (56.0%) were Grade ≥3. Serious bone marrow depression occurred in 36 of 300 patients (12.0%), and, of these, a causal relationship to pomalidomide could not be ruled out for the events in 26 of 300 patients (8.7%). Bone marrow depression leading to treatment discontinuation occurred in 4 of 300 patients (1.3%), and, of these, a causal relationship to pomalidomide could not be ruled out for the events in 3 of 300 patients (1.0%). Bone marrow depression leading to dose reduction or interruption occurred in 113 of 300 patients (37.7%), and, of these, a causal relationship to pomalidomide could not be ruled out for the events in 97 of 300 patients (32.3%).

In the pomalidomide + DEX group of Study MM-002, bone marrow depression occurred in 85 of 112 patients (75.9%), and, of these, the events in 63 of 112 patients (56.3%) were Grade ≥3. Bone marrow depression for which a causal relationship to pomalidomide could not be ruled out occurred in 77 of 112 patients (68.8%), and, of these, the events in 58 of 112 patients (51.8%) were Grade ≥3. Serious bone marrow depression occurred in 6 of 112 patients (5.4%), and, of these, a causal relationship to pomalidomide could not be ruled out for the events in 3 of 112 patients (2.7%). Bone marrow depression leading to treatment discontinuation occurred in 1 of 112 patients (0.9%), and its causal relationship to pomalidomide could not be ruled out. Bone marrow depression leading to dose reduction or interruption occurred in 18 of 112 patients (16.1%), and, of these, a causal relationship to pomalidomide could not be ruled out for the events in 16 of 112 patients (14.3%).

In Study MM-004, bone marrow depression occurred in 12 of 12 patients (100%), and, of these, the events in 10 of 12 patients (83.3%) were Grade ≥3, and for all the cases of bone marrow depression, a causal relationship to pomalidomide could not be ruled out. Serious bone marrow depression or bone marrow depression leading to treatment discontinuation was not observed. Bone marrow depression leading to dose reduction or interruption occurred in 3 of 12 patients (25.0%), and a causal relationship to pomalidomide could not be ruled out for any event in any of these patients.

In Study MM-011, bone marrow depression occurred in 30 of 36 patients (83.3%), and, of these, 27 of 36 patients (75.0%) were Grade ≥3. Bone marrow depression for which a causal relationship to pomalidomide could not be ruled out occurred in 29 of 36 patients (80.6%), and, of these, the events in 26 of 36 patients (72.2%) were Grade ≥3. Serious bone marrow depression occurred in 5 of 36 patients (13.9%), and a causal relationship to pomalidomide was ruled out for all the events in the 5 patients. Bone marrow depression leading to treatment discontinuation occurred in 1 of 36 patients (2.8%), and its causal relationship to pomalidomide could not be ruled out. Bone marrow depression leading to dose reduction or interruption occurred in 8 of 36 patients (22.2%), and a causal relationship to pomalidomide could not be ruled out for any of these events.

(b) Haemorrhage

Adverse events categorized as the MedDRA SMQ “haemorrhages” were retrieved.

In the pomalidomide + DEX group of Study MM-003, haemorrhage leading to death occurred in 3 of 300 patients (1.0%). These events were classified as cerebral haemorrhage, subarachnoid haemorrhage, and subdural haematoma (1 patient each), and a causal relationship to pomalidomide was ruled out for all of the events. In the pomalidomide + DEX group of Study MM-002, haemorrhage occurred in 2 of 112 patients (1.8%). These events were classified as cerebral haemorrhage and subarachnoid haemorrhage (1 patient each), and a causal relationship to pomalidomide was ruled out for both events. There was no haemorrhage leading to death in Study MM-004 or MM-011.

In the pomalidomide + DEX group of Study MM-003, haemorrhage occurred in 67 of 300 patients (22.3%), and, of these, the events in 12 of 300 patients (4.0%) were Grade ≥3. Haemorrhage for which a causal relationship to pomalidomide could not be ruled out occurred in 7 of 300 patients (2.3%), and, of these, the event in 1 of 300 patients (0.3%) was Grade ≥3. This event was classified as haemorrhoidal haemorrhage. Serious haemorrhage occurred in 11 of 300 patients (3.7%), and a causal relationship to pomalidomide was ruled out for these events. Haemorrhage leading to treatment discontinuation occurred in 1 of 300 patients (0.3%). This event was classified subdural haematoma, and a causal relationship to pomalidomide was ruled out for this event. Haemorrhage leading to dose reduction or interruption occurred in 2 of 300 patients (0.7%). These events were classified as haemorrhoidal haemorrhage and subarachnoid haemorrhage (1 patient, 0.3% each). For haemorrhoidal haemorrhage, a causal relationship to pomalidomide could not be ruled out.

In the pomalidomide + DEX group of Study MM-002, haemorrhage occurred in 30 of 112 patients (26.8%), and, of these, the events in 6 of 112 patients (5.4%) were Grade ≥3. Haemorrhage for which a causal relationship to pomalidomide could not be ruled out occurred in 9 of 112 patients (8.0%), and, of these, the event in 1 of 112 patients (0.9 %) was Grade ≥3. This event was classified as haemoglobin decreased. Serious haemorrhage occurred in 2 of 112 patients (1.8%), and a causal relationship to pomalidomide was ruled out for both events. Haemorrhage leading to treatment discontinuation was not observed. Haemorrhage leading to dose reduction or interruption occurred in 2 of 112 patients (1.8%), and a causal relationship to pomalidomide was ruled out for both events.

In Study MM-004, haemorrhage occurred in 3 of 12 patients (25.0%), and all of these events were Grade ≤2. Haemorrhage for which a causal relationship to pomalidomide could not be ruled out occurred in 1 in 12 patients (8.3%). Neither serious haemorrhage nor haemorrhage leading to dose reduction, interruption, or discontinuation was observed.

In Study MM-011, haemorrhage occurred in 10 of 36 patients (27.8%), and the events in 2 of 36 patients (5.6%) were Grade ≥3. These events were classified as blood fibrinogen decreased and shock haemorrhagic (1 patient, 2.8% each). Haemorrhage for which a causal relationship to pomalidomide could not be ruled out occurred in 3 of 36 patients (8.3%). These events were classified as conjunctival haemorrhage, epistaxis, and petechiae (1 patient, 2.8% each), and all of these events were Grade ≤2. Serious haemorrhage occurred in 2 of 36 patients (5.6%). These events were classified as blood fibrinogen decreased and shock haemorrhagic (1 patient, 2.8% each), and a causal relationship to pomalidomide was ruled out for both of these patients. Haemorrhage leading to dose reduction, interruption, or discontinuation was not observed.

In studies MM-003 and MM-011, all patients who were to receive pomalidomide were also to receive an antithrombotic drug or anticoagulant throughout the treatment period with the study drug [see "4.(iii).D.(3).5) Thromboembolism"]. PMDA asked the applicant to explain the events of haemorrhage in relation to co-administration of an antithrombotic drug or anticoagulant.

The applicant responded as follows:
The occurrences of haemorrhage in patients with and without co-administration of an antithrombotic drug or anticoagulant in each study were as follows: 59 of 277 patients (21.3%) in patients with co-administration and 8 of 23 patients (34.8%)* in patients without co-administration in the pomalidomide + DEX group of Study MM-003; 28 of 108 patients (25.9%) and 2 of 4 patients (50.0%), respectively, in the pomalidomide + DEX group of Study MM-002; 3 of 12 patients (25.0%) and 0 patients, respectively, in Study MM-004; 10 of 36 patients (27.8%) and 0 patients, respectively, in Study MM-011. Although analysis has a limitation due to the small number of patients who did not receive an antithrombotic drug or anticoagulant, an increased risk of haemorrhage was not observed in patients receiving concomitantly an antithrombotic drug or anticoagulant.

The applicant stated that, of the patients who experienced haemorrhage in the pomalidomide + DEX group of Study MM-003, 27 of 67 patients (40.3%) had concurrent thrombocytopenia, and 40 of 67 patients (59.7%) did not; of the patients who experienced Grade ≥3 haemorrhage, 7 of 12 patients (58.3%) had concurrent thrombocytopenia, and 5 of 12 patients (41.7%) did not. The applicant is being requested to provide data on the occurrence of concurrent thrombocytopenia in patients who experienced haemorrhage in clinical studies besides Study MM-003.

PMDA considers as follows:
With regard to bone marrow depression, the incidence of neutropenia and other forms of bone marrow depression is higher in Japanese patients than in foreign patients, in addition, serious adverse events have occurred for which a causal relationship to pomalidomide cannot be ruled out; therefore, caution should be exercised when administering pomalidomide. The occurrence of bone marrow depression in clinical studies should be provided to healthcare professionals in clinical settings using a suitable method; in addition, it is necessary to appropriately provide information on the criteria for dose reduction, interruption, and discontinuation defined in the clinical studies using the package insert and other relevant documents so that physicians are able to take appropriate measures when patients develop neutropenia or thrombocytopenia [see"4.(iii).D.(6).3) Criteria for dose reduction, interruption, and discontinuation"].

4.(iii).D.(3).4) Peripheral neuropathy
Adverse events categorized as the MedDRA SMQ "peripheral neuropathy" were retrieved.

In Study MM-003 (pomalidomide + DEX group), MM-002 (pomalidomide + DEX group), MM-004, or MM-011, peripheral neuropathy leading to death was not observed.

* The patient who received co-administration of an antithrombotic drug or anticoagulant after exhibiting haemorrhage was counted as a patient without co-administration.

In Study MM-003, peripheral neuropathy occurred in 66 of 300 patients (22.0%) in the pomalidomide + DEX group, and the events in 8 of 300 patients (2.7%) were Grade ≥3. Peripheral neuropathy for which a causal relationship to pomalidomide could not be ruled out occurred in 32 of 300 patients (10.7%), and the events in 5 of 300 patients (1.7%) were Grade ≥3. These were classified as polyneuropathy (2 patients, 0.7%), muscular weakness, peripheral motor neuropathy, and peroneal nerve palsy (1 patient, 0.3% each). Serious peripheral neuropathy or peripheral neuropathy leading to treatment discontinuation was not observed. Peripheral neuropathy leading to dose reduction or interruption occurred in 7 of 300 patients (2.3%), and a causal relationship to pomalidomide could not be ruled out for any of these events.

In the pomalidomide + DEX group of Study MM-002, peripheral neuropathy occurred in 29 of 112 patients (25.9%), and the events in 4 of 112 patients (3.6%) were Grade ≥3. Peripheral neuropathy for which a causal relationship to pomalidomide could not be ruled out occurred in 10 of 112 patients (8.9%), and all of these events were Grade ≤2. Serious peripheral neuropathy occurred in 1 of 112 patients (0.9%), and a causal relationship to pomalidomide was ruled out. Peripheral neuropathy leading to treatment discontinuation was not observed. Peripheral neuropathy leading to dose reduction or interruption occurred in 2 of 112 patients (1.8%), and for one of them, a causal relationship to pomalidomide could not be ruled out.

In Study MM-004, peripheral neuropathy occurred in 5 of 12 patients (41.7%), and all of these events were Grade ≤2. Peripheral neuropathy for which a causal relationship to pomalidomide could not be ruled out occurred in 2 of 12 patients (16.7%). Serious peripheral neuropathy or peripheral neuropathy leading to treatment discontinuation was not observed. Peripheral neuropathy leading to dose reduction or interruption occurred in 1 of 12 patients (8.3%), and a causal relationship to pomalidomide could not be ruled out.

In Study MM-011, peripheral neuropathy occurred in 4 of 36 patients (11.1%), and all of these events were Grade ≤2. Neither serious peripheral neuropathy nor peripheral neuropathy leading to dose reduction, interruption, or discontinuation was observed.

PMDA considers as follows:
Some patients experienced peripheral neuropathy leading to dose adjustment for which a causal relationship to pomalidomide cannot be ruled out; therefore, caution should be exercised when administering pomalidomide. It is necessary to advise careful administration of pomalidomide in the package insert or relevant documents so that physicians will closely monitor patients' conditions and take appropriate measures such as discontinuing treatment if any abnormalities are observed.

4.(iii).D.(3).5) Thromboembolism

Adverse events categorized as the MedDRA SMQ "embolic and thrombotic events" (thromboembolism [arterial], thromboembolism [arterial and venous], and thromboembolism [venous]) were retrieved.

In Study MM-003, thromboembolism leading to death occurred in 1 of 300 patients (0.3%) in the pomalidomide + DEX group. This event was ischaemic cerebral infarction, and a causal relationship to pomalidomide could not be ruled out. In Studies MM-002 (pomalidomide + DEX group), MM-004, and MM-011, thromboembolism leading to death was not observed.

In the pomalidomide + DEX group of Study MM-003, the number of patients in whom thromboembolism (arterial), thromboembolism (arterial and venous), and thromboembolism (venous) occurred was 5 of 300 patients (1.7%), 6 of 300 patients (2.0%), and 12 of 300 patients (4.0%), respectively (the same applies hereinafter in this section, for the order for the incidence of these thromboembolism), and, of those, the events in 3 of 300 patients (1.0%), 0 patients, and 5 of 300 patients (1.7%) were Grade ≥3. Thromboembolism for which a causal relationship to pomalidomide could not be ruled out occurred in 3 of 300 patients (1.0%), 4 of 300 patients (1.3%), and 10 of 300 patients (3.3%) and the events in 1 of 300 patients (0.3%), 0 patients, and 4 of 300 patients (1.3%) were Grade ≥3. Thromboembolism of Grade ≥3 for which a causal relationship to pomalidomide could not be ruled out was classified as deep vein thrombosis and pulmonary embolism (2 patients each), and ischaemic cerebral infarction (1 patient). Serious thromboembolism occurred in 3 of 300 patients (1.0%), 1 of 300 patients (0.3%), and 6 of 300 patients (2.0%) and a causal relationship to pomalidomide could not be ruled out for ischaemic cerebral infarction (1 patient), cerebrovascular accident (1 patient), pulmonary embolism (3 patients), or deep vein thrombosis (2 patients). Thromboembolism leading to treatment discontinuation was not observed. Thromboembolism leading to dose reduction or interruption occurred in 2 of 300 patients (0.7%), 2 of 300 patients (0.7%), and 6 of 300 patients (2.0%). Of these, a causal relationship to pomalidomide could not be ruled out for the events in 2 of 300 patients (0.7%), 2 of 300 patients (0.7%), or 5 of 300 patients (1.7%).

In the pomalidomide + DEX group of Study MM-002, thromboembolism (arterial), thromboembolism (arterial and venous), and thromboembolism (venous) occurred in 0 patients, 0 patients, and 3 of 112 patients (2.7%). The thromboembolic events observed in the 3 patients were all serious, and a causal relationship to pomalidomide could not be ruled out for any of these cases. These events were classified as deep vein thrombosis and pulmonary embolism (2 patients each) (including duplicates). Thromboembolism leading to treatment discontinuation was not observed. Thromboembolism leading to dose reduction or interruption occurred in 1 of 112 patients (0.9%). This event was classified as deep vein thrombosis and a causal relationship to pomalidomide could not be ruled out.

No thromboembolism occurred in Study MM-004 or Study MM-011.

In studies MM-003 and MM-011 stipulated, all patients who were to receive pomalidomide were also receive co-administration of an antithrombotic drug or anticoagulant throughout the treatment period with the study drug. PMDA asked the applicant to explain the specific condition of co-administration of an antithrombotic drug or anticoagulant during the treatment of pomalidomide and DEX.

The applicant responded as follows:
In clinical studies of thalidomide and lenalidomide, an increased risk of venous thromboembolism was reported; in addition, it was reported that the incidence of venous thromboembolism decreased after administration of aspirin to MM patients treated with thalidomide and lenalidomide (e.g., *Mayor Clin Proc.* 2005;80:1568-74). Therefore, co-administration of an antithrombotic drug or anticoagulant to all patients who were to receive pomalidomide was required in Studies MM-003 and MM-011. In Study MM-003, an antithrombotic drug or anticoagulant was co-administered in 278 of 300 patients (92.7%) in the pomalidomide + DEX group. The agents used in ≥10% of the patients were aspirin in 170 of 300 patients (56.7%), enoxaparin sodium in 47 of 300 patients (15.7%), and acetylsalicylate lysine (unapproved in Japan) in 35 of 300 patients (11.7%). No antithrombotic drug or anticoagulant was administered in 22 of 300 patients (7.3%), and none of these patients developed thromboembolism. Reasons for omitting co-administration of an antithrombotic drug or anticoagulant to these patients are unknown because no data were collected.

In Study MM-011, an antithrombotic drug or anticoagulant was co-administered to all patients who were to receive pomalidomide. The agents used were aspirin in 33 of 36 patients (91.7%), aspirin-dialuminate compounding agent in 4 of 36 patients (11.1%), and warfarin potassium in 1 of 36 patients (2.8%) (including duplicates).

PMDA considers as follows:
Death and other adverse events associated with thromboembolism for which a causal relationship to pomalidomide could not be ruled out have occurred after administration of pomalidomide and DEX. Therefore, caution should be exercised when administering pomalidomide. It is necessary to advise careful administration of pomalidomide in the package insert or relevant documents so that physicians will closely observe and take appropriate measures such as discontinuing treatment and preventive administration of an antithrombotic drug as necessary if any abnormalities are observed. In addition, healthcare professionals in clinical settings should be appropriately informed, through the package insert or relevant documents, that prophylactic administration of an antithrombotic drug or anticoagulant was required in all patients who were to receive pomalidomide and DEX in Studies MM-003 and MM-011.

