Report on the Deliberation Results

February 8, 2021

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

Brand Name	Thaled Capsules 25 Thaled Capsules 50 Thaled Capsules 100
Non-proprietary Name	Thalidomide (JAN*)
Applicant	Fujimoto Pharmaceutical Corporation
Date of Application	March 26, 2020

Results of Deliberation

In its meeting held on January 27, 2021, the First Committee on New Drugs concluded that the partial change application for 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.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to properly comply with the Thalidomide Education and Risk Management System (TERMS) for the marketing, management, and use of the product. Any change to the procedures of the TERMS requires prior approval by the Ministry of Health, Labour and Welfare.
3. The applicant is required to take stringent and proper measures to ensure that the product will be administered only to patients identified to be appropriate to receive the treatment, under the supervision of a physician with sufficient knowledge and experience, at a medical facility capable of providing adequate emergency medical care. Prior to initiation of treatment, patients or their family members must be fully informed of its efficacy and risks in written form, and their consent must be obtained in writing.
4. Because the number of patients studied in Japan is extremely limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a specified number of patients will be collected to obtain information on the characteristics of patients treated with the product, and collect safety and efficacy data as soon as possible. The applicant is required to take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

January 18, 2021
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Thaled Capsules 25 Thaled Capsules 50 Thaled Capsules 100
Non-proprietary Name	Thalidomide
Applicant	Fujimoto Pharmaceutical Corporation
Date of Application	March 26, 2020
Dosage Form/Strength	Capsules, each containing 25 mg, 50 mg, or 100 mg of Thalidomide
Application Classification	Prescription drug (4) Drug with a new indication (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 352 of 2014 [*26 yaku*]; PFSB/ELD Notification No. 1120-1 dated November 20, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of Crow-Fukase (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes [POEMS]) syndrome, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indications

- Relapsed or refractory multiple myeloma
- Erythema nodosum leprosum
- <u>Crow-Fukase (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes [POEMS]) syndrome</u>

(Underline denotes additions.)

Dosage and Administration

- Relapsed or refractory multiple myeloma

The usual adult dosage is 100 mg of thalidomide orally once daily at bedtime. The dose may be adjusted according to the patient's condition. The daily dose should not exceed 400 mg.

- Erythema nodosum leprosum

Usually, thalidomide is administered orally once daily at bedtime. The adult starting dose is 50 to 100 mg of thalidomide and may be gradually increased as necessary until symptoms are alleviated. The daily dose should not exceed 400 mg. Gradually decrease the dose if symptoms improve. Control the symptoms at a lower maintenance dose.

- Crow-Fukase (POEMS) syndrome

The usual adult starting dose is 100 mg of thalidomide on alternate days. After an interval of at least 1 week, gradually increase the dose to 200 mg once daily. Thalidomide should be administered orally at bedtime. The dose should be adjusted according to the patient's condition; however, the daily dose should not exceed 300 mg.

(Underline denotes additions.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to properly comply with the Thalidomide Education and Risk Management System (TERMS) for the marketing, management, and use of the product. Any change to the procedures of the TERMS requires prior approval by the Ministry of Health, Labour and Welfare.
3. The applicant is required to take stringent and proper measures to ensure that the product will be administered only to patients identified to be appropriate to receive the treatment, under the supervision of a physician with sufficient knowledge and experience, at a medical facility capable of providing adequate emergency medical care. Prior to initiation of treatment, patients or their family members must be fully informed of its efficacy and risks in written form, and their consent must be obtained in writing.
4. Because the number of patients studied in Japan is extremely limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a specified number of patients will be collected to obtain information on the characteristics of patients treated with the product, and collect safety and efficacy data as soon as possible. The applicant is required to take necessary measures to ensure proper use of the product.

Attachment

Review Report (1)

November 27, 2020

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

Product Submitted for Approval

Brand Name	Thaled Capsules 25 Thaled Capsules 50 Thaled Capsules 100
Non-proprietary Name	Thalidomide
Applicant	Fujimoto Pharmaceutical Corporation
Date of Application	March 26, 2020
Dosage Form/Strength	Capsules, each containing 25 mg, 50 mg, or 100 mg of Thalidomide

Proposed Indications

- Relapsed or refractory multiple myeloma
- Erythema nodosum leprosum
- Crow-Fukase (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes [POEMS]) syndrome

(Underline denotes additions.)

Proposed Dosage and Administration

- Relapsed or refractory multiple myeloma

The usual adult dosage is 100 mg of Thalidomide orally once daily at bedtime. The dose may be adjusted according to the patient's condition. The daily dose should not exceed 400 mg.

- Erythema nodosum leprosum

Usually, thalidomide is administered orally once daily at bedtime. The adult starting dose is 50 to 100 mg of thalidomide and may be gradually increased as necessary until symptoms are alleviated. The daily dose should not exceed 400 mg. Gradually decrease the dose if symptoms improve. Control the symptoms at a lower maintenance dose.

- Crow-Fukase (POEMS) syndrome

Usually, thalidomide is administered orally once daily at bedtime. The adult starting dose is 100 mg of thalidomide on alternate days. Gradually increase the dose to the maintenance dose of 200 mg once daily. The dose should be adjusted according to the patient's condition; however, the daily dose should not exceed 300 mg.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

Crow-Fukase (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes [POEMS]) syndrome is a multisystem disorder considered to be related to multiple myeloma characterized by unique clinical manifestations including polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, pigmentation, osteosclerotic lesions, coarse hair, oedema, pleural effusion, and ascites. As the disease progresses, symptoms such as neurological disorder, respiratory failure, and renal failure emerge, leading to a poor prognosis (e.g., *Neurology*. 1984;34:712-20, *Neurol Neurosurg Psychiatry*. 1997;63:385-7). While the pathological mechanism of POEMS syndrome is not completely elucidated, overproduction of vascular endothelial growth factor (VEGF), associated with plasma cell proliferation is thought to be involved in the development of POEMS syndrome (e.g., *Lancet.* 1996;347:702, *Muscle Nerve.* 1998;21:1390-7). It has been suggested that the frequency of POEMS syndrome in Japan is higher than the US and Europe (*Peripheral Neuropathy, 4th edition.* Elsevier Saunders;2005.p2453-69, *Annual Review: Neurology 2007.* [in Japanese] Chugai-Igakusha;2007.p214-20). In Japan, the estimated number of patients with POEMS syndrome is 392, with an estimated prevalence of 0.3 per 100,000 (*Neurology.* 2019;93:e975-83).

Studies have shown the inhibitory effect of thalidomide on VEGF production (*Expert Opin Drug Metab Toxicol.* 2008;4:973-85) in addition to its various antitumor effects including angiogenesis inhibition, inhibition of cell adhesion factor expression, apoptosis induction, and cell growth inhibition. Thalidomide was approved for the indication of "relapsed or refractory multiple myeloma" in October 2008, and for the indication of "erythema nodosum leprosum" in May 2012, with approval conditions including the following: registration of prescribing physicians, responsible pharmacists, patients, and distributor's responsible pharmacists under the scheme of the Thalidomide Education and Risk Management System (TERMS) to ensure centralized management; and thorough compliance with drug management as well as strict measures to avoid pregnancy.

In Japan, a clinical study started in October 2010 in patients with POEMS syndrome at Chiba University Hospital as an investigator-initiated clinical trial funded by Health and Labour Sciences Research Grants. Recently, the applicant filed an application for partial change approval based on the data that demonstrated efficacy and safety in the treatment of POEMS syndrome. Thalidomide was designated as an orphan drug (Orphan Drug Designation No. 352 of 2014 [*26 yaku*]) dated November 20, 2014, for the intended indication of "Crow-Fukase syndrome."

Outside Japan, as of March 2020, thalidomide has been approved in 50 or more countries or regions including Europe and the US, but has not been approved for the indication of POEMS syndrome in any country or region.

In Japan, there are no approved drugs that are indicated for the treatment of POEMS syndrome.

2. Quality and Outline of the Review Conducted by PMDA

Since the present application relates to a new indication and new dosage, "Data Relating to Quality" were not submitted.