4.(iii).D.(3).6) Infections
Adverse events categorized as the MedDRA System Organ Class (SOC) “Infections and infestations” were retrieved.

Infections leading to death occurred in 11 of 300 patients (3.7%) in the pomalidomide + DEX group of Study MM-003. These events were classified as pneumonia (3 patients; 1.0%), sepsis (2 patients; 0.7%), bronchopneumonia, Klebsiella sepsis, lower respiratory tract infection, lung infection, pneumonia pneumococcal, and septic shock (1 patient, 0.3% each). A causal relationship to pomalidomide could not be ruled out for pneumonia (3 patients), Klebsiella sepsis, lower respiratory tract infection, lung

infection, pneumonia pneumococcal, or septic shock (1 patient each). In the pomalidomide + DEX group of Study MM-002, infections leading to death occurred in 3 of 112 patients (2.7%). These events were classified as pneumonia (2 patients; 1.8%) and bronchopneumonia (1 patient; 0.9%). In one of the patients with pneumonia, a causal relationship to pomalidomide could not be ruled out. No infection-related death was found in Study MM-004. Of 36 patients in Study MM-011, 1 patient (2.8%) died of pneumonia, for which a causal relationship to pomalidomide could not be ruled out.

In the pomalidomide + DEX group of Study MM-003, infections occurred in 203 of 300 patients (67.7%), and the events in 91 of 300 patients (30.3%) were Grade ≥3. Infections for which a causal relationship to pomalidomide could not be ruled out occurred in 72 of 300 patients (24.0%), and the events in 40 of 300 patients (13.3%) were Grade ≥3. Serious infections occurred in 97 of 300 patients (32.3%). Of these, a causal relationship to pomalidomide could not be ruled out for infections in 41 of 300 patients (13.7%). The most common serious infection was pneumonia (39 of 300 patients, [13.0%]). Of these, a causal relationship to pomalidomide could not be ruled out in 19 of 300 patients (6.3%). Infections leading to discontinuation occurred in 6 of 300 patients (2.0%). Of these, a causal relationship to pomalidomide could not be ruled out for the events in 2 of 300 patients (0.7%). Infections leading to dose reduction or interruption occurred in 68 of 300 patients (22.7%). Of these, a causal relationship to pomalidomide could not be ruled out for events in 34 of 300 patients (11.3%).

In the pomalidomide + DEX group of Study MM-002, infections occurred in 80 of 112 patients (71.4%), and the events in 43 of 112 patients (38.4%) were Grade ≥3. Infections for which a causal relationship to pomalidomide could not be ruled out occurred in 25 of 112 patients (22.3%), and the events in 12 of 112 patients (10.7%) were Grade ≥3. Serious infections occurred in 38 of 112 patients (33.9%), and a causal relationship to pomalidomide could not be ruled out for the events in 9 of 112 patients (8.0%). The most common serious infection was pneumonia (21 of 112 patients [18.8%]). Of these, a causal relationship to pomalidomide could not be ruled out for the events in 6 of 112 patients (5.4%). Infections leading to discontinuation occurred in 1 of 112 patients (0.9%), and a causal relationship to pomalidomide was ruled out. Infections leading to dose reduction or interruption occurred in 34 of 112 patients (30.4%). Of these, a causal relationship to pomalidomide could not be ruled out for the events in 8 of 112 patients (7.1%).

In Study MM-004, infections occurred in 10 of 12 patients (83.3%), and the events in 4 of 12 patients (33.3%) were Grade ≥3. Infections for which a causal relationship to pomalidomide could not be ruled out occurred in 6 of 12 patients (50.0%), and the events in 3 of 12 patients (25.0%) were Grade ≥3. Serious infections occurred in 3 of 12 patients (25.0%). These events were classified as pneumonia (2 patients; 16.7%) and lung infection (1 patient; 8.3%). Of these events, a causal relationship to pomalidomide could not be ruled out for pneumonia and lung infection (1 patient each). Infections leading to discontinuation were not observed. Infections leading to dose reduction or interruption occurred in 4 of 12 patients (33.3%). Of these, a causal relationship to pomalidomide could not be ruled out for the events in 3 of 12 patients (25.0%).

In Study MM-011, infections occurred in 13 of 36 patients (36.1%), and the events in 3 of 36 patients (8.3%) were Grade ≥3. Infections for which a causal relationship to pomalidomide could not be ruled out occurred in 7 of 36 patients (19.4%), and the events in 2 of 36 patients (5.6%) were Grade ≥3. Serious infections occurred in 3 of 36 patients (8.3%). These events were classified as pneumonia (3 patients; 8.3%), and pneumonia pneumococcal (1 patient; 2.8%). Of these events, a causal relationship to pomalidomide could not be ruled out for pneumonia in 2 patients. Infections leading to discontinuation occurred in 1 of 36 patients (2.8%), and a causal relationship to pomalidomide could not be ruled out. Infections leading to dose reduction or interruption occurred in 1 in 36 patients (2.8%), and a causal relationship to pomalidomide could not be ruled out.

PMDA considers as follows:
With regard to infections, the incidence of respiratory system infections such as lung infection and bronchopneumonia is higher in Japanese patients than in foreign patients, and death and other adverse events for which a causal relationship to pomalidomide could not be ruled out have occurred after administration of pomalidomide. Therefore, caution should be exercised when administering pomalidomide. The information on the occurrence of infections in clinical studies should be provided to healthcare professionals in clinical settings using a suitable method; in addition, it is necessary to advise careful administration of pomalidomide in the package insert or relevant documents so that physicians will perform hematological examinations and imaging tests, as necessary, and take appropriate measures if any abnormalities are observed.

4.(iii).D.(3).7) Cardiac arrhythmia

Adverse events categorized as the MedDRA SMQ “cardiac arrhythmias” were retrieved.

In Study MM-003, cardiac arrhythmia that leading to death occurred in 3 of 300 patients (1.0%) in the pomalidomide + DEX group. These were classified as cardiac arrest, cardio-respiratory arrest, and sudden death (1 patient, 0.3% each), and a causal relationship to pomalidomide could not be ruled out for sudden death. No deaths occurred as a result of cardiac arrhythmia in Study MM-002 (pomalidomide + DEX group), MM-004, or MM-011.

In Study MM-003, cardiac arrhythmia occurred in 51 of 300 (17.0%) in the pomalidomide + DEX group, and the events in 17 of 300 patients (5.7%) were Grade ≥3. Cardiac arrhythmia for which a causal relationship to pomalidomide could not be ruled out occurred in 9 of 300 patients (3.0%), and the events in 3 of 300 patients (1.0%) were Grade ≥3. These were classified as sudden death, syncope, and tachyarrhythmia (1 patient, 0.3% each). Serious cardiac arrhythmia occurred in 14 of 300 patients (4.7%). These were classified as atrial fibrillation (4 patients; 1.3%), syncope (2 patients; 0.7%), atrial flutter, cardiac arrest, cardio-respiratory arrest, loss of consciousness, sick sinus syndrome, sudden death, tachyarrhythmia, and ventricular tachycardia (1 patient, 0.3% each). Of these, a causal relationship to pomalidomide could not be ruled out for atrial fibrillation, loss of consciousness, sudden

death, and tachyarrhythmia (1 patient each). Cardiac arrhythmia leading to discontinuation was not observed. Cardiac arrhythmia leading to dose reduction or interruption were observed in 7 of 300 patients (2.3%). Among these, a causal relationship to pomalidomide could not be ruled out in 4 of 300 patients (1.3%).

In Study MM-002, cardiac arrhythmia occurred in 20 of 112 patients (17.9%) in the pomalidomide + DEX group, and the events in 7 of 112 patients (6.3%) were Grade ≥3. Cardiac arrhythmia for which a causal relationship could not be ruled out occurred in 2 of 112 patients (1.8%), and the event in 1 of 112 patients (0.9%) was Grade ≥3. These were classified as ECG QT prolonged. Serious cardiac arrhythmia occurred in 4 of 112 patients (3.6%). These were classified as atrial fibrillation (3 patients; 2.7%) and ECG QT prolonged (1 patient; 0.9%). For the ECG QT prolonged, a causal relationship to pomalidomide could not be ruled out. Cardiac arrhythmia leading to discontinuation occurred in 1 of 112 patients (0.9%), and a causal relationship to pomalidomide could not be ruled out. Cardiac arrhythmia leading to dose reduction or interruption occurred in 3 of 112 patients (2.7%). Among these, a causal relationship to pomalidomide could not be ruled out in 1 of 112 patients (0.9%).

In Study MM-004, cardiac arrhythmia occurred in 3 of 12 patients (25.0%), and all of these events were Grade ≤2. Among these, a causal relationship to pomalidomide could not be ruled out in 1 of 12 patients (8.3%). Serious cardiac arrhythmia or cardiac arrhythmia leading to discontinuation was not observed. Cardiac arrhythmia leading to dose reduction or interruption occurred in 1 of 12 patients (8.3%), and a causal relationship to pomalidomide was ruled out.

In Study MM-011, cardiac arrhythmia occurred in 2 of 36 patients (5.6%), and the event in 1 of 36 patients (2.8%) was Grade ≥3. Cardiac arrhythmia for which a causal relationship to pomalidomide could not be ruled out was not observed. Neither serious cardiac arrhythmia nor cardiac arrhythmia leading to dose reduction, interruption, or discontinuation was observed.

PMDA considers as follows:
The incidence of cardiac arrhythmia such as atrial fibrillation tended to be higher in Japanese patients than in foreign patients, and death and other adverse events for which a causal relationship to pomalidomide could not be ruled out have occurred after administration of pomalidomide. Therefore, caution should be exercised when administering pomalidomide. The information on the occurrence of cardiac arrhythmia in clinical studies should be provided using the package insert or relevant documents; in addition, it is necessary to advise careful administration of pomalidomide so that physicians will perform a 12-lead ECG during treatment with pomalidomide, and take appropriate measures if any abnormalities are observed.

4.(iii).D.(3).8) Cardiac failure

Adverse events categorized as the MedDRA SMQ “cardiac failure” were retrieved.

In the pomalidomide + DEX group of Study MM-002, cardiac failure congestive leading to death occurred in 1 of 112 patients (0.9%), and a causal relationship to pomalidomide was ruled out. In Studies MM-003 (pomalidomide + DEX group), MM-004, and MM-011, cardiac failure leading to death was not observed.

In the pomalidomide + DEX group of Study MM-003, cardiac failure occurred in 6 of 300 patients (2.0%), cardiac failure congestive in 2 of 300 patients (0.7%), cardiac failure acute in 1 of 300 patients (0.3%), pulmonary oedema in 1 of 300 (0.3%), and acute pulmonary oedema in 2 of 300 patients (0.7%); of those, the respective events of Grade ≥3 were reported in 3 of 300 patients (1.0%), 1 of 300 patients (0.3%), 0 patients, 1 of 300 patients (0.3%), and 2 of 300 patients (0.7%). Among the Grade ≥3 adverse events, cardiac failure in 3 patients, cardiac failure congestive in 1 patient, and acute pulmonary oedema in 1 patient were considered as serious. Of these events, a causal relationship to pomalidomide could not be ruled out for cardiac failure in 1 patient.

In the pomalidomide + DEX group of Study MM-002, cardiac failure congestive occurred in 4 of 112 patients (3.6%), and the events in 3 of 112 patients (2.7%) were Grade ≥3. Of the Grade ≥3 adverse events, 2 of 3 events were considered as serious. A causal relationship to pomalidomide was ruled out for all of the events.

In Studies MM-004 and MM-011, cardiac failure congestive occurred in 1 patient in each study. Both were non-serious events and a causal relationship to pomalidomide was ruled out.

PMDA considers as follows:
A serious adverse event of cardiac failure for which a causal relationship could not be ruled out has occurred after administration of pomalidomide. Therefore, the occurrence of cardiac failure in clinical studies should be informed through the package insert or relevant documents.

4.(iii).D.(3).9) Acute renal failure

Adverse events categorized as the MedDRA SMQ “acute renal failure” were retrieved.

In the pomalidomide + DEX group of Study MM-003, acute renal failure leading to death occurred in 3 of 300 patients (1.0%), and a causal relationship to pomalidomide was ruled out for all of these events. In Studies MM-002 (pomalidomide + DEX group), MM-004, and MM-011, acute renal failure leading to death was not observed.

In the pomalidomide + DEX group of Study MM-003, acute renal failure occurred in 48 of 300 patients, (16.0%), and the events in 24 of 300 patients (8.0%) were Grade ≥3. Acute renal failure for which a causal relationship to pomalidomide could not be ruled out occurred in 6 of 300 patients (2.0%), and the events in 4 of 300 patients (1.3%) were Grade ≥3. The events were classified as renal failure in 3 patients (1.0%), acute renal failure and glomerular filtration rate decreased (1 patient, 0.3% each) (including

duplicates). Serious acute renal failure occurred in 22 of 300 patients (7.3%). These events were classified as acute renal failure in 11 patients (3.7%), renal failure in 8 patients (2.7%), renal impairment in 4 patients (1.3%), and blood creatinine increased in 1 patient (0.3%). Of these events, a causal relationship to pomalidomide could not be ruled out for renal failure (3 patients) and acute renal failure (1 patient). Acute renal failure leading to discontinuation occurred in 3 of 300 patients (1.0%), and a causal relationship to pomalidomide could not be ruled out for the events in 2 of 300 patients (0.7%). Acute renal failure leading to dose reduction or interruption occurred in 13 of 300 patients (4.3%), and a causal relationship to pomalidomide could not be ruled out for the events in 3 of 300 patients (1.0%).

In the pomalidomide + DEX group of Study MM-002, acute renal failure occurred in 21 of 112 patients (18.8%), and, of these, the events in 9 of 112 patients (8.0%) were Grade ≥3. A causal relationship to pomalidomide was ruled out in these patients. Serious acute renal failure occurred in 8 of 112 patients (7.1%), and a causal relationship to pomalidomide was ruled out for the events in these patients. Acute renal failure leading to discontinuation of treatment occurred in 2 of 112 patients (1.8%), and a causal relationship to pomalidomide was ruled out for the events in these patients. Acute renal failure leading to dose reduction or interruption occurred in 4 of 112 patients (3.6%), and a causal relationship to pomalidomide was ruled out for the events in these patients.

In Study MM-004, acute renal failure occurred in 3 of 12 patients (25.0%), and all of these events were Grade ≤2. Acute renal failure for which a causal relationship to pomalidomide could not be ruled out occurred in 2 of 12 patients (16.7%). Neither serious acute renal failure nor acute renal failure leading to dose reduction, interruption, or discontinuation was observed.

In Study MM-011, acute renal failure occurred in 2 of 36 patients (5.6%), and the events in 1 of 36 patients (2.8%) were Grade ≥3. No acute renal failure for which a causal relationship to pomalidomide could not be ruled out was observed. Neither serious acute renal failure nor acute renal failure leading to discontinuation was observed. Acute renal failure leading to dose reduction or interruption occurred in 1 of 36 patients (2.8%).

PMDA considers as follows:
A serious adverse event for which a causal relationship could not be ruled out has occurred after administration of pomalidomide. Therefore, caution should be exercised when administering pomalidomide. It is necessary to advise careful administration in the package insert or relevant documents so that physicians will perform hematological examinations, urine tests, etc., on a regular basis during treatment with pomalidomide, and take appropriate measures if any abnormalities are observed.

4.(iii).D.(3).10) Interstitial lung disease

Adverse events categorized as the MedDRA PT “Interstitial lung disease” were retrieved (the table below). In Studies MM-004 and MM-011, interstitial lung disease was not observed.

List of patients who developed interstitial lung disease in clinical studies

Study	Group	Age	Sex	Time of onset*	Causal relationship	Degree of seriousness	Outcome	Grade
MM-003	Pomalidomide + DEX	57	F	431 days	No	Non-serious	Resolved	2
MM-002	Pomalidomide alone	65	F	56 days	Yes	Serious	Resolving	3
				66 days	No	Non-serious	Ongoing	2
IFM 2009-02	Pomalidomide + DEX	42	M	87 days	Yes	Serious	Resolved	2

*, Day 1 is defined as the day on which administration of study drug was started.

PMDA considers as follows:

With regard to interstitial lung disease, serious adverse events for which a causal relationship could not be ruled out have occurred after administration of pomalidomide. Therefore, the occurrence of interstitial lung disease in clinical studies should be informed through the package insert or relevant documents.

4.(iii).D.(3).11) Tumour lysis syndrome

Adverse events corresponding to the MedDRA PT "tumour lysis syndrome" were retrieved.

No tumour lysis syndrome was observed in patients in the pomalidomide + DEX group. Tumour lysis syndrome was observed in 1 patient in the pomalidomide group in Study MM-002. This episode was considered to be Grade 3 serious tumour lysis syndrome, and a causal relationship to pomalidomide could not be ruled out.

PMDA considers as follows:

Tumour lysis syndrome, a serious adverse event for which a causal relationship could not be ruled out, has occurred after administration of pomalidomide. Therefore, the information on the occurrence of tumour lysis syndrome in clinical studies should be provided using the package insert or relevant documents.

4.(iii).D.(3).12) Others

(a) Teratogenicity

Like thalidomide, the results of embryonic and fetal development studies in pregnant female rats and rabbits orally given pomalidomide have shown that pomalidomide is teratogenic [see "3.(iii).A.(5). Reproductive and developmental toxicity"]. The applicant explained the availability of clinical information on exposure to pomalidomide during pregnancy and the possible effects on fetuses, neonates, and perinatal mothers as follows:

No confirmed cases of exposure to pomalidomide during pregnancy have been reported (data cut-off on [redacted], 20[redacted]). A piece of related information concerning exposure during pregnancy was obtained in

which a pregnant woman is known to have worked at the site where pomalidomide was manufactured, however, this cannot be categorized as exposure during pregnancy because this woman neither entered the manufacturing area nor took any dose of pomalidomide. There is thus no clinical information of exposure to pomalidomide during pregnancy, and therefore the possible effects of pomalidomide on fetuses, neonates, and perinatal mothers are unknown. However, given that pomalidomide is a derivative of thalidomide, which has been shown to be teratogenic in humans, and that pomalidomide has been shown to cause fetal teratogenicity in reproductive and developmental toxicity studies in rabbits and rats, it cannot be ruled out that pomalidomide has an effect on fetuses, neonates, and perinatal mothers.

PMDA considers as follows:
After the market launch of pomalidomide, strict safety measures will be needed to avoid exposing pregnant women to pomalidomide [see "4.(iii).D.(8) Proper management procedures"]

(b) Somnolence, depressed level of consciousness, confusion, fatigue, and dizziness/vertigo
The applicant stated that it is necessary to advise patients that driving a car or operating machinery may be riskier than usual during treatment with pomalidomide because neuropsychiatric disorder and consciousness disturbed have been reported in Japanese and foreign clinical studies. Also, the applicant explained the occurrence of adverse event categorized as the MedDRA PT "Somnolence, depressed level of consciousness, confusion, fatigue, dizziness, vertigo, and vertigo CNS origin" as follows:

In Studies MM-003 (pomalidomide + DEX group), MM-002, and MM-011, the occurrence of somnolence, depressed level of consciousness, confusion, fatigue, dizziness, vertigo, and vertigo CNS origin is summarized in the table below. Among adverse events evaluated as Grade ≥3, a causal relationship to pomalidomide could not be ruled out for the following: confusion in 2 patients (Study MM-003), fatigue in 18 patients (10 patients in Study MM-003, and 8 patients in Study MM-002), dizziness in 4 patients (3 patients in Study MM-003, and 1 patient in Study MM-002), and vertigo CNS origin in 1 patient (Study MM-003). In Study MM-004, confusion and fatigue (1 patient each) were observed, and both were assessed as Grade ≤2 and non-serious. A causal relationship to pomalidomide was ruled out for either event.

Occurrence of somnolence, depressed level of consciousness, confusion, fatigue, and dizziness/vertigo

Preferred term (PT)	Number of patients (%)					
	MM-003 (pomalidomide +DEX group) 300 patients		MM-002* 257 patients		MM-011 36 patients	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Somnolence	4 (1.3)	1 (0.3)	7 (2.7)	0	2 (5.6)	0
Depressed level of consciousness	5 (1.7)	3 (1.0)	0	0	0	0
Confusion	13 (4.3)	8 (2.7)	19 (7.4)	4 (1.6)	0	0
Fatigue	101 (33.7)	16 (5.3)	87 (33.9)	17 (6.6)	2 (5.6)	0
Dizziness	37 (12.3)	4 (1.3)	27 (10.5)	1 (0.4)	1 (2.8)	0
Vertigo	11 (3.7)	1 (0.3)	1 (0.4)	0	1 (2.8)	0
Vertigo CNS origin	1 (0.3)	1 (0.3)	0	0	0	0

Versions of MedDRA used in the studies: v14.0 (MM-003), v14.0 (MM-002), v14.1 (MM-004), and v16.1 (MM-011); *, sum of phase I and phase II parts of study

PMDA considers as follows:

Grade ≥3 adverse events of somnolence, depressed level of consciousness, confusion, fatigue, and dizziness/vertigo, for which a causal relationship could not be ruled out have occurred after administration of pomalidomide. Therefore, caution should be exercised when using pomalidomide. It is necessary to advise caution in operating machinery associated with hazardous activities including driving a car during treatment with pomalidomide. In addition, the occurrence of these adverse events in clinical studies should be informed through the package insert or relevant documents.

(c) Second primary malignancy

The applicant explained the second primary malignancy as follows:

Among foreign studies in which patients with MM were enrolled, second primary malignancy was assessed in Studies MM-003 and MM-002. Second primary malignancies were observed in 5 patients (4 patients in the pomalidomide + DEX group, and 1 patient in DEX group) and 8 patients (2 patients in the pomalidomide + DEX, and 6 patients in the pomalidomide group), respectively (the table below). In Studies MM-004 and MM-011, second primary malignancy was not observed.

List of patients who developed second primary malignancies in the clinical studies (pomalidomide-administered patients)

Study	Group	Age	Sex	Name	Onset * (Day)	Causal relation	Degree of seriousness	Outcome	Grade
MM-003	Pomalidomide + DEX	59	M	Basal cell carcinoma	60	No	Serious	Unresolved	3
		78	M	Basal cell carcinoma	105	No	Serious	Resolved	2
				Basal cell carcinoma	136	No	Serious	Resolved	2
				Basal cell carcinoma	165	No	Serious	Resolved	2
				Basal cell carcinoma	186	No	Serious	Resolved	2
		67	F	Epithelial tumor	182	Yes	Serious	Sequelae	3
		84	F	Epithelial tumor	58	No	Serious	Death	5
MM-002	Pomalidomide	75	M	Squamous cell carcinoma of skin	14	No	Non-serious	Resolved	1
				Squamous cell carcinoma	163	No	Non-serious	Resolved	1
		76	M	Basal cell carcinoma	92	Unknown	Unknown	Unknown	Unknown
		73	M	Basal cell carcinoma	104	No	Non-serious	Resolved	1
		53	M	Neoplasm skin	71	No	Non-serious	Resolved	1
		65	F	Plasma cell leukemia	67	No	Serious	Resolved	3
		68	F	Thyroid neoplasms	42	No	Non-serious	Ongoing	1
	Pomalidomide + DEX	67	M	Neoplasm skin	126	No	Non-serious	Ongoing	1
		67	M	Colon cancer	312	No	Serious	Ongoing	4

*: Day 1 is defined as the day on which administration of study drug was started

PMDA considers as follows:

Although a causal relationship to pomalidomide has not been clearly demonstrated for any of the second primary malignancies, the occurrence of second primary malignancies in clinical studies should be informed through the package insert or relevant documents.

4.(iii).D.(4) Clinical positioning

PMDA verified the descriptions on co-administration of pomalidomide and DEX in the treatment of MM in representative clinical oncology textbooks published in and out of Japan, and clinical practice guidelines outside Japan as follows:

Clinical practice guidelines

- *The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology* (version 2, 2015): The guidelines recommend pomalidomide + DEX as a therapeutic regimen in MM patients who have received at least two prior therapies, including bortezomib and immunomodulatory agents (lenalidomide or bortezomib), and have demonstrated disease progression on or within 60 days of completion of the last therapy.
- The U.S. National Cancer Institute Physician Data Query (NCI-PDQ, June 24 2014 version): This document states that phase I and II studies of pomalidomide in patients after treatment with bortezomib or lenalidomide yielded a response rate of 26% to 63%. It also states that pomalidomide

has a better safety profile than other drugs of the same class, as shown by a lower incidence of neuropathy and asthenia than with thalidomide and a lower incidence of bone marrow depression and rash than with lenalidomide.

Textbooks

- *Wintrobe's Clinical Hematology*, Thirteenth Edition (Lippincott Williams & Wilkins, 2013, USA): This book states that in a foreign phase II study (*J Clin Oncol*. 2009;27:5008-14), patients with relapsed MM who had received 2 or 3 prior regimens responded to a combination of 2 mg of pomalidomide daily and DEX regardless of the composition of the prior regimens. However, it states that the optimum dosage and administration of pomalidomide is still unknown.
- *Therapeutic Manual of Multiple Myeloma*, First Edition (Nankodo, 2012, Japan): This book states that the results of Study MM-001 and other studies suggested that pomalidomide is effective even in patients with MM refractory to new therapeutic agents such as bortezomib and lenalidomide.

PMDA considers the clinical positioning of pomalidomide as follows:
From the review results in "4.(iii).D.(2) Efficacy" and "4.(iii).D.(3) Safety," and the statements in the above publications, combination of pomalidomide and DEX can be positioned as a treatment option for patients with relapsed or refractory MM after treatment with lenalidomide and bortezomib.

4.(iii).D.(5) Indications

Proposed indication of pomalidomide was the treatment of "Relapsed or refractory multiple myeloma." The applicant, when it filed the new drug application, also explained its plan to advise, in the "Precautions for Indication" section of the package insert, that pomalidomide be administered to patients already treated with lenalidomide and proteasome inhibitors, after a careful review of other treatment options.

PMDA considers, as discussed in "4.(iii).D.(2) Efficacy" and "4.(iii).D.(4) Clinical positioning," the proposed indication, "Relapsed or refractory multiple myeloma," is acceptable on condition that the following measures be taken: (i) the "Clinical studies" section of the package insert provide the information that patients enrolled in the clinical studies were those with relapsed or refractory MM who had previously treated with lenalidomide and bortezomib, based on the results of Studies MM-003 and MM-011 in which such patients were enrolled; (ii) the "Precautions for Indication" section provide the advice below.

- Eligible patients should be carefully selected after the other therapeutic options are thoroughly reviewed by the physicians who fully understand the efficacy and safety of pomalidomide as well as prior treatment history of the patients enrolled in clinical studies described in the "Clinical studies" section.

4.(iii).D.(6) Dosage and administration

As a result of the following review, PMDA concluded that it is acceptable to specify the dosage and administration of pomalidomide, according to the applicant's proposal, as follows: "In combination with dexamethasone, the usual adult dosage is 4 mg as pomalidomide given orally once daily on a 21-day on/7-day off schedule; The dose may be reduced according to the patient's condition." In addition, the following items should be specified in the "Precautions for dosage and administration" section:

- Cancer chemotherapy including pomalidomide should be undertaken only after the contents of "Clinical studies" section, especially, dosage and administration, are fully understood.
- When adverse drug reactions of Grade 3 or 4 develop (excluding decreased platelet count and decreased neutrophil count), administration of pomalidomide should be interrupted until these conditions have resolved to Grade ≤2, and resume administration at 1 mg less than the dose before interruption. Resume administration depending on the patient's condition. If adverse drug reactions develop again after dose reductions to 1 mg, administration of pomalidomide should be discontinued.
- If decreased platelet count or decreased neutrophil count occurs, consider treatment interruption or other measures with reference to the table below.

Guide on dose interruption or other measures for decreased platelet count or decreased neutrophil count

	Platelet/neutrophil counts	Actions during treatment, and guide on dose reduction at the resumption of pomalidomide treatment
Decreased platelet count	Decreased to <25,000/μL	Interrupt pomalidomide treatment until platelet count returns to ≥50,000/μL. Resume pomalidomide treatment at 1 mg less than the dose before interruption. Follow the same steps if the adverse drug reaction appears after the resumption of treatment. If the adverse drug reaction appears after dose reductions to 1 mg, administration of pomalidomide should be discontinued.
Decreased neutrophil count	Decreased to <500/μL, or febrile neutropenia (neutrophil count of <1000/μL, and at the same time, fever of >38.3°C at least once, or ≥38°C continuously for >1 hour)	Interrupt pomalidomide treatment until neutrophil count returns to ≥1000/μL. Resume pomalidomide treatment at 1 mg less than the dose before interruption. Consider treatment with G-CSF if it has not been used. Follow the same steps above if the adverse drug reaction appears after the resumption of treatment. If the adverse drug reaction appears after dose reductions to 1 mg, administration of pomalidomide should be discontinued.

4.(iii).D.(6).1) Dosage and administration

The applicant explained that dosage and administration of pomalidomide were determined as follows: In Study MM-001 (foreign phase I study), the following regimens were studied to determine MTD: 1, 2, 5, or 10 mg QD of pomalidomide for 4 weeks (Cohort 1); and 1, 2, 5, or 10 mg QOD of pomalidomide for 4 weeks (Cohort 2). The MTD was determined to be 2 mg (once daily) or 5 mg (on alternate days). In the phase I part of Study MM-002 (foreign phase I/II study), the MTD of pomalidomide was studied by administration of pomalidomide on Days 1 to 21 on a 28-day cycle to alleviate bone marrow depression; and the MTD was determined to be 4 mg. In the phase II part of Study MM-002, the efficacy

and safety of pomalidomide were compared between pomalidomide group and pomalidomide + DEX group with the same pomalidomide dosage regimen (pomalidomide 4 mg QD on Days 1-21 on a 28-day cycle) for both groups. Higher efficacy was demonstrated in the pomalidomide + DEX group than in the pomalidomide group, and the dosage regimen was determined to be tolerable based on the safety results. In Study MM-003 (foreign phase III study), the efficacy and safety in the DEX group and pomalidomide + DEX group were compared (pomalidomide dosage regimen was 4 mg QD on Days 1-21 on a 28-day cycle). Higher efficacy was demonstrated in the pomalidomide + DEX group than in the DEX group, and the dosage regimen was tolerable based on the safety results. Study MM-004 (Japanese phase I study) was designed for pomalidomide to be administered at 2 mg QD (in the first cycle) on Days 1 to 21 on a 28-day cycle, and at an escalated dose of 4 mg QD in the second cycle or later; and the results showed DLTs at 2 and 4 mg occurred in 1 of 6 patients (Grade 4 neutropenia) and 0 patients, respectively, and 4 mg QD was also found to be tolerable in Japanese patients with MM. In Study MM-011 (Japanese phase II study) in which patients received pomalidomide 4 mg QD on Days 1 to 21 on a 28-day cycle in combination with DEX, the dosage regimen demonstrated efficacy in Japanese patients with MM, and was determined to be tolerable based on the safety results. Based on the results above, the dosage and administration investigated in Studies MM-003 and MM-011 was selected as the proposed dosage and administration.

Proposed dosage and administration directed that pomalidomide be administered in combination with DEX, for which the applicant explained the rationale as follows:

On the basis of several studies reporting that higher efficacy can be expected by administering thalidomide or lenalidomide in combination with DEX compared with each monotherapy (*Ann Oncol*. 2001;12:991-5; *Blood*. 2000;96:2943-50; *J Clin Oncol*. 2003;21:16-9), combination of pomalidomide and DEX has been proposed. In major clinical studies of pomalidomide, such as Studies MM-003 and MM-011, oral dose of 40 mg of DEX at a time was administered on Days 1, 8, 15, and 22 on a 28-day cycle, on the ground of clinical study for lenalidomide. For patients older than 75 years, the dose of DEX was determined to be 20 mg at a time because drug-induced adverse events are expected to occur at a higher frequency in elderly patients due to a decline in physiological functions and multiple organ disorders due to aging.

PMDA considers as follows:
As a result of review in “4.(iii).D.(2) Efficacy” and “4.(iii).D.(3) Safety,” PMDA has concluded that it is acceptable to select oral doses of 4 mg of pomalidomide QD on Days 1 to 21 on a 28-day cycle in combination with DEX as the dosage and administration of pomalidomide for patients with relapsed or refractory MM. PMDA has also considered that the rule for combination regimens with DEX specified in Studies MM-003 and MM-011 should be included in the “Precautions for Indication” section so that the regimens are regarded as a guide to the administration of pomalidomide.

4.(iii).D.(6).2) Administration of pomalidomide in combination with other antineoplastic drugs

PMDA asked the applicant to explain whether or not pomalidomide can be administered in combination with other antineoplastic drugs other than DEX.

The applicant responded as follows:

The efficacy and safety of pomalidomide in combination with other antineoplastic drugs than DEX are unknown because study results are not available at this point. However, a foreign phase I study (Study CC-4047-MM-005) has been being conducted since March 2012 to determine the MTD of pomalidomide in combination with bortezomib and DEX.

PMDA considers as follows:

The efficacy and safety of pomalidomide in combination with other antineoplastic drugs than DEX are unknown; therefore, administration of pomalidomide in combination with other antineoplastic drugs is not recommended. The statement that the safety and efficacy of pomalidomide in combination with other antineoplastic drugs than DEX have not been established should be included in appropriate information materials and provided to healthcare professionals in clinical settings.

4.(iii).D.(6).3) Criteria for dose reduction, interruption, and discontinuation

PMDA asked the applicant to explain how the applicant had determined the proposed criteria for dose reduction, interruption, and discontinuation in the event of adverse drug reactions to be included in the "Precautions for dosage and administration" section of the package insert.

The applicant responded as follows:

The proposed criteria for dose reduction, interruption, and discontinuation in the event of adverse drug reactions included in the "Precautions for dosage and administration" section are based on the corresponding criteria used in Study MM-002. Decreased platelet count and decreased neutrophil count warrant particular attention because these are major adverse drug reactions to pomalidomide, and the criteria for dose reduction, interruption, and discontinuation in the event of decreased platelet count and decreased neutrophil count were specified based on specific clinical laboratory test values. Therefore, advice on the measures for decreased platelet count and decreased neutrophil count was provided separately from the advice on the measures for other adverse drug reactions.

The criteria for dose reduction, interruption, and discontinuation were mostly the same between Study MM-002 and 2 other studies, Studies MM-003 and MM-011, but differed in that in Study MM-002, after dose interruption due to decreased neutrophil count, pomalidomide was resumed at 1 mg less than the dose before interruption when the neutrophil count returned to ≥500/μL, while in Studies MM-003 and MM-011, pomalidomide was resumed when the neutrophil count returned to ≥1000/μL, a criterion stricter than that in Study MM-002. The difference in the criteria was attributable to the fact that the results of Study MM-002 were not available when the criterion for Study MM-003 was designed. In Study MM-002, the events of decreased neutrophil count caused by pomalidomide were manageable;

therefore, it would be appropriate only to advise in the package insert, based on the criterion of Study MM-002, on the resumption of treatment after interruption due to decreased neutrophil count, that pomalidomide be resumed at 1 mg less than the dose before interruption when the neutrophil count has returned to ≥500/μL.