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

Although the present application is for a new indication, the cause of POEMS syndrome has not been elucidated, and patients with POEMS syndrome are treated with treatment regimens similar to those for multiple myeloma, a disorder related to POEMS syndrome. No new data were submitted because no suitable animal models or experimental systems have been established for POEMS syndrome; in addition, thalidomide has been approved for the indication of relapsed or refractory multiple myeloma, and "Data Relating to Non-clinical Pharmacology" have already been evaluated.

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

The present application relates to a new dosage, which is however within the approved dose levels, and "Data Relating to non-clinical pharmacokinetics" have already been evaluated at the initial approval; therefore, no new data were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

"Data Relating to Toxicity" have already been evaluated at the initial approval, and therefore, no new data were submitted.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

No "Data Relating to Biopharmaceutic Studies" were submitted. Plasma thalidomide concentrations were determined by high performance liquid chromatography coupled with ultraviolet absorption spectroscopy (HPLC-UV), with a lower limit of quantitation of 0.05 μg/mL.

6.2 Clinical pharmacology

No new clinical pharmacology studies were conducted for the present application. Data from Study JPOST-10 (CTD 5.3.5.1.3), a Japanese phase II/III study conducted in patients with POEMS syndrome, were submitted for evaluation. The following sections summarize the results based on the plasma thalidomide concentrations measured in the study.

6.2.1 Investigation in patients

Pharmacokinetic parameters were investigated in Japanese patients with POEMS syndrome (the number of patients whose pharmacokinetic data were assessed, 18 patients). In the first week after the start of treatment (Week 1), thalidomide 100 mg was administered on alternate days, and from Week 2, thalidomide was administered once daily every day at the dose levels indicated in Table 1.

Table 1. Pharmacokinetic parameters after single or repeated oral dose administration of thalidomide to Japanese patients with POEMS syndrome (Study JPOST-10)

Time point of blood collection[a)]	Dosage regimen before blood collection	C_{24h} (μg/mL)
1 day after the start of treatment	100 mg on alternate days	0.0866 ± 0.0461 (16[b)])
14 days after the start of treatment	100 mg every day	0.1072 ± 0.0596 (17)
48 weeks after the start of treatment	200 mg every day	0.2449 ± 0.0729 (5)
	300 mg every day	0.3357 ± 0.1720 (2)

Mean ± standard deviation (N)

a) Blood samples were taken from subjects who were registered at 1 specified study center at the following time points:
- 100 mg on alternate days: on Day 2 in Cycle 1 in the long-term open-label period, at 24 ± 1 hour after administration of the previous day's dose
- 100 mg/day dosing: on Day 15 in Cycle 1 in the long-term open-label period, at 24 ± 1 hour after administration of the previous day's dose and immediately before the administration of the dose on Day 15 (if Day 15 is not the last day of the 100 mg/day dosing regimen, a blood sample should be taken on the final day of 100 mg/day administration instead)
- 200 or 300 mg/day: at 48 weeks after the start of treatment (the last dosing day) in the long-term open-label period, or at 24 ± 1 hour after administration of the previous day's dose if treatment is discontinued

b) Data from 2 subjects are missing due to impurity peaks at the time of measurement of blood thalidomide concentrations, and are therefore excluded

6.R Outline of the review conducted by PMDA

The submitted data show that the trough plasma concentrations following administration of repeated dose thalidomide are dose dependent, and PMDA concluded that the data indicated no particular problems.

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

Data from the 2 studies presented in Table 2 were submitted as efficacy and safety evaluation data.

Table 2. List of clinical studies on efficacy and safety

Data category	Location	Study ID CTD	Phase	Study population	N	Summary of dosage regimen	Major endpoints
Evaluation	Japan	Study JPOST-10 5.3.5.1.1 5.3.5.1.2	II/III	Patients with POEMS syndrome ineligible for autologous PBSCT	24[a)]	**Double-blind period** Treatment consisted of 6 cycles, each cycle lasting 4 weeks. In Cycle 1 Week 1, placebo or thalidomide 100 mg was administered on alternate days. From Week 2, the dose was increased to 100 mg/day. From Week 3, the dose was increased to 200 mg/day. **Long-term open-label period** Treatment consisted of 12 cycles, each cycle lasting 4 weeks. In Cycle 1 Week 1, thalidomide 100 mg was administered on alternate days. From Week 2, the dose was increased to 100 mg/day. From Week 3, the dose was increased to 200 mg/day. In the event of a subacute exacerbation[b)] of the primary disease, the dose could be increased up to 300 mg/day.	Efficacy Safety Pharmacokinetics
		Study JPOST-13 5.3.5.2.1	II	Patients with POEMS syndrome eligible for autologous PBSCT	10	Treatment consisted of 6 cycles, each cycle lasting 4 weeks. In Cycle 1 Week 1, thalidomide 100 mg was administered on alternate days. From Week 2, the dose was increased to 100 mg/day. From Week 3, the dose was increased to 200 mg/day. In the event of subacute exacerbation[b)] of the primary disease, the dose could be increased up to 300 mg/day.	Efficacy Safety

a) Number of subjects randomized

b) If one of the following conditions is present and is considered to be subacute exacerbation by the investigator or subinvestigator
- Worsening by a total score of ≥2 in the overall neuropathy limitation scale, or worsening of pleural fluid volume by ≥1 level compared with the test results at the start of double-blind period
- Increased body weight by ≥5 kg/month

7.1 Japanese phase II/III study (CTD 5.3.5.1.1, 5.3.5.1.2, Study JPOST-10 [October 2010 to June 2015])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with POEMS syndrome aged ≥20 years who were ineligible for autologous peripheral blood stem cell transplantation

(PBSCT) and were classified as at least "Probable" of the diagnostic criteria[1)] to assess the safety and efficacy of thalidomide.

The study consisted of a 24-week double-blind period (six 4-week cycles), a 48-week long-term open-label period (twelve 4-week cycles), and a 4-week follow-up period. Patients who experienced subacute exacerbation[2)] of the primary disease in the double-blind period entered the long-term open-label period.

In the double-blind period, placebo or thalidomide 100 mg was administered orally on alternate days in Cycle 1 Week 1. Thereafter, the doses in both the thalidomide and placebo groups were to be increased in accordance with the dose escalation criteria. In the absence of skin or haematological toxicity (neutrophil count decreased, platelet count decreased) of Grade ≥3, the dose was to be increased to 100 mg once daily every day at Week 2. Likewise, in the absence of skin or haematological toxicity, the dose was to be increased to 200 mg once daily every day at Week 3. At each dose level, treatment was to continue for ≥7 days as a guide, and dose increase was to be completed within 28 days in principle. Patients were to take the dose at bedtime at all dose levels. In the double-blind period, treatment consisted of 6 cycles, with each cycle lasting for 4 weeks. In the long-term open-label period, all subjects who were assigned to placebo or thalidomide in the double-blind period were to receive thalidomide. The dosage regimen was similar to that in the double-blind period, while in the long-term open-label period, the dose could be increased up to 300 mg once daily every day in the event of a subacute exacerbation[2)] of the primary disease [for pharmacokinetics, see Section 6.2.1 Investigation in patients].

In the double-blind period, dexamethasone 12 mg/m^2 (body surface area) once daily (maximum dose of 20 mg/day) was to be coadministered for 4 days in a cycle (Days 2-5) after breakfast. In the long-term open-label period, use of dexamethasone was to be considered only when patients experienced subacute exacerbation[2)] of the primary disease after the dose increase to 300 mg/day of thalidomide.

In the double-blind period, of the 25 subjects who received the study drug, 1 subject was excluded because of a critical violation of Good Clinical Practice (GCP),[3)] and the remaining 24 subjects (11 in the placebo and 13 in the thalidomide groups) were included in the full analysis set (FAS), which is the safety analysis set and

1) Definite: patients meeting 3 major criteria and at least 1 minor criteria
Probable: patients meeting both of the following major criteria, peripheral nerve disorders (polyneuropathy) and elevated serum VEGF, and at least 1 minor criteria
Possible: patients meeting the major criterion of peripheral nerve disorders (polyneuropathy), and at least 2 minor criteria
Major criteria: polyneuropathy (required), elevated serum VEGF level (≥1000 pg/mL), M protein (blood M protein-positive
Minor criteria: osteosclerotic lesions, Castleman's disease, organomegaly, oedema, pleural effusion, ascites, hydropericardium, endocrinopathy (functions of the adrenal gland, thyroid gland, pituitary gland, gonad, parathyroid gland, and pancreas), skin abnormalities (pigmentation, coarse hair, haemangioma, cyanosis, pale nail beds), nipple oedema, increased platelets
However, thyroid or pancreatic function abnormalities alone are not considered to be examples of 1 minor criteria because of their high prevalence.