PMDA considers as follows:
The safety of pomalidomide was evaluated with a focus on Studies MM-003 and MM-011. Therefore, in terms of resumption of pomalidomide after dose interruption due to decreased neutrophil count, the package insert should provide the criteria based on the criteria of not Study MM-002 but Studies MM-003 and MM-011. PMDA accepted the applicant's explanation about other criteria for dose reduction, interruption, and discontinuation for adverse drug reactions provided in the package insert.

4.(iii).D.(7) Post-marketing investigations

A post-marketing surveillance will be conducted by the applicant in all patients with relapsed or refractory MM who will be receiving pomalidomide to investigate the safety and other aspects of pomalidomide in routine clinical use after the market launch. The following adverse events, which were observed in Study MM-003 and other studies and assessed as important based on the incidence and degree of seriousness, were specified as priority survey items: neutropenia, thromboembolism, neuropathy peripheral, infections, thrombocytopenia, haemorrhage, tumour lysis syndrome, and somnolence. In addition to these adverse events, teratogenicity was also included as a priority survey item because pomalidomide is an analogue of thalidomide, a confirmed human teratogen, and fetal teratogenic effects were observed in the reproductive and developmental toxicity studies in rabbits and rats.

The target number of patients to be surveyed was determined as 400 for an enrolment period of 1 year because among the target population of pomalidomide, that is, patients with MM who did not respond at least to the treatment with lenalidomide and bortezomib or relapsed after the treatment (which is approximately 3000 patients per year), the number of patients to use pomalidomide was estimated to be approximately 400 per year. This target number of patients allows, at a probability of ≥95%, detection of arterial thromboembolism in 1 patient, an adverse event which is included in the priority survey items specified above and had the lowest incidence among fatal adverse events in Study MM-003.

The follow-up period was determined to be 6 cycles (24 weeks) for the following reasons: in Study MM-003, the median PFS and median cycles of pomalidomide therapy were 15.7 weeks and 5 cycles, respectively; the majority of adverse events occurred during the early stages of the therapy; no new safety-related events were observed in patients who received pomalidomide for longer than 6 cycles; and an increased incidence of adverse events was not found in the 7th cycle or later, compared to the incidence of adverse events in the 6th cycle or earlier.

PMDA considers as follows:

Due to the limited amount of safety data on Japanese patients with relapsed or refractory MM who received pomalidomide, it is necessary to promptly collect information in an unbiased manner for a certain period after the market launch through a survey covering all patients who will be receiving pomalidomide, and to promptly provide the safety information obtained to healthcare professionals in clinical settings. Further, based on the survey results, the need for implementing another survey to identify safety concerns should also be considered.

As priority survey items for the post-marketing surveillance, the following adverse events, which require special attention when administering pomalidomide, should also be included in addition to those proposed by the applicant: acute renal failure, arrhythmia, cardiac failure, interstitial lung disease, depressed level of consciousness, confusion, fatigue, and dizziness/vertigo. Neutropenia, thrombocytopenia, and haemorrhage should collectively be included under bone marrow depression, a category which should be established given the higher occurrence of and seriousness of other forms of bone marrow depression. The target number of patients and follow-up period proposed by the applicant are considered acceptable.

4.(iii).D.(8) Proper management procedures

The applicant has planned to implement a controlled distribution program (called "RevMate," a proper management procedures for Revlimid and Pomalyst) to prevent embryo-fetal exposure to pomalidomide by registering and managing all patients who receive this agent and monitoring their condition including pregnancy. The applicant explained the implementation plan for the program as follows.

RevMate ensures the following:

1. Restriction of medical institutions that are allowed to use pomalidomide;
2. Distribution control;
3. Education, registration, and management of prescribing physicians and responsible pharmacists;
4. Education, registration, and management of all patients awaiting treatment with pomalidomide;
5. Regular education and adherence monitoring of all patients under treatment with pomalidomide;
6. Regular pregnancy testing of female patients of childbearing potential; and
7. Drug control

RevMate also stipulates regular reviews by the RevMate Steering Committee and the RevMate Third-party Review Committee and other measures such as revision of implementing procedures in accordance with the review results.

PMDA considers as follows:

As discussed in "4.(iii).D.(3).12).(a) Teratogenicity," a strictly controlled distribution program should be established to prevent embryo-fetal exposure, and post-marketing safety management should be implemented for the clinical use of pomalidomide.

The procedures stipulated by this program are currently under review by the Ministry of Health, Labour and Welfare (MHLW) to assess whether they are appropriate.

4.(iv) Adverse events and other findings observed in clinical studies

The following sections describe major adverse events included in the results of clinical studies submitted for safety evaluation, except the results for death, which are described in "4.(iii) Summary of clinical efficacy and safety."

4.(iv).(1) Japanese Phase I study (Study CC-4047-MM-004)

Adverse events were observed in 6 of 6 patients (100%) in Cohort 1 (2 mg), and 6 of 6 patients (100%) in Cohort 2 (4 mg). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in all patients of both cohorts. The table below lists adverse events that occurred with an incidence of ≥20% in at least one of the cohorts.

Adverse events that occurred with an incidence of ≥20% in at least one of the cohorts

System Organ Class (SOC) Preferred Term (PT) (MedDRA/J ver. 14.1)	Number of patients (%)			
	Cohort 1 (2 mg)* 6 patients		Cohort 2 (4 mg) 6 patients	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	5 (83.3)	6 (100)	6 (100)
Blood and lymphatic system disorders				
Anaemia	4 (66.7)	1 (16.7)	3 (50.0)	2 (33.3)
Leukopenia	4 (66.7)	2 (33.3)	3 (50.0)	0
Lymphopenia	3 (50.0)	2 (33.3)	3 (50.0)	1 (16.7)
Neutropenia	6 (100)	4 (66.7)	6 (100)	4 (66.7)
Thrombocytopenia	4 (66.7)	2 (33.3)	4 (66.7)	0
Cardiac disorders				
Atrial fibrillation	3 (50.0)	0	0	0
Gastrointestinal disorders				
Constipation	2 (33.3)	0	2 (33.3)	0
Diarrhoea	3 (50.0)	0	1 (16.7)	0
Nausea	2 (33.3)	0	0	0
General disorders and administration site conditions				
Malaise	3 (50.0)	0	0	0
Oedema peripheral	3 (50.0)	0	4 (66.7)	0
Hepatobiliary disorders				
Hepatic function abnormal	2 (33.3)	1 (16.7)	1 (16.7)	0
Infections and infestations				
Nasopharyngitis	2 (33.3)	0	1 (16.7)	0
Pneumonia	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)
Upper respiratory tract infection	1 (16.7)	0	3 (50.0)	0
Investigations				
Alanine aminotransferase increased	0	0	2 (33.3)	0
C-reactive protein increased	2 (33.3)	0	0	0
Metabolism and nutrition disorders				
Dehydration	2 (33.3)	1 (16.7)	1 (16.7)	0
Hyperglycaemia	0	0	2 (33.3)	1 (16.7)
Hypoalbuminaemia	1 (16.7)	0	2 (33.3)	0
Hypokalaemia	2 (33.3)	1 (16.7)	0	0
Hyponatraemia	2 (33.3)	1 (16.7)	0	0
Musculoskeletal and connective tissue disorders				
Back pain	2 (33.3)	0	0	0
Muscular weakness	3 (50.0)	0	0	0
Myalgia	2 (33.3)	0	0	0
Respiratory, thoracic and mediastinal disorders				
Asthma	2 (33.3)	0	0	0
Dyspnoea	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)
Skin and subcutaneous tissue disorders				
Rash	3 (50.0)	0	0	0
Rash maculo-papular	2 (33.3)	0	0	0

*: including adverse events after a single administration at 0.5 mg

Serious adverse events were observed in 3 of 6 patients (50.0%) in Cohort 1 (2 mg), and 2 of 6 patients (33.3%) in Cohort 2 (4 mg). These adverse events were classified as pneumonia, lung infection, ilium fracture, and back pain (1 patient, 16.7% each) in Cohort 1 (2 mg); and pneumonia and inguinal hernia (1 patient, 16.7% each) in Cohort 2 (4 mg). Among these, a causal relationship to the study drug could not be ruled out for lung infection (1 patient) in Cohort 1 (2 mg) and pneumonia (1 patient) in Cohort 2 (4 mg).

No adverse events led to discontinuation of treatment with the study drug.

4.(iv).(2) Japanese phase II study (Study CC-4047-MM-011)

Adverse events occurred in 33 of 36 patients (91.7%), and those for which a causal relationship to the study drug could not be ruled out occurred in 32 of 36 patients (88.9%). The table below lists adverse events that occurred with an incidence of ≥10%.

Adverse events that occurred with an incidence of ≥10%

System Organ Class (SOC) Preferred Term (PT) (MedDRA/J ver. 16.1)	Number of patients (%) Pomalidomide group 36 patients	
	All Grades	Grade ≥3
All adverse events	33 (91.7)	28 (77.8)
Blood and lymphatic system disorders		
Anaemia	16 (44.4)	14 (38.9)
Leukopenia	6 (16.7)	4 (11.1)
Lymphopenia	7 (19.4)	6 (16.7)
Neutropenia	25 (69.4)	22 (61.1)
Thrombocytopenia	17 (47.2)	11 (30.6)
Gastrointestinal disorders		
Constipation	7 (19.4)	2 (5.6)
Diarrhoea	7 (19.4)	0
Nausea	7 (19.4)	0
General disorders and administration site conditions		
Malaise	5 (13.9)	0
Oedema peripheral	6 (16.7)	0
Pyrexia	9 (25.0)	0
Infections and infestations		
Pneumonia	4 (11.1)	3 (8.3)
Metabolism and nutrition disorders		
Decreased appetite	5 (13.9)	3 (8.3)
Nervous system disorders		
Dysgeusia	4 (11.1)	0
Psychiatric disorders		
Insomnia	6 (16.7)	0
Respiratory, thoracic and mediastinal disorders		
Epistaxis	4 (11.1)	0
Hypoxia	4 (11.1)	1 (2.8)
Skin and subcutaneous tissue disorders		
Rash	6 (16.7)	0

Serious adverse events occurred in 11 of 36 patients (30.6%). These adverse events were classified as anaemia (4 patients; 11.1%); pneumonia (3 patients, 8.3%); neutropenia and cancer pain (2 patients, 5.6% each); and thrombocytopenia, pneumonia pneumococcal, asthma, chronic obstructive pulmonary disease, hypoxia, pleural effusion, multi-organ failure, pyrexia, decreased appetite, hyponatraemia, constipation, hepatic function abnormal, spinal compression fracture, blood fibrinogen decreased, back pain, urinary retention, and shock haemorrhagic (1 patient, 2.8% each). A causal relationship to the study

drug could not be ruled out for pneumonia (2 patients), asthma, constipation, hyponatraemia, pyrexia, and urinary retention (1 patient each).

Adverse events leading to discontinuation of study drug treatment were observed in 3 of 36 patients (8.3%). These adverse events were classified as pneumonia, asthma, dyspnoea, pleural effusion, anaemia, and pyrexia (1 patient, 2.8% each), and a causal relationship to the study drug could not be ruled out for any of these events.

4.(iv).(3) Foreign phase I study (Study CC-4047-CP-005)

Adverse events were observed in 11 of 28 subjects (39.3%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 6 of 28 subjects (21.4%).

Neither adverse events with an incidence of ≥10% nor serious adverse events were observed.

An adverse event led to discontinuation of study drug treatment in 1 of 28 subjects (3.6%), and this event was urticaria (1 subject, 3.6%), for which a causal relationship to the study drug could not be ruled out.

4.(iv).(4) Foreign phase I study (Study CC-4047-CP-007)

Adverse events were observed in 3 of 36 subjects (8.3%) in Treatment A (one 4-mg capsule), 5 of 35 subjects (14.3%) in Treatment B (two 2-mg capsules), 3 of 35 subjects (8.6%) in Treatment C (one 3-mg capsule), and 2 of 35 subjects (5.7%) in Treatment D (one 2-mg capsule plus one 1-mg capsule). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 3 of 36 subjects (8.3%), 4 of 35 subjects (11.4%), 2 of 35 subjects (5.7%), and 1 of 35 subjects (2.9%) in Treatments A, B, C, and D, respectively.

None of the adverse events occurred with an incidence of ≥10%.

A serious adverse event was observed in 1 of 35 subjects (2.9%) in Treatment B. This adverse event was classified as atrial fibrillation (1 subject, 2.9%), for which a causal relationship to the study drug could not be ruled out.

An adverse event led to discontinuation of study drug treatment in 1 of 35 subjects (2.9%) in Treatment D. The event was classified as white blood cells urine (1 subject, 2.9%), for which a causal relationship to the study drug was ruled out.

4.(iv).(5) Foreign phase I study (Study CC-4047-1398/132)

Adverse events were observed in 0 of 4 subjects (0%), 2 of 4 subjects (50.0%), 1 of 4 subjects (25.0%), 2 of 4 subjects (50.0%), 4 of 4 subjects (100%), and 3 of 10 subjects (30.0%) in the 1, 5, 10, 25, and 50 mg and placebo groups, respectively. Adverse events for which a causal relationship to the study drug

could not be ruled out occurred in 1 of 4 subjects (25.0%) in the 5 mg group, and 3 of 4 subjects (75.0%) in the 50 mg group.

The adverse event that occurred in ≥2 subjects was skin disorder (2 subjects, 50.0%) in the 50 mg group with mild severity.

Neither serious adverse events nor adverse events leading to discontinuation of study drug treatment were observed.

4.(iv).(6) Foreign phase I study (Study CC-4047-CP-006)

Adverse events were observed in 3 of 8 subjects (37.5%), 0 of 8 subjects (0%), 1 of 8 subjects (12.5%), and 2 of 9 subjects (22.2%) in the 0.5, 1, and 2 mg and placebo groups, respectively. No adverse events for which a causal relationship to the study drug could not be ruled occurred.

The adverse event that occurred in ≥2 subjects was nasal congestion in the 0.5 mg group (2 subjects, 25.0%) with mild severity.

Neither serious adverse events, nor adverse events leading to treatment discontinuation were observed.

4.(iv).(7) Foreign phase I study (Study CC-4047-CP-004)

Adverse events were observed in 3 of 8 subjects (37.5%), and adverse events for which a causal relationship to the study drug could not be ruled out did not occur.

The adverse event that occurred in ≥2 subjects was diarrhoea (2 subjects, 25.0%) with mild severity.

Neither serious adverse events, nor adverse events leading to discontinuation of study drug treatment were observed.

4.(iv).(8) Foreign phase I study (Study CC-4047-CP-008)

In Part 1, adverse events occurred in 9 of 16 subjects (56.3%) in Period A (pomalidomide alone), 9 of 16 subjects (56.3%) in Period B (pomalidomide in combination with ketoconazole), 10 of 16 subjects (62.5%) in Period C (pomalidomide in combination with ketoconazole and fluvoxamine); while in Part 2, adverse events occurred in 5 of 16 subjects (31.3%) in Period D (pomalidomide alone), and 4 of 16 subjects (25.0%) in Period E (pomalidomide in combination with carbamazepine). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 2 of 16 subjects (12.5%), 2 of 16 subjects (12.5%), 2 of 16 subjects (12.5%), 1 of 16 subjects (6.3%), and 0 of 16 subjects (0%) in Periods A, B, C, D, and E, respectively.

The adverse events that occurred with an incidence of ≥20% were headache (6 subjects, 37.5%), nausea (5 subjects, 31.3%), dizziness (4 subjects, 25.0%) in Period C. Their severities were either mild or moderate.

No serious adverse events were observed.

Adverse events led to treatment discontinuation in 3 of 16 subjects (18.8%) in Period C, and these events were classified as vomiting, dizziness, headache (2 subjects, 12.5% each), abdominal tenderness, and blood creatinine increased (1 subject, 6.3% each). A causal relationship to the study drug was ruled out for all of these events.

4.(iv).(9) Foreign phase I study (Study CC-4047-CP-010)

Adverse events occurred in 1 of 70 subjects (1.4%) in the 4 mg pomalidomide group, 7 of 68 subjects (10.3%) in the 20 mg pomalidomide group, 9 of 67 subjects (13.4%) in the moxifloxacin group, and 1 of 67 subjects (1.5%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 4 of 68 subjects (5.9%) in the 20 mg pomalidomide group, and 8 of 67 subjects (11.9%) in the moxifloxacin group, but did not occur in the 4 mg pomalidomide group or placebo group.

Neither adverse events with an incidence of ≥10% nor serious adverse events were observed.

An adverse event led to discontinuation of study drug treatment in 1 of 68 subjects (1.5%) in the 20 mg pomalidomide group, and this adverse event was classified as erythema, for which a causal relationship to the study drug could not be ruled out.

4.(iv).(10) Foreign phase I study (Study CC-4047-MM-001)

4.(iv).(10).1) Cohort 1 (QD)

Adverse events occurred in 6 of 6 subjects (100%), 8 of 9 subjects (88.9%), 6 of 6 subjects (100%), and 3 of 3 subjects (100%) in the 1, 2, 5, and 10 mg groups, respectively. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 4 of 6 subjects (66.7%), 7 of 9 subjects (77.8%), 4 of 6 subjects (66.7%), 3 of 3 subjects (100%) in the 1, 2, 5, and 10 mg groups, respectively.