2) If one of the following conditions is present, and is determined to be a subacute exacerbation by the investigator or subinvestigator
- Worsening by a total score of ≥2 in the overall neuropathy limitation scale, or worsening of pleural fluid volume by ≥1 level compared with the test results at the start of double-blind period. The pleural fluid volume was determined based on the chest X-ray with the patient in sitting/standing position, in combination with CT if necessary. Fluid retention in up to 1/4, 1/3, and 1/2 of the lung field was defined as small volume, moderate volume, and large volume, respectively.
- Increased body weight by ≥5 kg/month. Body weight was measured whenever necessary as determined by the investigator or subinvestigator regardless of scheduled visit.

3) This case violated the rule that screening must be performed after obtaining consent. The patient was registered using data obtained before informed consent, and this case was determined to be a critical GCP violation.

efficacy analysis set. Two subjects discontinued the study in the double-blind period due to "patient's request for withdrawal" and "adverse event" in 1 subject each.

Table 3 shows the reduction rate of serum VEGF[4] levels at Week 24, the primary efficacy endpoint. In the primary analysis, in which missing data were imputed by last observation carried forward (LOCF),[5] the reduction rate of serum VEGF levels was significantly higher in the thalidomide group than in the placebo group.

Table 3. Reduction rate of serum VEGF levels at Week 24 (Study JPOST-10, FAS, LOCF)

Treatment	N	Serum VEGF (pg/mL)		Reduction rate of serum VEGF[a) b)]	Thalidomide vs placebo[b)]	
		Baseline	Week 24		Between-group difference [95% CI]	*P*-value
Placebo	11	4742.7 ± 4096.99	4582.7 ± 5144.21	−0.021 ± 0.149	0.409 [0.020, 0.799]	0.040
Thalidomide	13	5037.7 ± 3296.68	2641.2 ± 2092.42	0.388 ± 0.135		

Mean ± standard deviation
a) Least squares mean ± standard error
b) Based on the analysis of covariance (ANCOVA) model with baseline VEGF (<3000 pg/mL vs ≥3000 pg/mL) and pleural effusion (present vs absent) as covariates.

In the double-blind period, adverse events (including laboratory abnormalities) were reported in 11 subjects in the placebo group and all 13 subjects in the thalidomide group. No deaths were reported. Serious adverse events other than death occurred in 2 subjects in the placebo group (ileus and pyrexia in 1 subject each), 3 subjects in the thalidomide group (cardiac arrest, cardiac failure, and dehydration in 1 subject each). A causal relationship to the study drug could not be ruled out except for 1 subject (dehydration) in the thalidomide group. Adverse events (including laboratory abnormalities) for which a causal relationship to the study drug could not be ruled out occurred in 8 of 11 subjects (72.7%) in the placebo group, 10 of 13 subjects (76.9%) in the thalidomide group, and these adverse events were classified as follows: constipation (4 subjects and 8 subjects in the placebo and thalidomide groups, respectively; the same applies hereinafter for the order of treatment groups), sinus bradycardia (0 subjects, 7 subjects), hyperkalaemia (1 subject, 3 subjects), somnolence (1 subject, 3 subjects), pyrexia (2 subjects, 2 subjects), neutrophil count decreased (1 subject, 2 subjects), eosinophil count increased (0 subjects, 2 subjects), white blood cell count decreased (0 subjects, 2 subjects), dry skin (0 subjects, 2 subjects), urticaria (0 subjects, 2 subjects), and other events.

Of the vital parameters (blood pressure, pulse rate, and body weight) examined in the double-blind period, the pulse rate declined from baseline in the thalidomide group from the end of Cycle 3 to the end of Cycle 5.

In the long-term open-label period, a total of 23 subjects, 22 subjects who entered the long-term open-label study (13 subjects after completing Week 24, and 9 subjects before Week 24 due to subacute exacerbation) and 1 subject[3] who was excluded due to GCP violation in the double-blind period, were included in the FAS, which is the safety analysis set and efficacy analysis set. In the long-term open-label period, 9 subjects were

4) Rate of reduction in serum VEGF = (Serum VEGF level at baseline − Serum VEGF level at 24 Weeks) / Serum VEGF level at baseline
5) In the addendum to the statistical analysis plan prepared after unmasking, LOCF is defined as follows: "If the data at the end of the random period, i.e., the final evaluation time point, are missing, and evaluation values at scheduled visit before the final evaluation time point are available, the missing value should be imputed with the evaluation value at the closest time point to the end of the random period. If the baseline value is the only evaluation value available prior to the final evaluation time point, the missing value should be imputed with the baseline value" [see Section 7.R.1].

discontinued from the study for the reasons of "adverse event" (4 subjects), "study drug treatment discontinuation was deemed necessary by the physician" (4 subjects), and "study drug administration was deemed inappropriate by the physician" (1 subject).

In the long-term open-label period, the reduction rate of serum VEGF levels at the completion of treatment compared with baseline (mean ± standard deviation) was 0.278 ± 0.401.

In the long-term open-label period, adverse events (including laboratory abnormalities) were reported in 21 of 23 subjects (91.3%). Two subjects died (due to an exacerbation of POEMS syndrome in both subjects). Serious adverse events other than death occurred in 11 subjects (exacerbation of POEMS syndrome in 3 subjects; pneumonia in 2 subjects; exacerbation of POEMS syndrome/lung infection/pleural effusion, exacerbation of POEMS syndrome/Prinzmetal angina/ileus/sinus arrest/cerebral infarction, exacerbation of POEMS syndrome/neutrophil count decreased, inguinal hernia/cerebral infarction/lipoma/cardio-respiratory arrest/cataract, intestinal obstruction, and syncope in 1 subject each). Among these events, a causal relationship to the study drug could not be ruled out for cerebral infarction (2 subjects), pneumonia (2 subjects), ileus, intestinal obstruction, Prinzmetal angina, sinus arrest, neutrophil count decreased, and syncope. Adverse events (including laboratory abnormalities) for which a causal relationship to the study drug could not be ruled out occurred in 18 of 23 subjects (78.3%), with major events including constipation (7 subjects), peripheral sensory neuropathy (5 subjects), sinus bradycardia (4 subjects), neutrophil count decreased (3 subjects), disseminated intravascular coagulation (2 subjects), pneumonia (2 subjects), lung infection (2 subjects), and cerebral infarction (2 subjects).

In the long-term open-label period, the following vital sign-related events were reported: sinus bradycardia (4 subjects), cardio-respiratory arrest (1 subject), and sinus arrest (1 subject).

7.2 Japanese phase II study (CTD 5.3.5.2.1, Study JPOST-13 [August 2013 to August 2015])

A single-center, open-label, uncontrolled study was conducted in patients with POEMS syndrome aged ≥20 years and ≤65 years who were classified as at least "Probable" of the diagnostic criteria[1)] to assess the safety and efficacy of thalidomide as induction treatment prior to autologous PBSCT.

The study consisted of a 24-week treatment period (six 4-week cycles) and a 4-week follow-up period.

Thalidomide 100 mg was administered orally on alternate days in Cycle 1 Week 1, and thereafter, the doses were to be increased in accordance with the dose escalation criteria. In the absence of skin or haematological toxicity (neutrophil count decreased, platelet count decreased) of Grade ≥3, the dose was to be increased to 100 mg once daily every day at Week 2. Likewise, in the absence of skin or haematological toxicity, the dose was to be increased to 200 mg once daily every day at Week 3. At each dose level, treatment was to continue for ≥7 days as a guide, and dose increase was to be completed within 28 days in principle. Patients were to take the dose at bedtime at all dose levels.