The adverse events that occurred with an incidence of ≥40% were neutropenia, which was observed in 4 subjects (44.4%) in the 2 mg group, 5 subjects (83.3%) in the 5 mg group, and 2 subjects (66.7%) in the 10 mg group. Severity was Grade ≥3 for all of these events.

Serious adverse events occurred in 1 of 6 subjects (16.7%), 3 of 9 subjects (33.3%), 2 of 6 subjects (33.3%), and 2 of 3 subjects (66.7%) in the 1, 2, 5, and 10 mg groups, respectively. These adverse events were classified as deep vein thrombosis (1 subject, 16.7%) in the 1 mg group; neutropenia (2 subjects, 22.2%) and infection without neutropenia (1 subject, 11.1%) in the 2 mg group; neutropenia (2 subjects,

33.3%) in the 5 mg group; and neutropenia (2 subjects, 66.7%) in the 10 mg group. Of these, adverse events for which a causal relationship to the study drug could not be ruled out were deep vein thrombosis (1 subject) in the 1 mg group, and neutropenia (2 subjects each) in the 2, 5, and 10 mg groups.

Adverse events led to discontinuation of study drug treatment in 1 of 6 subjects (16.7%), 2 of 9 subjects (22.2%), 3 of 6 subjects (50.0%), and 3 of 3 subjects (100%) in the 1, 2, 5, and 10 mg groups, respectively. These adverse events were classified as deep vein thrombosis (1 subject, 16.7%) in the 1 mg group; and neutropenia (2 subjects, 22.2%) in the 2 mg groups; neutropenia (3 subjects, 50.0%) in the 5 mg groups; and neutropenia (3 subjects, 100%) in the 10 mg groups. A causal relationship to the study drug could not be ruled out for any of these events.

4.(iv).(10).2) Cohort 2 (QOD)

Adverse events occurred in 4 of 4 subjects (100%), 4 of 4 subjects (100%), 8 of 10 subjects (80.0%), and 3 of 3 subjects (100%), in the 1, 2, 5, and 10 mg groups, respectively. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 2 of 4 subjects (50.0%), 2 of 4 subjects (50.0%), 8 of 10 subjects (80.0%), and 3 of 3 subjects (100%) in the 1, 2, 5, and 10 mg groups, respectively.

The table below lists adverse events that occurred with an incidence of ≥40% in at least one group.

Adverse events that occurred with an incidence of ≥40% in at least one group

System Organ Class (SOC) Preferred Term (PT) (MedDRA/J ver. 14.0)	Number of subjects (%)							
	1 mg group		2 mg group		5 mg group		10 mg group	
	4 subjects		4 subjects		10 subjects		3 subjects	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	4 (100)	3 (75.0)	4 (100)	2 (50.0)	8 (80.0)	3 (30.0)	3 (100)	3 (100)
Blood and lymphatic system disorders								
Neutropenia	1 (25.0)	1 (25.0)	2 (50.0)	2 (50.0)	1 (10.0)	1 (10.0)	3 (100)	3 (100)
Thrombocytopenia	2 (50.0)	2 (50.0)	0	0	0	0	1 (33.3)	1 (33.3)
Gastrointestinal disorders								
Abdominal distension	0	0	0	0	0	0	2 (66.7)	0
General disorders and administration site conditions								
Chest pain	0	0	0	0	1 (10.0)	1 (10.0)	2 (66.7)	0
Pain	1 (25.0)	0	2 (50.0)	0	0	0	0	0
Musculoskeletal and connective tissue disorders								
Musculoskeletal chest pain	0	0	2 (50.0)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders								
Oropharyngeal pain	0	0	0	0	5 (50.0)	0	1 (33.3)	1 (33.3)

Serious adverse events occurred in 1 of 4 subjects (25.0%) in the 1 mg group, and 3 of 3 subjects (100%) in the 10 mg group. These adverse events were classified as infection without neutropenia (1 subject, 25.0%) in the 1 mg group, and neutropenia (3 subjects, 100%) in the 10 mg group. A causal relationship to the study drug could not be ruled out for neutropenia (3 subjects) in the 10 mg group.

Adverse events led to discontinuation of study drug treatment in 1 of 4 subjects (25.0%), 1 of 4 subjects (25.0%), and 3 of 3 subjects (100%) in the 1, 2, and 10 mg groups, respectively. These adverse events were classified as neutropenia and thrombocytopenia (1 subject, 25.0% each) in the 1 mg group; neutropenia (1 subject, 25.0%) in the 2 mg group; and neutropenia (3 subjects, 100%) in the 10 mg group. A causal relationship to the study drug could not be ruled out for neutropenia in the 10 mg group (3 subjects).

4.(iv).(11) Foreign phase I/II study (Study CC-4047-MM-002)

4.(iv).(11).1) Phase I part of study

Adverse events occurred in 6 of 6 patients (100%), 8 of 8 patients (100%), 14 of 14 patients (100%), and 10 of 10 patients (100%) in the 2, 3, 4, and 5 mg groups, respectively. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 4 of 6 patients (66.7%), 6 of 8 patients (75.0%), 13 of 14 patients (92.9%), and 10 of 10 patients (100%) in the 2, 3, 4, and 5 mg groups, respectively.

The table below shows adverse events that occurred with an incidence of ≥30% in at least one group.

Adverse events that occurred with an incidence of ≥30% in at least one group

System Organ Class (SOC) Preferred Term (PT) (MedDRA/J ver. 14.0)	Number of patients (%)							
	2 mg group 6 patients		3 mg group 8 patients		4 mg group 14 patients		5 mg group 10 patients	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	5 (83.3)	8 (100)	6 (75.0)	14 (100)	12 (85.7)	10 (100)	9 (90.0)
Blood and lymphatic system disorders								
Anaemia	5 (83.3)	4 (66.7)	4 (50.0)	2 (25.0)	5 (35.7)	2 (14.3)	3 (30.0)	0
Neutropenia	1 (16.7)	1 (16.7)	5 (62.5)	4 (50.0)	8 (57.1)	7 (50.0)	9 (90.0)	8 (80.0)
Thrombocytopenia	2 (33.3)	2 (33.3)	3 (37.5)	2 (25.0)	2 (14.3)	1 (7.1)	3 (30.0)	2 (20.0)
Eye disorders								
Vision blurred	0	0	1 (12.5)	0	2 (14.3)	0	3 (30.0)	0
Gastrointestinal disorders								
Constipation	2 (33.3)	0	1 (12.5)	0	2 (14.3)	0	4 (40.0)	0
Diarrhoea	1 (16.7)	0	1 (12.5)	0	2 (14.3)	1 (7.1)	4 (40.0)	1 (10.0)
Nausea	2 (33.3)	0	1 (12.5)	0	3 (21.4)	0	5 (50.0)	0
General disorders and administration site conditions								
Asthenia	3 (50.0)	0	2 (25.0)	0	2 (14.3)	1 (7.1)	0	0
Fatigue	4 (66.7)	2 (33.3)	5 (62.5)	1 (12.5)	9 (64.3)	2 (14.3)	7 (70.0)	1 (10.0)
Malaise	0	0	2 (25.0)	1 (12.5)	2 (14.3)	0	3 (30.0)	0
Oedema peripheral	2 (33.3)	0	1 (12.5)	0	1 (7.1)	0	2 (20.0)	0
Pyrexia	2 (33.3)	0	2 (25.0)	0	3 (21.4)	0	3 (30.0)	0
Infections and infestations								
Upper respiratory tract infection	0	0	2 (25.0)	0	5 (35.7)	0	2 (20.0)	0
Metabolism and nutrition disorders								
Decreased appetite	1 (16.7)	0	2 (25.0)	0	3 (21.4)	0	3 (30.0)	0
Dehydration	2 (33.3)	0	1 (12.5)	1 (12.5)	2 (14.3)	0	0	0
Musculoskeletal and connective tissue disorders								
Back pain	3 (50.0)	1 (16.7)	0	0	3 (21.4)	0	2 (20.0)	1 (10.0)
Muscle spasms	2 (33.3)	0	1 (12.5)	0	6 (42.9)	0	2 (20.0)	0
Musculoskeletal pain	0	0	1 (12.5)	0	0	0	3 (30.0)	0
Neuropathy peripheral	1 (16.7)	1 (16.7)	0	0	1 (7.1)	0	3 (30.0)	0
Respiratory, thoracic and mediastinal disorders								
Cough	1 (16.7)	0	0	0	7 (50.0)	0	2 (20.0)	0
Dyspnoea	3 (50.0)	0	6 (75.0)	0	2 (14.3)	0	3 (30.0)	0
Nasal congestion	2 (33.3)	0	1 (12.5)	0	1 (7.1)	0	0	0

Serious adverse events occurred in 3 of 6 groups (50.0%), 4 of 8 patients (50.0%), 8 of 14 patients (57.1%), and 4 of 10 patients (40.0%) in the 2, 3, 4, and 5 mg groups, respectively. These serious adverse events were classified as sepsis, pneumonia, bacteraemia, back pain, renal failure, and confusional state (1 patient, 16.7% each) in the 2 mg group; sepsis (2 patients, 25.0%), arthritis infective, pharyngeal abscess, anaemia, gastrointestinal haemorrhage, syncope, atrioventricular block second degree, and dehydration (1 patient, 12.5% each) in the 3 mg group; pneumonia (2 patients, 14.3%), abscess limb, cellulitis, H1N1 influenza, influenza, lung infection pseudomonal, meningitis bacterial, leukopenia, neutropenia, thrombocytopenia, musculoskeletal chest pain, diarrhoea, headache, renal failure, deep vein thrombosis, asthenia, and metastases to meninges (1 patient, 7.1% each) in the 4 mg group; and

sepsis, respiratory syncytial virus infection, back pain, deep vein thrombosis, femur fracture, humerus fracture, and lung infiltration (1 patient, 10.0% each) in the 5 mg group. Among these, a causal relationship to the study drug could not be ruled out for the following adverse events: pharyngeal abscess, sepsis, atrioventricular block second degree, and syncope (1 patient each) in the 3 mg group, cellulitis, deep vein thrombosis, neutropenia, asthenia, and musculoskeletal chest pain (1 patient each) in the 4mg group, and deep vein thrombosis (1 patient) in the 5 mg group.

Adverse events led to discontinuation of study drug treatment in 1 of 6 patients (16.7%), 1 of 8 patients (12.5%), and 5 of 14 patients (35.7%) in the 2, 3, and 4 mg groups, respectively. These adverse events were thrombocytopenia (1 patient, 16.7%) in the 2 mg group, gastrointestinal haemorrhage (1 patient, 12.5%) in the 3 mg group, anaemia, neutropenia, vomiting, chills, fatigue, pyrexia, meningitis bacterial, metastases to meninges, and renal failure (1 patient, 7.1% each) in the 4 mg group. A causal relationship to the study drug could not be ruled out for any of these events.

4.(iv).(11).2) Phase II part of study

Adverse events occurred in 112 of 112 patients (100%) in the pomalidomide + DEX group, and 107 of 107 patients (100%) in the overall pomalidomide group. Adverse events for which a causal relationship to the study drug (pomalidomide) could not be ruled out occurred in 100 of 112 patients (89.3%) in the pomalidomide + DEX group, and 95 of 107 patients (88.8%) in the overall pomalidomide group. The table below shows adverse events that occurred with an incidence of ≥10% in at least one group.

Adverse events that occurred with an incidence of ≥10% in at least one group

System Organ Class (SOC) Preferred Term (PT) (MedDRA/J ver. 14.0)	Number of patients (%)							
	Pomalidomide + DEX group		Pomalidomide group					
			Before DEX was added		After DEX was added		Overall	
	112 patients		107 patients		61 patients		107 patients	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	112 (100)	101 (90.2)	106 (99.1)	92 (86.0)	57 (93.4)	43 (70.5)	107 (100)	98 (91.6)
Blood and lymphatic system disorders								
Anaemia	44 (39.3)	23 (20.5)	36 (33.6)	18 (16.8)	11 (18.0)	8 (13.1)	41 (38.3)	24 (22.4)
Leukopenia	20 (17.9)	11 (9.8)	11 (10.3)	5 (4.7)	2 (3.3)	1 (1.6)	12 (11.2)	6 (5.6)
Lymphopenia	17 (15.2)	8 (7.1)	4 (3.7)	2 (1.9)	0	0	4 (3.7)	2 (1.9)
Neutropenia	53 (47.3)	43 (38.4)	54 (50.5)	48 (44.9)	18 (29.5)	12 (19.7)	56 (52.3)	50 (46.7)
Thrombocytopenia	26 (23.2)	21 (18.8)	25 (23.4)	22 (20.6)	7 (11.5)	5 (8.2)	27 (25.2)	24 (22.4)
Gastrointestinal disorders								
Constipation	39 (34.8)	3 (2.7)	29 (27.1)	1 (0.9)	11 (18.0)	1 (1.6)	38 (35.5)	2 (1.9)
Diarrhoea	37 (33.0)	2 (1.8)	22 (20.6)	0	18 (29.5)	1 (1.6)	36 (33.6)	1 (0.9)
Nausea	25 (22.3)	3 (2.7)	29 (27.1)	4 (3.7)	11 (18.0)	1 (1.6)	38 (35.5)	5 (4.7)
Vomiting	15 (13.4)	0	10 (9.3)	1 (0.9)	5 (8.2)	2 (3.3)	15 (14.0)	3 (2.8)
General disorders and administration site conditions								
Asthenia	22 (19.6)	3 (2.7)	11 (10.3)	1 (0.9)	5 (8.2)	0	15 (14.0)	1 (0.9)
Chills	12 (10.7)	0	9 (8.4)	0	2 (3.3)	0	10 (9.3)	0
Fatigue	62 (55.4)	11 (9.8)	47 (43.9)	8 (7.5)	11 (18.0)	3 (4.9)	54 (50.5)	11 (10.3)
Oedema peripheral	18 (16.1)	0	18 (16.8)	0	8 (13.1)	0	25 (23.4)	0
Pyrexia	34 (30.4)	2 (1.8)	16 (15.0)	2 (1.9)	6 (9.8)	1 (1.6)	20 (18.7)	3 (2.8)
Infections and infestations								
Pneumonia	27 (24.1)	22 (19.6)	14 (13.1)	10 (9.3)	10 (16.4)	7 (11.5)	23 (21.5)	16 (15.0)
Upper respiratory tract infection	23 (20.5)	1 (0.9)	17 (15.9)	0	10 (16.4)	0	27 (25.2)	0

System Organ Class (SOC) Preferred Term (PT) (MedDRA/J ver. 14.0)	Number of patients (%)							
	Pomalidomide + DEX group		Pomalidomide group					
			Before DEX was added		After DEX was added		Overall	
	112 patients		107 patients		61 patients		107 patients	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Urinary tract infection	18 (16.1)	9 (8.0)	7 (6.5)	2 (1.9)	2 (3.3)	0	8 (7.5)	2 (1.9)
Investigations								
Blood creatinine increased	12 (10.7)	3 (2.7)	13 (12.1)	5 (4.7)	6 (9.8)	2 (3.3)	16 (15.0)	6 (5.6)
Weight decreased	9 (8.0)	0	9 (8.4)	0	6 (9.8)	0	15 (14.0)	0
Weight increased	12 (10.7)	0	0	0	1 (1.6)	0	1 (0.9)	0
Metabolism and nutrition disorders								
Decreased appetite	20 (17.9)	0	15 (14.0)	1 (0.9)	8 (13.1)	0	23 (21.5)	1 (0.9)
Hypercalcaemia	13 (11.6)	1 (0.9)	20 (18.7)	8 (7.5)	4 (6.6)	3 (4.9)	22 (20.6)	10 (9.3)
Hyperglycaemia	17 (15.2)	3 (2.7)	10 (9.3)	1 (0.9)	4 (6.6)	2 (3.3)	13 (12.1)	3 (2.8)
Hypocalcaemia	13 (11.6)	1 (0.9)	5 (4.7)	0	2 (3.3)	0	6 (5.6)	0
Hypokalaemia	12 (10.7)	2 (1.8)	6 (5.6)	2 (1.9)	5 (8.2)	1 (1.6)	11 (10.3)	3 (2.8)
Hyponatraemia	14 (12.5)	5 (4.5)	7 (6.5)	3 (2.8)	4 (6.6)	2 (3.3)	11 (10.3)	5 (4.7)
Musculoskeletal and connective tissue disorders								
Arthralgia	17 (15.2)	1 (0.9)	14 (13.1)	3 (2.8)	3 (4.9)	2 (3.3)	17 (15.9)	5 (4.7)
Back pain	34 (30.4)	10 (8.9)	27 (25.2)	9 (8.4)	11 (18.0)	6 (9.8)	34 (31.8)	13 (12.1)
Bone pain	5 (4.5)	1 (0.9)	8 (7.5)	1 (0.9)	6 (9.8)	1 (1.6)	13 (12.1)	2 (1.9)
Muscle spasms	21 (18.8)	1 (0.9)	17 (15.9)	3 (2.8)	7 (11.5)	0	20 (18.7)	3 (2.8)
Muscular weakness	13 (11.6)	4 (3.6)	8 (7.5)	4 (3.7)	5 (8.2)	2 (3.3)	13 (12.1)	6 (5.6)
Musculoskeletal chest pain	22 (19.6)	0	17 (15.9)	3 (2.8)	8 (13.1)	0	23 (21.5)	3 (2.8)
Musculoskeletal pain	17 (15.2)	2 (1.8)	8 (7.5)	1 (0.9)	4 (6.6)	1 (1.6)	12 (11.2)	2 (1.9)
Pain in extremity	16 (14.3)	2 (1.8)	4 (3.7)	0	1 (1.6)	0	5 (4.7)	0
Nervous system disorders								
Dizziness	19 (17.0)	1 (0.9)	17 (15.9)	1 (0.9)	4 (6.6)	1 (1.6)	21 (19.6)	2 (1.9)
Headache	9 (8.0)	1 (0.9)	12 (11.2)	0	2 (3.3)	0	14 (13.1)	0
Neuropathy peripheral	8 (7.1)	0	11 (10.3)	0	0	0	11 (10.3)	0
Tremor	14 (12.5)	0	7 (6.5)	0	3 (4.9)	0	10 (9.3)	0
Psychiatric disorders								
Anxiety	8 (7.1)	0	9 (8.4)	0	3 (4.9)	0	12 (11.2)	0
Confusional state	15 (13.4)	3 (2.7)	6 (5.6)	1 (0.9)	5 (8.2)	3 (4.9)	11 (10.3)	4 (3.7)
Insomnia	16 (14.3)	0	0	0	7 (11.5)	0	7 (6.5)	0
Renal and urinary disorders								
Renal failure acute	8 (7.1)	5 (4.5)	8 (7.5)	6 (5.6)	4 (6.6)	2 (3.3)	12 (11.2)	8 (7.5)
Respiratory, thoracic and mediastinal disorders								
Cough	23 (20.5)	0	14 (13.1)	0	4 (6.6)	0	15 (14.0)	0
Dyspnoea	37 (33.0)	14 (12.5)	24 (22.4)	4 (3.7)	8 (13.1)	3 (4.9)	28 (26.2)	7 (6.5)
Dyspnoea exertional	17 (15.2)	1 (0.9)	9 (8.4)	0	4 (6.6)	0	12 (11.2)	0
Epistaxis	12 (10.7)	0	12 (11.2)	2 (1.9)	4 (6.6)	0	16 (15.0)	2 (1.9)
Skin and subcutaneous tissue disorders								
Dry skin	12 (10.7)	0	9 (8.4)	0	1 (1.6)	0	10 (9.3)	0
Hyperhidrosis	18 (16.1)	0	4 (3.7)	0	2 (3.3)	0	6 (5.6)	0
Night sweats	14 (12.5)	0	3 (2.8)	0	2 (3.3)	0	5 (4.7)	0
Pruritus	8 (7.1)	0	14 (13.1)	0	1 (1.6)	0	15 (14.0)	0
Rash	18 (16.1)	1 (0.9)	22 (20.6)	0	2 (3.3)	0	23 (21.5)	0