Dexamethasone 20 mg was to be coadministered once daily for 8 days in a cycle (Days 2-5 and Days16-19) after breakfast.[6)]

All 10 subjects who received thalidomide were included in the FAS, which is the safety analysis set and efficacy analysis set. One subject was discontinued from the study (adverse events that inhibit continuation of study drug treatment/physician's decision).

The reduction rate of serum VEGF levels (mean ± standard deviation) from baseline at Week 24 was 0.69 ± 0.33. At Week 24, 20% (2 of 10) of subjects achieved complete remission,[7)] 30% (3 of 10) of subjects achieved partial remission,[8)] and (9 of 10) of subjects achieved treatment completion 90%.

Adverse events (including laboratory abnormalities) occurred in all subjects. No deaths were reported. Serious adverse events other than death were cerebral infarction, syncope, blood immunoglobulin G decreased, and acute renal failure (1 subject each). Among these events, a causal relationship to the study drug could not be ruled out for cerebral infarction and acute renal failure. Adverse events (including laboratory abnormalities) for which a causal relationship to the study drug could not be ruled out occurred in all subjects, with major events including constipation (9 subjects), sinus bradycardia (5 subjects), and somnolence (2 subjects). A vital sign-related event, sinus bradycardia, occurred in 5 subjects.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Primary endpoint and secondary endpoints

PMDA asked the applicant to explain the appropriateness of efficacy endpoint specifications in the Japanese phase II/III study (CTD 5.3.5.1.1, 5.3.5.1.2, Study JPOST-10) including the rationale.

The applicant's explanation:

- In some cases, specific symptoms may be selected as a primary endpoint; however, given that POEMS syndrome is characterized by a wide variety of clinical manifestations including polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, pigmentation, osteosclerotic lesions, coarse hair, oedema, pleural effusion, and ascites, it was considered difficult to specify the primary endpoint as an improvement of a certain clinical symptom at the time of planning of the study.
- It has been suggested that the proliferation of plasma cells and associated excess secretion of VEGF are involved in the various clinical manifestations of POEMS syndrome (e.g., *Lancet.* 1996;347:702, *J Rheumatol.* 1998;25:813-5), and multiple studies (e.g., *Blood.* 2011;118:4663-5, *Blood.* 2018;131:2173-6) have reported a correlation between serum VEGF levels and clinical symptoms.
- In addition, while serum VEGF levels are stabilized at 24 weeks after the start of pharmacotherapy, clinical symptoms are expected to improve after serum VEGF levels have been lowered and stabilized. For this

6) Coadministration on Days 16-19 is only in Cycles 1 and 2.
7) A serum VEGF of <1000 pg/mL and M-protein qualitative test negative (blood, immunofixation), or a serum VEGF of <1000 pg/mL and disappearance of oedema
8) A serum VEGF of <1000 pg/mL

reason, it is appropriate to evaluate at 12 months after the start of treatment. However, continuation of the base treatment in the placebo group for >24 weeks may affect development of a subacute exacerbation or life prognosis, and therefore it was considered difficult from an ethical point of view.

- The above points indicated that the treatment duration of 24 weeks is appropriate for a placebo-controlled study, and it was decided to specify an evaluable primary endpoint in the double-blind period during the 24 weeks. Accordingly, the reduction rate of serum VEGF levels was selected as the primary endpoint as it is a quantitative, objective indicator which can avoid measurement error between local laboratories through a centralized measurement system. It was also decided to assess the effects on clinical symptoms by specifying secondary endpoints, namely, pleural fluid volume, manual muscle strength testing, overall neuropathy limitation scale, median nerve conduction study parameters, and quality of life (QOL) assessed by the MOS 36-Item Short-Form Health Survey (SF-36[9)]) for comprehensive evaluation of efficacy.

Regarding the primary endpoint for Study JPOST-10 (double-blind period and long-term open-label period), the statistical analysis plan prepared before unmasking specified that missing values were to be imputed by LOCF without detailed description, and gave no specifications as to which data should and should not be included. In the addendum to the statistical analysis plan prepared after database lock and unmasking, LOCF is clearly defined. PMDA asked the applicant to explain the circumstance leading to the change, and the justification for using the analysis results after the change for efficacy evaluation.