Serious adverse events occurred in 69 of 112 patients (61.6%) in the pomalidomide + DEX group, and 72 of 107 patients (67.3%) in the overall pomalidomide group. The serious adverse events that occurred in ≥2 patients in the pomalidomide + DEX group were as follows: pneumonia (21 patients, 18.8%), multiple myeloma (8 patients, 7.1%), dyspnoea (7 patients, 6.3%), urinary tract infection and renal failure acute (6 patients, 5.4% each), pyrexia (5 patients, 4.5%), sepsis, dehydration, constipation, atrial fibrillation, cardiac failure congestive (3 patients 2.7%), pneumonia respiratory syncytial viral, urosepsis, bronchospasm, pulmonary embolism, respiratory failure, hypercalcaemia, compression

fracture, general physical health deterioration, anaemia, neutropenia, thrombocytopenia, back pain, angina pectoris, confusional state, and mental status changes (2 patients, 1.8% each). The serious adverse events that occurred in ≥2 patients in the overall pomalidomide group were as follows: pneumonia (15 patients, 14.0%), multiple myeloma (10 patients, 9.3%), renal failure acute (7 patients, 6.5%), sepsis (6 patients, 5.6%), dyspnoea, dehydration, hypercalcaemia, febrile neutropenia (5 patients, 4.7% each), back pain (4 patients, 3.7%), pyrexia (3 patients, 2.8%), lobar pneumonia, viral infection, failure to thrive, renal failure, fall, hip fracture, fatigue, non-cardiac chest pain, anaemia, neutropenia, thrombocytopenia, nausea, vomiting, atrial fibrillation, confusional state, mental status changes, blood creatinine increased, and haemoglobin decreased (2 patients, 1.9% each). Of these, a causal relationship to the study drug (pomalidomide) could not be ruled out for the following adverse events: in the pomalidomide + DEX group, pneumonia (7 patients), pulmonary embolism, neutropenia, constipation (2 patients each), pneumonia respiratory syncytial viral, anaemia, thrombocytopenia, dyspnoea, and respiratory failure (1 patient each); in the pomalidomide groups, pneumonia (7 patients), febrile neutropenia (2patients), lobar pneumonia, sepsis, viral infection, neutropenia, haemoglobin decreased, fall, and multiple myeloma (1 patient each).

Adverse events led to discontinuation of the study drug (pomalidomide) treatment in 9 of 112 patients (8.0%) in the pomalidomide + DEX group, and 13 of 107 patients (12.1%) in the overall pomalidomide group. These adverse events were neutropenia, general physical health deterioration, diverticulitis, blood creatinine increased, ECG QT prolonged, renal failure acute, pleural effusion, caecitis, colon cancer, completed suicide (1 patient, 0.9% each) in the pomalidomide + DEX group; thrombocytopenia, fatigue, renal failure acute (2 patients, 1.9% each), febrile neutropenia, pyrexia, pneumonia, sepsis, staphylococcal sepsis, blood creatinine increased, gamma-glutamyltransferase increased, cough, and neuropathy peripheral (1 patient, 0.9% each) in the overall pomalidomide group. Of these, a causal relationship to the study drug (pomalidomide) could not be ruled out for the following adverse events: in the pomalidomide + DEX group, ECG QT prolonged, caecitis, neutropenia (1 patient each); in the pomalidomide groups, febrile neutropenia, fatigue, staphylococcal sepsis, and neuropathy peripheral (1 patient each).

4.(iv).(12) Foreign phase III study (Study CC-4047-MM-003)

Adverse events occurred in 297 of 300 patients (99.0%) in the pomalidomide + DEX group, and 149 of 150 patients (99.3%) in the DEX group (before crossover). Adverse events for which a causal relationship to the study drug (pomalidomide and DEX) could not be ruled out occurred in 269 of 300 patients (89.7%) in the pomalidomide + DEX group, and 115 of 150 patients (76.7%) in the DEX group. The table below lists adverse events that occurred with an incidence of ≥10% in at least one of the two groups: the pomalidomide + DEX group or the overall DEX group.

Adverse events that occurred with an incidence of ≥10% in at least one of the two groups (pomalidomide + DEX group or overall DEX group)

System Organ Class (SOC) / Preferred Term (PT) (MedDRA/J ver. 14.0)	Number of patients (%)							
	Pomalidomide + DEX group		DEX Group					
	300 patients		Before crossover 150 patients		After crossover 9 patients		Overall 150 patients	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	297 (99.0)	261 (87.0)	149 (99.3)	127 (84.7)	7 (77.8)	1 (11.1)	149 (99.3)	127 (84.7)
Blood and lymphatic system disorders								
Anaemia	156 (52.0)	98 (32.7)	77 (51.3)	58 (38.7)	1 (11.1)	0	78 (52.0)	58 (38.7)
Leukopenia	38 (12.7)	27 (9.0)	8 (5.3)	5 (3.3)	0	0	8 (5.3)	5 (3.3)
Neutropenia	154 (51.3)	145 (48.3)	30 (20.0)	23 (15.3)	1 (11.1)	1 (11.1)	31 (20.7)	24 (16.0)
Thrombocytopenia	89 (29.7)	66 (22.0)	44 (29.3)	39 (26.0)	0	0	44 (29.3)	39 (26.0)
Gastrointestinal disorders								
Constipation	65 (21.7)	7 (2.3)	22 (14.7)	0	0	0	22 (14.7)	0
Diarrhoea	66 (22.0)	3 (1.0)	28 (18.7)	2 (1.3)	0	0	28 (18.7)	2 (1.3)
Nausea	45 (15.0)	3 (1.0)	16 (10.7)	2 (1.3)	1 (11.1)	0	17 (11.3)	2 (1.3)
General disorders and administration site conditions								
Asthenia	50 (16.7)	11 (3.7)	27 (18.0)	10 (6.7)	1 (11.1)	0	28 (18.7)	10 (6.7)
Fatigue	101 (33.7)	16 (5.3)	40 (26.7)	9 (6.0)	1 (11.1)	0	41 (27.3)	9 (6.0)
General physical health deterioration	35 (11.7)	31 (10.3)	16 (10.7)	14 (9.3)	0	0	16 (10.7)	14 (9.3)
Oedema peripheral	52 (17.3)	4 (1.3)	17 (11.3)	3 (2.0)	0	0	17 (11.3)	3 (2.0)
Pyrexia	80 (26.7)	9 (3.0)	35 (23.3)	7 (4.7)	0	0	35 (23.3)	7 (4.7)
Infections and infestations								
Bronchitis	30 (10.0)	4 (1.3)	8 (5.3)	0	0	0	8 (5.3)	0
Pneumonia	45 (15.0)	38 (12.7)	16 (10.7)	12 (8.0)	0	0	16 (10.7)	12 (8.0)
Upper respiratory tract infection	48 (16.0)	5 (1.7)	11 (7.3)	1 (0.7)	1 (11.1)	0	11 (7.3)	1 (0.7)
Metabolism and nutrition disorders								
Decreased appetite	38 (12.7)	3 (1.0)	11 (7.3)	2 (1.3)	1 (11.1)	0	12 (8.0)	2 (1.3)
Hypercalcaemia	21 (7.0)	13 (4.3)	16 (10.7)	7 (4.7)	0	0	16 (10.7)	7 (4.7)
Musculoskeletal and connective tissue disorders								
Back pain	59 (19.7)	15 (5.0)	24 (16.0)	6 (4.0)	0	0	24 (16.0)	6 (4.0)
Bone pain	54 (18.0)	22 (7.3)	20 (13.3)	7 (4.7)	0	0	21 (14.0)	7 (4.7)
Muscle spasms	46 (15.3)	1 (0.3)	11 (7.3)	1 (0.7)	0	0	11 (7.3)	1 (0.7)
Muscular weakness	9 (3.0)	2 (0.7)	19 (12.7)	5 (3.3)	1 (11.1)	0	20 (13.3)	5 (3.3)
Nervous system disorders								
Dizziness	37 (12.3)	4 (1.3)	14 (9.3)	2 (1.3)	0	0	14 (9.3)	2 (1.3)
Psychiatric disorders								
Insomnia	32 (10.7)	3 (1.0)	32 (21.3)	5 (3.3)	0	0	32 (21.3)	5 (3.3)
Respiratory, thoracic and mediastinal disorders								
Cough	60 (20.0)	2 (0.7)	15 (10.0)	1 (0.7)	0	0	15 (10.0)	1 (0.7)
Dyspnoea	59 (19.7)	15 (5.0)	22 (14.7)	7 (4.7)	0	0	22 (14.7)	7 (4.7)
Epistaxis	28 (9.3)	3 (1.0)	15 (10.0)	3 (2.0)	1 (11.1)	0	16 (10.7)	3 (2.0)

Serious adverse events occurred in 183 of 300 patients (61.0%) in the pomalidomide + DEX group, and 80 of 150 patients (53.3%) in the DEX group. The serious adverse events that occurred in ≥2 patients in

the pomalidomide + DEX group were as follows: pneumonia (39 patients, 13.0%), general physical health deterioration (26 patients, 8.7%), pyrexia (23 patients, 7.7%), febrile neutropenia (17 patients, 5.7%), hypercalcaemia (13 patients, 4.3%), renal failure acute (11 patients, 3.7%), anaemia, bone pain (10 patients, 3.3% each), neutropenia (9 patients, 3.0%), back pain, renal failure (8 patients, 2.7% each), sepsis, dyspnoea (7 patients, 2.3% each), upper respiratory tract infection, thrombocytopenia (6 patients, 2.0% each), bronchitis, bronchopneumonia, lower respiratory tract infection, lung infection, femur fracture (5 patients, 1.7% each), respiratory tract infection, multi-organ failure, renal impairment, atrial fibrillation, cardiac failure (4 patients, 1.3% each), infection, neutropenic sepsis, septic shock, fatigue, urinary retention, dehydration, hyponatraemia, chronic obstructive pulmonary disease, epistaxis, pulmonary embolism, plasmacytoma, confusional state (3 patients, 1.0% each), cellulitis, Escherichia sepsis, pneumonia bacterial, sinusitis, malaise, pain, pancytopenia, pain in extremity, pathological fracture, cough, lung disorder, respiratory failure, depressed level of consciousness, syncope, myocardial infarction, abdominal pain, diarrhoea, vomiting, basal cell carcinoma, deep vein thrombosis, and hypotension (2 patients, 0.7% each). The serious adverse events that occurred in ≥2 patients in the DEX group were as follows: pneumonia (13 patients, 8.7%), general physical health deterioration (12 patients, 8.0%), pyrexia, renal failure acute, anaemia (7 patients, 4.7% each), septic shock (6 patients, 4.0%), hypercalcaemia, urinary tract infection (5 patients, 3.3% each), thrombocytopenia, lower respiratory tract infection (4 patients, 2.7% each), sepsis, confusional state, hyperglycaemia (3 patients, 2.0% each), back pain, renal impairment, cardiac failure, dehydration, epistaxis, pancytopenia, diarrhoea, asthenia, hyperviscosity syndrome, plasma cell leukaemia, blood creatinine increased, muscular weakness, and pulmonary oedema (2 patients, 1.3% each). Among these, a causal relationship to the study drug (pomalidomide) could not be ruled out for the following adverse events in the pomalidomide + DEX group: pneumonia (19 patients), febrile neutropenia (14 patients), pyrexia (10 patients), neutropenia (8 patients), anaemia (6 patients), dyspnoea (5 patients), thrombocytopenia, pulmonary embolism, renal failure (3 patients each), bronchopneumonia, lower respiratory tract infection, lung infection, respiratory tract infection, sepsis, general physical health deterioration, chronic obstructive pulmonary disease, lung disorder, deep vein thrombosis, hypotension (2 patients each), bronchitis, cellulitis, Escherichia sepsis, infection, neutropenic sepsis, pneumonia bacterial, septic shock, sinusitis, upper respiratory tract infection, fatigue, multi-organ failure, atrial fibrillation, cardiac failure, renal failure acute, and dehydration (1 patient each).

Adverse events led to discontinuation of the study drug (pomalidomide) treatment in 24 of 300 patients (8.0%) in the pomalidomide + DEX group. These adverse events were as follows: thrombocytopenia (3 patients, 1.0%), renal failure acute, general physical health deterioration, hypercalcaemia (2 patients, 0.7% each), bronchopneumonia, bronchopulmonary aspergillosis, meningitis cryptococcal, pneumonia, pneumonia pneumococcal, sepsis, neutropenia, renal failure, cardiac amyloidosis, ischaemic cardiomyopathy, pelvic fracture, subdural haematoma, depressed level of consciousness, dizziness, chronic obstructive pulmonary disease, lung disorder, back pain, and bradyphrenia (1 patient, 0.3% each). Among these, a causal relationship to the study drug (pomalidomide) could not be ruled out for the following adverse events: thrombocytopenia (2 patients), lung disorder, bronchopulmonary

aspergillosis, ischaemic cardiomyopathy, renal failure acute, pneumonia pneumococcal, bradyphrenia, renal failure, dizziness, and neutropenia (1 patient each).

4.(iv).(13) Foreign phase II study (Study IMF 2009-02)

Adverse events occurred in 43 of 43 patients (100%), and 41 of 41 patients (100%) in the 21-day treatment group, and 28-day treatment group, respectively. A causal relationship to the study drug could not be ruled out in 42 of 43 patients (97.7%), and 37 of 41 patients (90.2%) in the 21-day and 28-day treatment groups, respectively. The table below lists adverse events that occurred with an incidence of ≥10% in at least one group.

Adverse events that occurred with an incidence of ≥10% in at least one group

System Organ Class (SOC) Preferred Term (PT) (MedDRA/J ver. 13.0)	Number of patients (%)			
	21-day treatment group 43 patients		28-day treatment group 41 patients	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	43 (100)	40 (93.0)	41 (100)	34 (82.9)
Blood and lymphatic system disorders				
Anaemia	19 (44.2)	14 (32.6)	20 (48.8)	13 (31.7)
Neutropenia	29 (67.4)	27 (62.8)	24 (58.5)	23 (56.1)
Thrombocytopenia	17 (39.5)	12 (27.9)	11 (26.8)	10 (24.4)
Gastrointestinal disorders				
Constipation	9 (20.9)	0	11 (26.8)	0
Diarrhoea	9 (20.9)	0	8 (19.5)	2 (4.9)
Nausea	11 (25.6)	0	4 (9.8)	0
General disorders and administration site conditions				
Asthenia	20 (46.5)	6 (14.0)	20 (48.8)	2 (4.9)
Oedema peripheral	5 (11.6)	0	9 (22.0)	1 (2.4)
Pain	5 (11.6)	2 (4.7)	5 (12.2)	2 (4.9)
Pyrexia	11 (25.6)	1 (2.3)	8 (19.5)	0
Infections and infestations				
Bronchitis	12 (27.9)	2 (4.7)	12 (29.3)	2 (4.9)
Nasopharyngitis	5 (11.6)	0	3 (7.3)	0
Pneumonia	9 (20.9)	5 (11.6)	9 (22.0)	5 (12.2)
Metabolism and nutrition disorders				
Hypercalcaemia	4 (9.3)	2 (4.7)	5 (12.2)	2 (4.9)
Musculoskeletal and connective tissue disorders				
Back pain	5 (11.6)	1 (2.3)	10 (24.4)	1 (2.4)
Bone pain	13 (30.2)	6 (14.0)	7 (17.1)	3 (7.3)
Muscle spasms	8 (18.6)	1 (2.3)	15 (36.6)	2 (4.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Plasmacytoma	6 (14.0)	0	2 (4.9)	0
Nervous system disorders				
Dizziness	7 (16.3)	0	3 (7.3)	0
Tremor	3 (7.0)	0	8 (19.5)	1 (2.4)
Psychiatric disorders				
Insomnia	5 (11.6)	0	6 (14.6)	0
Renal and urinary disorders				
Renal failure	9 (20.9)	5 (11.6)	7 (17.1)	3 (7.3)
Respiratory, thoracic and mediastinal disorders				
Cough	4 (9.3)	1 (2.3)	5 (12.2)	0

System Organ Class (SOC) Preferred Term (PT) (MedDRA/J ver. 13.0)	Number of patients (%)			
	21-day treatment group 43 patients		28-day treatment group 41 patients	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Dyspnoea	5 (11.6)	4 (9.3)	7 (17.1)	1 (2.4)
Skin and subcutaneous tissue disorders				
Pruritus	4 (9.3)	0	5 (12.2)	0

Serious adverse events occurred in 32 of 43 patients (74.4%) in the 21-day treatment group, and 30 of 41 patients (73.2%) in the 28-day treatment group. The serious adverse events that occurred in ≥2 patients were the following events: in the 21-day treatment group, pneumonia (10 patients, 23.3%), general physical health deterioration (4 patients, 9.3%), renal failure (3 patients, 7.0%), hyperthermia, lung infection, hypercalcaemia, bone pain, dyspnoea (2 patients, 4.7% each); in the 28-day treatment group, pneumonia (7 patients, 17.1%), renal failure (3 patients, 7.3%), bone pain, pneumocystis jirovecii pneumonia, and limb operation (2 patients, 4.9% each). Of these, a causal relationship to the study drug could not be ruled out for pneumonia (5 patients), and dyspnoea (1 patient) in the 21-day group, and pneumonia (4 patients), and pneumocystis jirovecii pneumonia (2 patients) in the 28-day treatment group.

Adverse events led to discontinuation of study drug treatment in 14 of 43 patients (32.6%) in the 21-day treatment group, and 13 of 41 patients (31.7%) in the 28-day treatment group. The adverse events leading to discontinuation of study drug treatment in ≥2 patients were as follows: general physical health deterioration (3 patients, 7.0%), hypercalcaemia, and plasmacytoma (2 patients, 4.7% each) in the 21-day treatment group; and pneumonia (4 patients, 9.8%), renal failure (3 patients, 7.3%), and hypercalcaemia (2 patients, 4.9%) in the 28-day treatment group. Of these, a causal relationship to the study drug could not be ruled out for the pneumonia (2 patients) in the 28-day treatment group.

4.(iv).(14) Foreign phase III study (Study CC-4047-MF-002)

Adverse events occurred in 163 of 167 patients (97.6%) in the pomalidomide group, and 80 of 83 patients (96.4%) in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 89 of 167 patients (53.3%) and in 32 of 83 patients (38.6%) in the pomalidomide and placebo groups, respectively. The table below lists adverse events that occurred with an incidence of ≥10% in at least one group.

Adverse events that occurred with an incidence of ≥10% in at least one group

System Organ Class (SOC) Preferred Term (PT) (MedDRA/J ver. 15.1)	Number of patients (%)			
	Pomalidomide group 167 patients		Placebo group 83 patients	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	163 (97.6)	94 (56.3)	80 (96.4)	45 (54.2)
Blood and lymphatic system disorders				
Neutropenia	26 (15.6)	24 (14.4)	5 (6.0)	5 (6.0)
Thrombocytopenia	22 (13.2)	21 (12.6)	12 (14.5)	9 (10.8)
Gastrointestinal disorders				
Abdominal pain	17 (10.2)	0	10 (12.0)	0
Constipation	23 (13.8)	0	9 (10.8)	0
Diarrhoea	32 (19.2)	0	18 (21.7)	3 (3.6)
Nausea	18 (10.8)	1 (0.6)	16 (19.3)	2 (2.4)
General disorders and administration site conditions				
Asthenia	22 (13.2)	6 (3.6)	8 (9.6)	1 (1.2)
Fatigue	33 (19.8)	6 (3.6)	16 (19.3)	2 (2.4)
Oedema peripheral	53 (31.7)	5 (3.0)	14 (16.9)	0
Pyrexia	32 (19.2)	1 (0.6)	12 (14.5)	1 (1.2)
Metabolism and nutrition disorders				
Decreased appetite	18 (10.8)	2 (1.2)	7 (8.4)	0
Nervous system disorders				
Dizziness	17 (10.2)	0	12 (14.5)	1 (1.2)
Respiratory, thoracic and mediastinal disorders				
Cough	23 (13.8)	1 (0.6)	9 (10.8)	0
Dyspnoea	27 (16.2)	5 (3.0)	9 (10.8)	1 (1.2)

Serious adverse events occurred in 72 of 167 patients (43.1%) in the pomalidomide group, and 28 of 83 patients (33.7%) in the overall placebo group. The serious adverse events that occurred in ≥2 patients were as follows: myelofibrosis (9 patients, 5.4%), anaemia (7 patients, 4.2%), pneumonia (6 patients, 3.6%), pyrexia, cardiac failure (5 patients, 3.0% each), oedema peripheral (4 patients, 2.4%), lung infection, febrile neutropenia, thrombocytopenia (3 patients, 1.8% each), bronchitis, staphylococcal sepsis, asthenia, multi-organ failure, atrial fibrillation, cardiac arrest, cardiac failure congestive, pulmonary embolism, pulmonary hypertension, respiratory failure, and renal failure (2 patients, 1.2% each) in the pomalidomide group; myelofibrosis, anaemia, pneumonia, pyrexia (3 patients, 3.6% each), thrombocytopenia, multi-organ failure, diarrhoea (2 patients, 2.4% each) in the overall placebo group. Of these, a causal relationship to the study drug could not be ruled out for the following serious adverse events: anaemia, pyrexia, cardiac failure, pulmonary hypertension (2 patients each), febrile neutropenia, thrombocytopenia, asthenia, oedema peripheral, staphylococcal sepsis, and pulmonary embolism (1 patient each) in the pomalidomide group; and anaemia, thrombocytopenia, multi-organ failure, myelofibrosis, and diarrhoea (1 patient each) in the placebo group.

Adverse events led to discontinuation of the study drug in 46 of 167 patients (27.5%) in the pomalidomide group, and 14 of 83 patients (16.9%) in the placebo group. The adverse events leading to discontinuation of study drug treatment in ≥2 patients were as follows: thrombocytopenia, myelofibrosis (6 patients, 3.6% each), neutropenia (3 patients, 1.8%), fatigue (2 patients, 1.2%) in the pomalidomide

group; myelofibrosis (4 patients, 4.8% each) in the overall placebo group. Of these, a causal relationship to the study drug could not be ruled out for the thrombocytopenia (5 patients), neutropenia, and fatigue (1 patient each) in the pomalidomide group, and myelofibrosis (1 patient) in the placebo group.

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 inspections are currently underway, and 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 inspection is currently underway, and the results and PMDA's conclusion will be reported in Review Report (2).

IV. Overall Evaluation

Based on the submitted data, the efficacy of pomalidomide in the treatment of relapsed or refractory MM has been demonstrated and its safety is acceptable in view of its observed benefits. Pomalidomide is a new active pharmaceutical ingredient which has several activities including induction of apoptosis, suppression of the production of cytokines such as tumor necrosis factor (TNF)-α, activation of T lymphocytes and natural killer cells, and inhibition of angiogenesis, and is believed to inhibit the proliferation of myeloma cells by these activities. Pomalidomide is thus considered to be a clinically significant treatment option for relapsed or refractory MM. PMDA will continue to review its indication, dosage and administration, post-marketing investigation, and other issues in the Expert Discussion.

This application may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

February 16, 2015

I. Product Submitted for Registration

[Brand name]	Pomalyst Capsules 1 mg, Pomalyst Capsules 2 mg, Pomalyst Capsules 3 mg, Pomalyst Capsules 4 mg
[Non-proprietary name]	Pomalidomide
[Name of applicant]	Celgene K.K.
[Date of application]	July 25, 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) is 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

As a result of the review described in "4.(iii).D.(2) Efficacy" of Review Report (1), PMDA has concluded that the efficacy of pomalidomide in the treatment of relapsed or refractory multiple myeloma (MM) has been demonstrated because a foreign phase III study (Study CC-4047-MM-003 [Study MM-003]) conducted in patients with relapsed or refractory MM showed the superiority of pomalidomide in combination with DEX (pomalidomide + DEX) over the high-dose DEX treatment (DEX), the control group of the study, in terms of the progression free survival (PFS) used as the primary endpoint for the study.

The conclusion of PMDA described above was supported by the expert advisors at the Expert Discussion. Furthermore, the following comments were raised by the expert advisors:

- The latest PFS results (data cut-off on [redacted], 20[redacted]) for the ongoing Japanese phase II study, Study CC-4047-MM-011(Study MM-011), do not differ significantly from the results of Study MM-003. Although comparison of the PFS results of Study MM-011 with those of other studies has a limitation since Study MM-011 is an uncontrolled study, the results do not indicate evidence of decreased efficacy of pomalidomide in Japanese patients compared to foreign patients. However, it is necessary to provide relevant information to healthcare professionals in clinical settings using

suitable materials as soon as the results for the follow-up analyses of Study MM-011 including PFS and response duration become available.

PMDA instructed the applicant to provide relevant information to healthcare professionals in clinical settings using appropriate materials as soon as the results for the efficacy follow-up analyses of Study MM-011 including PFS become available, and the applicant agreed to follow the instruction.

(2) Safety

After the discussion in "4.(iii).D.(3) Safety" of Review Report (1), PMDA concluded that particular vigilance against the following adverse events is required when using pomalidomide: bone marrow depression, neuropathy peripheral, thromboembolism, infection, arrhythmia, cardiac failure, acute renal failure, interstitial lung disease, tumour lysis syndrome, somnolence, depressed level of consciousness, confusion, fatigue, dizziness/vertigo, and second primary malignancy.

PMDA concluded that pomalidomide is tolerable provided appropriate measures including monitoring and control of adverse events are taken by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancy.

During the preparation of the Review Report (1), the applicant was asked, with reference to the clinical studies of pomalidomide, to investigate the incidence of haemorrhage in association with concurrent thrombocytopenia, and the applicant explained the results of the investigation as follows:

The table below shows the incidence of haemorrhage in association with concurrent thrombocytopenia in the following studies that were conducted in patients with relapsed or refractory MM: foreign clinical studies, Studies MM-003 and CC-4047-MM-002 (Study MM-002), and Japanese clinical studies, CC-4047-MM-004 (Study MM-004), and Study MM-011.

Incidence of haemorrhage in association with concurrent thrombocytopenia

Study	Group	Number of patients (%)			
		Concurrent thrombocytopenia			
		Concurrent		No concurrent	
		All Grades	Grade ≥3	All Grades	Grade ≥3
MM-003	Pomalidomide/DEX	27/67 (40.3)	7/12 (58.3)	40/67 (59.7)	5/12 (41.7)
	DEX	13/40 (32.5)	4/8 (50.0)	27/40 (67.5)	4/8 (50.0)
MM-002	Pomalidomide/DEX	7/30 (23.3)	2/6 (33.3)	23/30 (76.7)	4/6 (66.7)
	Pomalidomide	14/32 (43.8)	5/5 (100)	18/32 (56.3)	0
MM-004	Pomalidomide /DEX*	2/3 (66.7)	0	1/3 (33.3)	0
MM-011	Pomalidomide /DEX	6/10 (60.0)	1/2 (50.0)	4/10 (40.0)	1/2 (50.0)

*: Pomalidomide monotherapy in the MTD determination stage (first cycle)

To identify risk factors for haemorrhagic events, major patient characteristics in each treatment group of Study MM-003 including age, sex, body weight, disease duration, disease stage, and the number of past anti-MM regimens were analyzed, but no noticeable differences in patient characteristics were

found between the patients who did and did not experience haemorrhagic events. Further, no noticeable differences in patient characteristics were found between the pomalidomide + DEX group and DEX group in association with or without haemorrhagic events. Studies MM-002, MM-004, and MM-011 did not differ noticeably from Study MM-003 in terms of patient demographics. The above findings identified no risk factors for haemorrhagic events.

On [redacted] 20[redacted], the applicant reported that the Core Data Sheet for pomalidomide was revised as of [redacted] 20[redacted] to include advice on angioedema and serious cutaneous reactions due to pomalidomide.

The applicant explained the circumstances of this revision as follows:
Celgene Corporation in the US, in response to a request made in [redacted] 20[redacted] by the European Medicines Agency to conduct a detailed survey on the occurrence of angioedema due to pomalidomide and to submit the results, reviewed the occurrence of adverse events categorized as the MedDRA SMQ "angioedema (narrow scope)" captured in the safety database containing foreign post-marketing data (data cut-off on [redacted] 20[redacted]). A total of 74 patients were identified to have experienced adverse events categorized as the MedDRA SMQ "angioedema (narrow scope)," 43 of whom experienced serious events. A causal relationship of the serious events occurring in 29 of the 43 patients to pomalidomide could not be ruled out. Among patients who experienced adverse events classified under "Angioedema," 19 patients had a history of hypersensitivity to lenalidomide hydrate (lenalidomide) or thalidomide. After re-challenge with pomalidomide, angioedema recurred in 5 patients. Of these 5 patients, it was concluded that there was no alternative explanation other than that pomalidomide was the causative agent in 4. From the above findings, angioedema was listed in the Core Data Sheet. Adverse events corresponding to "angioedema" occurred in 11 patients in Study MM-002, 2 patients in Study MM-003, and 1 patient in Study MM-011, however, all cases were non-serious, and no adverse events corresponding to "Angioedema" occurred in Study MM-004.

Further, PMDA asked the applicant to explain the latest data on the occurrence of serious cutaneous reactions and hypersensitivity reactions including anaphylaxis in addition to angioedema after administration of pomalidomide.

The applicant responded as follows:
The occurrence of these adverse events categorized as the MedDRA SMQ "angioedema (broad scope)," "severe cutaneous reactions," and "hypersensitivity" in the safety database* mentioned above was assessed. The results showed that adverse events falling under the categories of MedDRA SMQ on "angioedema (broad scope)" occurred in 276 patients. The adverse events that occurred in ≥4 patients were as follows: oedema peripheral (96 patients, of whom 28 patients were serious), peripheral swelling (45 patients, of whom 19 patients were serious), urticaria (27 patients, of whom 14 patients were

* Data on MedDRA SMQ "angioedema (broad scope)" were based on those cut off on [redacted] 20[redacted], and "severe cutaneous reactions" and "hypersensitivity" on [redacted] 20[redacted].

serious), swelling face (22 patients, of whom 13 patients were serious), hypersensitivity (21 patients, of whom 16 patients were serious), oedema (18 patients, of whom 6 patients were serious), swelling (12 patients, of whom 8 patients were serious), generalised oedema (6 patients, of whom 3 patients were serious), wheezing (6 patients, of whom 2 patients were serious), eyelid oedema (5 patients, all non-serious), eye swelling (5 patients, of whom 2 patients were serious), angioedema (5 patients, all serious), lip swelling (5 patients, of whom 1 patient was serious), face oedema (4 patients, of whom 3 patients were serious), swollen tongue (4 patients, of whom 1 patient was serious), and drug hypersensitivity (4 patients, of whom 3 patients were serious). Among the serious adverse events, a causal relationship to pomalidomide could not be ruled out for the following adverse events: oedema peripheral (20 patients), peripheral swelling (17 patients), urticaria (12 patients), swelling face (13 patients), hypersensitivity (14 patients), oedema (4 patients), swelling (7 patients), generalised oedema (2 patients), wheezing (1 patient), eye swelling (1 patient), angioedema (5 patients), lip swelling (1 patient), face oedema (3 patients), swollen tongue (1 patient), and drug hypersensitivity (3 patients).

Dermatitis bullous, an adverse event that falls under "severe cutaneous reactions," occurred in 2 patients, of whom 1 patient was serious. For both cases, a causal relationship to pomalidomide could not be ruled out. The patient who was assessed as non-serious had a history of hypersensitivity to lenalidomide.

Adverse events classified under "hypersensitivity" occurred in 420 patients. Of these, the following are the adverse events reported by ≥10 patients and a causal relationship to pomalidomide could not be ruled out for: rash (221 patients, of whom 58 patients were serious), rash pruritic (42 patients, of whom 9 were serious), urticaria (25 patients, of whom 12 patients were serious), swelling face (22 patients, of whom 13 patients were serious), hypersensitivity (19 patients, of whom 14 patients were serious), rash generalised (17 patients, of whom 7 patients were serious), rash macular (12 patients, of whom 3 patients were serious), and rash erythematous (10 patients, of whom 4 patients were serious). Serious anaphylaxis occurred in 1 patient, however, a causal relationship to pomalidomide was ruled out. In Studies MM-002, MM-003, MM-004, and MM-011, no adverse events classified under "severe cutaneous reactions" occurred, and adverse events classified under "hypersensitivity" occurred in 55 patients (of whom, 3 patients were serious), 43 patients (all of whom were non-serious), 4 patients (all of whom were non-serious), and 10 patients (all of whom were non-serious), respectively.

PMDA considers as follows:
When providing the information to healthcare professionals in clinical settings on bone marrow depression after pomalidomide administration, it is necessary to provide relevant information including the occurrence of haemorrhage using a suitable method [see "II.4.(iii).D.(3).3) Bone marrow depression"].

In addition, serious hypersensitivity adverse events including angioedema, rash, and urticaria have occurred after administration of pomalidomide, and for some of these events, a causal relationship of the events to pomalidomide could not be ruled out; therefore, caution should be exercised when

administering pomalidomide. The information on the occurrence of hypersensitivity adverse events reported in the foreign post-marketing surveillance, including angioedema, rash, and urticaria, should be provided using the package insert or relevant documents; in addition, it is necessary to advise careful administration of pomalidomide so that physicians will take appropriate measures if any abnormalities are observed.

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

(3) Clinical positioning and indications

PMDA concluded, after the discussion in the "II.4.(iii).D.(4) Clinical positioning" in Review Report (1), that combination therapy with pomalidomide and DEX can be used as a treatment option for patients with relapsed or refractory MM who have received prior treatment with lenalidomide and bortezomib.

After the discussion in "4.(iii).D.(5) Indications" in Review Report (1), PMDA concluded that the indication of pomalidomide should be specified as "relapsed or refractory multiple myeloma" according to applicant proposal, and the following precautionary statement should be included in the "Precautions for Indication" section of the package insert:

- Eligible patients should be carefully selected after the other therapeutic options are thoroughly reviewed by the physicians who fully understand the efficacy and safety of pomalidomide as well as prior treatment history of the patients enrolled in the clinical studies described in the "Clinical studies" section.

In addition to the comments supporting PMDA's decision as described above, the following comment was also raised by the expert advisors at the Expert Discussion:

- In light of the clinical position of pomalidomide, advice should be given more explicitly that pomalidomide is indicated for patients who have received prior treatments including both lenalidomide and bortezomib; therefore, the need for listing both drug names in the "Precautions for Indication" section of the package insert should be considered.

Based on the discussion at the Expert Discussion, PMDA concluded that it is necessary for the applicant to provide precautionary statements by stating that pomalidomide is indicated for patients who have received prior treatments including both lenalidomide and bortezomib in the "Precautions for Indication" section of the package insert.

PMDA instructed the applicant to provide the "Indication" and "Precautions for Indication" sections as follows, and the applicant agreed to follow the instruction.

[Indication]
Relapsed or refractory multiple myeloma

[Precautions for Indication]

- Pomalidomide is indicated for patients who have received prior treatments including both lenalidomide and bortezomib. Treatment options besides pomalidomide should be considered carefully before starting treatment with pomalidomide.

(4) Dosage and administration

After the discussion in the "4.(iii).D.(6) Dosage and administration" in Review Report (1), PMDA concluded that it is appropriate to provide the dosage and administration for pomalidomide as follows in accordance with the applicant's proposal and the subsequent precautionary statements in the "Precautions for dosage and administration" section,: "In combination with dexamethasone, the usual adult dosage is 4 mg as pomalidomide given orally once daily on a 21-day on/7-day off schedule. The dose may be reduced according to the patient's condition."

- Cancer chemotherapy including pomalidomide should be undertaken only after the contents of "Clinical studies" section, especially, dosage and administration, are fully understood.
- When adverse drug reactions of Grade 3 or 4 develop (excluding decreased platelet count and decreased neutrophil count), administration of pomalidomide should be interrupted until these conditions have resolved to Grade ≤2, and resume administration at 1mg less than the dose before interruption. Resume administration depending on the patient's condition. If adverse drug reactions appear after dose reductions to 1 mg, administration of pomalidomide should be discontinued.
- If decreased platelet count or decreased neutrophil count occurs, consider interruption of treatment or other measures with reference to the table below.

Guide on treatment interruption or other measures for decreased platelet count or decreased neutrophil count

	Platelet/neutrophil counts	Actions during treatment, and guide on dose reduction at the resumption of pomalidomide treatment
Decreased platelet count	Decreased to <25,000/μL	Interrupt pomalidomide treatment until platelet count returns to ≥50,000/μL. Resume pomalidomide treatment at 1 mg less than the dose before interruption. Follow the same steps if the adverse drug reaction appears after the resumption of treatment. If the adverse drug reaction appears again after dose reductions to 1 mg, administration of pomalidomide should be discontinued.
Decreased neutrophil count	Decreased to <500/μL, or febrile neutropenia (neutrophil count of <1000/μL, and at the same time, fever of >38.3°C at least once, or ≥38°C continuously for >1 hour)	Interrupt pomalidomide treatment until neutrophil count returns to ≥1000/μL. Resume pomalidomide treatment at 1 mg less than the dose before interruption. Consider treatment with G-CSF if it has not been used. Follow the same steps if the adverse drug reaction appears after the resumption of treatment. If the adverse drug reaction appears after dose reductions to 1 mg, administration of pomalidomide should be discontinued.

The conclusion of PMDA described above was supported by the expert advisors at the Expert Discussion. Furthermore, the following comments were raised by the expert advisors:

- In Study MM-003, the median (minimum, maximum) time from randomization to response was 8.1 (4.0, 48.0) weeks in the responded patients of the pomalidomide + DEX group [see "4.(iii).D.(2).4) Efficacy of pomalidomide in Japanese patients"]; information regarding the results on the time to response and the duration of response of pomalidomide in the Study MM-003 should be provided using a suitable method.

PMDA considers as follows:
Information on the time to response and the duration of response of pomalidomide in the Study MM-003 should be provided to healthcare professionals in clinical settings using suitable materials because such information is considered to be useful when making a decision on whether or not to continue treatment with pomalidomide.

Based on the above, PMDA instructed the applicant to take appropriate measures according to the above advice, and provide the "Dosage and administration" and "Precautions for dosage and administration" sections as above. The applicant agreed to follow the instruction.

(5) Risk Management Plan (draft)

(5).1) Post-marketing surveillance

The applicant has planned to conduct a post-marketing surveillance covering all patients who will be receiving pomalidomide for the treatment of relapsed or refractory MM to investigate the safety and other aspects of pomalidomide in routine clinical use after the market launch.

After the discussion in the "4.(iii).D.(7) Post-marketing investigations" in Review Report (1), PMDA concluded that it is necessary to promptly collect information in an unbiased manner for a certain period after the market launch through the survey covering all patients who will be receiving pomalidomide, and to promptly provide the safety information obtained to healthcare professionals in clinical settings, since the limited amount of safety data are available on Japanese patients with relapsed or refractory MM who received pomalidomide.

With regard to the priority survey items for the post-marketing surveillance, PMDA concluded that: (1) adverse events which require special attention when administering pomalidomide, i.e., arrhythmia, cardiac failure, acute renal failure, interstitial lung disease, depressed level of consciousness, confusion, fatigue, dizziness/vertigo, should also be included in addition to the items proposed by the applicant; (2) neutropenia, thrombocytopenia, and haemorrhage should collectively be included under bone marrow depression, a category which should be established given the higher occurrence and seriousness of other forms of bone marrow depression.

It is also necessary to include hypersensitivity in priority survey items given that hypersensitivity adverse events including angioedema, rash, and urticaria have been reported in the foreign post-marketing drug use-results survey, and that the incidences of rash and rash maculo-papular were higher in Japanese clinical studies than in foreign clinical studies [see "(2) Safety"].

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

PMDA instructed the applicant to take appropriate measures for the above issues, and the applicant agreed to follow the instruction.

(5).2) Proper management procedures

The applicant has planned to implement a controlled distribution program ("RevMate," a proper management procedures for Revlimid and Pomalyst) to prevent embryo-fetal exposure to pomalidomide by registering and managing all patients who receive this agent and monitoring their condition including pregnancy.

After the discussion in the "4.(iii).D.(8) Proper management procedures" in Review Report (1), PMDA concluded that it is necessary to establish a strictly controlled distribution program to prevent embryo-fetal exposure, and implement post-marketing safety management when using pomalidomide.

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

Based on the above discussions on the post-marketing surveillance and proper management procedures, PMDA concluded that it is appropriate to establish a safety specification and efficacy specification for the risk management plan (draft) at this time as summarized in the table below, and implement additional pharmacovigilance and risk minimization actions.

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

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Teratogenicity • Bone marrow depression • Neuropathy peripheral • Thromboembolism • Infection • Arrhythmia • Cardiac failure • Acute renal failure • Interstitial lung disease • Tumour lysis syndrome • Somnolence, depressed level of consciousness, confusion, fatigue, dizziness/vertigo • Hypersensitivity	• Second primary malignancy	• Use in patients with hepatic impairment • Use in patients with renal impairment
Efficacy specifications		
• Efficacy in routine clinical use		

Outline of additional pharmacovigilance and risk minimization actions in the risk management plan (draft)

Additional pharmacovigilance actions	Additional risk minimization actions
• Early post-marketing phase vigilance • Post-marketing surveillance (all case surveillance) • Number of patients to be analyzed: 400 patients Follow-up period: 6 cycles (24 weeks) • Post-marketing clinical study (continued from Study MM-004) • Post-marketing clinical study (continued from Study MM-011)	• Information provision by implementing an early post-marketing phase vigilance system • Implementation of a controlled distribution program • Creation and distribution of materials for health care professionals in clinical settings • Creation and distribution of materials for patients • Publishing data on the occurrence of adverse drug reactions of pomalidomide on the company's website

Outline of post-marketing surveillance plan (draft)

Objective	To review safety and other aspects of pomalidomide in routine clinical use
Survey method	All-case surveillance by the central registration method
Patients population	All patients who received pomalidomide
Follow-up period	6 cycles (24 weeks)
Planned sample size	400
Main survey items	Priority survey items: teratogenicity, bone marrow depression, neuropathy peripheral, thromboembolism, infection, arrhythmia, cardiac failure, acute renal failure, interstitial lung disease, tumor lysis syndrome, somnolence, depressed level of consciousness, confusion, fatigue, dizziness/vertigo, and hypersensitivity. Other major survey items: patient characteristics (patient identification information, sex, pregnancy, date of birth, age, PS, medical history, complications, prior treatment history, and the like), pomalidomide treatment, co-administered drugs, combination treatment, presence/absence of bone lesion, clinical laboratory test results, adverse events, and the like

(6) Other

As the primary efficacy endpoint of Study MM-011, the applicant submitted the results of the primary analysis of response rate according to the IMWG criteria with a data cut-off date of [redacted], 20[redacted],

which is after the submission for registration of the drug product [see "4.(iii).D.(2).4) Efficacy of pomalidomide in Japanese patients"].

PMDA considers as follows:
Study MM-011 was conducted in Japanese patients with relapsed MM, and given the special importance of the study in evaluating the efficacy of pomalidomide in Japanese patients, the development plan for pomalidomide should have been scheduled so as to allow submission of the primary analysis results on efficacy as described above together with the results of foreign phase III study, which are the main evaluation data, without delay.

PMDA conveyed the above view to the applicant, and the applicant agreed that future development planning be carried out appropriately with taking the above issue into consideration.

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 was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, 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 (5.3.5.2.1 and 5.3.5.4.1). The results showed satisfactory overall GCP compliance in the conduct of clinical studies, and PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents. However, the following finding was noted regarding the sponsor, albeit with no major impact on the overall study evaluation, and was notified to the applicant (sponsor) as an issue to be redressed.

Issue to be improved
Sponsor

- Delay in distributing Periodic Safety Update Report to the study site director.

IV.Overall Evaluation

As a result of the above review, PMDA concludes that Pomalyst (pomalidomide) may be approved after modifying the indication, and dosage and administration statements as shown below, provided that

appropriate precautions will be included in the package insert and information concerning the proper use of pomalidomide will be provided appropriately after the market launch, and the compliance with the proper use of pomalidomide will be ensured under the supervision of physicians with sufficient knowledge and experience of treating hematopoietic malignancy at medical institutions capable of providing sufficient emergency care. As pomalidomide is an orphan drug, the re-examination period is 10 years. The drug substance and the drug product are both classified as poisonous drugs, but neither of them is classified as a biological product or a specified biological product.

[Indication] Relapsed or refractory multiple myeloma

[Dosage and administration] In combination with dexamethasone, the usual adult dosage is 4 mg as pomalidomide given orally once daily on a 21 day on/7 day off schedule. The dose may be reduced according to the patient's condition.

[Conditions for approval] The applicant is required to:

1. Develop and appropriately implement a risk management plan;
2. Take strict and appropriate measures to ensure that the drug product is given only to eligible patients under the supervision of physicians with sufficient knowledge and experience, at medical institutions capable of providing sufficient emergency care, only after the efficacy and risks of the drug product have been explained to patients or their families in writing, and written consent has been obtained;
3. Conduct a post-marketing drug use-results survey, covering all patients treated with the product until data from a specific number of patients have been collected, in order to keep track of the characteristics of patients treated with the product, to collect data on the safety and efficacy of the product as soon as possible and to ensure proper use of the product by taking necessary measures accordingly, because the number of patients included in the Japanese clinical studies was very small; and

The condition for approval concerning the appropriate implementation of the measures for safety management of pomalidomide will be considered separately by the MHLW.

4. Implement the measures for safety management (draft) appropriately.

[Warnings]

1. The drug product is a thalidomide analogue. Because it may cause teratogenic effects in humans, the drug product must not be given to pregnant women, or women who may be pregnant.

2. The proper management procedures have been established for the use of the drug product to prevent embryo-fetal exposure to the drug product. The relevant corporate entities, physicians, pharmacists, and other persons engaged in medical practice, patients, and their family members, and all other parties concerned must follow the proper management procedures.
3. Women of childbearing potential must be given a pregnancy test in advance, and a negative pregnancy result must be confirmed prior to initiating the treatment with the drug product. If the patient has sexual intercourse from 4 weeks before the initiation of treatment until 4 weeks after the end of treatment, the patient and the partner must commit to the use of effective contraceptive measures (male partner must wear a condom). Compliance with contraceptive measures must be closely monitored, and pregnancy tests must be performed on a regular basis. Patients must be instructed to stop taking the drug product immediately and report to their physicians if pregnancy is suspected during treatment.
4. The drug product is excreted into the semen of the patients receiving the drug. If a male patient has sexual intercourse until 4 weeks after the end of treatment, the patient must commit to the use of maximally effective contraceptive measures (the male patient must wear a condom). Compliance with contraceptive measures must be closely monitored. Male patients receiving the drug product must not have sexual intercourse with pregnant women during the above period.
5. The drug product should be administered only to patients for whom its administration is considered appropriate by physicians with sufficient knowledge and experience of treating hematopoietic malignancy at medical institutions capable of providing sufficient emergency care. Administration of the drug product should be initiated only after the efficacy and risks including embryo-fetal exposure have been sufficiently explained to patients or their families, and written consent has been obtained.
6. Since deep vein thrombosis and pulmonary embolism have been observed, patients should be closely monitored and the drug product should be administered carefully. If abnormalities are observed, administration of the drug product should be discontinued immediately, and appropriate measures should be taken.

[Contraindications]

1. Pregnant women, or women who may be pregnant
2. Patients who cannot adhere to the “proper management procedures”
3. Patients who have prior history of hypersensitivity to any of the ingredients contained in the drug product

[Precautions for Indication]

The drug product is indicated for patients who have received prior treatments including both lenalidomide and bortezomib, and treatment options besides the drug product should be considered carefully before starting a treatment with the drug product.

[Precautions for dosage and administration]

1. Cancer chemotherapy including the drug product should be undertaken only after the contents of "Clinical studies" section, especially, dosage and administration, are fully understood.
2. When adverse drug reactions of Grade 3 or 4 develop (excluding decreased platelet count and decreased neutrophil count), administration of the drug product should be interrupted until these conditions have resolved to Grade ≤2, and resume administration at 1mg less than the dose before interruption. Resume administration depending on the patient's condition. If adverse drug reactions appear after dose reductions to 1 mg, administration of the drug product should be discontinued.
3. If decreased platelet count or decreased neutrophil count occurs, consider interruption of treatment or other measures with reference to the table below.

Guide on dose interruption or other measures for decreased platelet count or decreased neutrophil count

	Platelet/neutrophil counts	Actions during treatment, and guide on dose reduction at the resumption of the drug product
Decreased platelet count	Decreased to <25,000/μL	Interrupt the drug product until platelet count returns to ≥50,000/μL. Resume the drug product at 1 mg less than the dose before interruption. Follow the same steps if the adverse drug reaction appears after the resumption of treatment. If the adverse drug reaction appears after dose reductions to 1 mg, administration of pomalidomide should be discontinued.
Decreased neutrophil count	Decreased to <500/μL, or febrile neutropenia (neutrophil count of <1000/μL, and at the same time, fever of >38.3°C at least once, or ≥38°C continuously for >1 hour)	Interrupt the drug product until neutrophil count returns to ≥1000/μL. Resume the drug product at 1 mg less than the dose before interruption. Consider treatment with G-CSF if it has not been used. Follow the same steps above if the adverse drug reaction appears after the resumption of treatment. If the adverse drug reaction appears after dose reductions to 1 mg, administration of pomalidomide should be discontinued.