The applicant's explanation:

- When the statistical analysis plan was prepared, the coordinating investigator and the advisor statistician understood the LOCF method as follows: the method imputes the measured values at the scheduled visit before entering the long-term open-label period before Week 24 or immediately before discontinuation from the study because (1) when a patient is discontinued from the study, it is unknown whether the patient is on treatment; (2) during a subacute exacerbation, both water and serum proteins leak out from vessels in large quantities, and thus serum VEGF level is not necessarily a suitable parameter for evaluation of efficacy. However, there are no documents that can verify the above understanding back then.
- On the contrary, the analysis result report (draft) and the clinical study report (draft) submitted to the coordinating investigator and the investigator by the statistical analysis manager after database lock and unmasking revealed that missing value imputation by LOCF had been performed using the measured values at the final evaluation time point in the double-blind period (i.e., at the time of discontinuation or entering the long-term open-label period before Week 24). Accordingly, to ensure the use of observation data measured at a scheduled visit at entering the long-term open-label period before Week 24 or immediately before discontinuation for missing data imputation, the definition for LOCF was included in the addendum to the statistical analysis plan: "If the data at the end of the random period, i.e., the final evaluation time point, are missing, and evaluation values at scheduled visit before the final evaluation

9) The survey consists of 8 subscale scores (36 questionnaire items, 3- to 5-point scale assessment): physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH).

time point are available, the missing value should be imputed with the evaluation value at the closest time point to the end of the random period."

- Table 4 shows the results for the reduction rate of serum VEGF levels at Week 24, the primary endpoint, which is based on the primary analysis, and the analyses with different imputation methods. While the statistical hypothesis test results differ among the analyses, a similar trend towards a greater reduction in serum VEGF levels in the thalidomide group compared with the placebo group was observed in all analyses.

Table 4. Reduction rate of serum VEGF levels at Week 24 (Study JPOST-10, FAS)

Missing data imputation method	Treatment	N	Reduction rate of serum VEGF levels (least squares mean ± standard error)[a)]	Thalidomide vs placebo[a)]	
				Between-group difference [95% CI]	*P*-value
LOCF[b)]	Placebo	11	−0.021 ± 0.149	0.409 [0.020, 0.799]	0.040
	Thalidomide	13	0.388 ± 0.135		
LOCF (before change)[c)]	Placebo	11	0.095 ± 0.1388	0.245 [−0.1180, 0.6089]	0.174
	Thalidomide	13	0.341 ± 0.1262		
WOCF	Placebo	11	−0.057 ± 0.150	0.373 [−0.019, 0.765]	0.061
	Thalidomide	13	0.316 ± 0.136		
MMRM	Placebo	10	−0.009 ± 0.157	0.550 [0.110, 0.990]	0.017
	Thalidomide	11	0.541 ± 0.149		

a) LOCF, LOCF (before change), and worst observation carried forward (WOCF) are based on the ANCOVA model with baseline VEGF (<3000 pg/mL vs ≥3000 pg/mL) and pleural effusion (present vs absent) as covariates.
MMRM is based on the mixed model repeated measures (MMRM) with treatment group, baseline VEGF (<3000 pg/mL vs ≥3000 pg/mL), pleural effusion (present vs absent), visit, and treatment group-by visit interaction as factors, using an unstructured correlation structure.
b) Primary analysis
c) Missing data of patients who were discontinued from the study and those who entered the long-term open-label period before Week 24 were imputed with data measured at the final evaluation time point.

- During a subacute exacerbation, both water and serum proteins leak out from vessels in large quantities, and thus serum VEGF levels are not necessarily a suitable parameter for evaluation of efficacy. It is therefore appropriate to perform missing data imputation with values measured at a scheduled visit at entering the long-term open-label period before Week 24 or immediately before discontinuation from the study to ensure that efficacy is evaluated appropriately. In addition, it later turned out that none of the patients were on treatment "at the time of entering the long-term open-label period before Week 24 or discontinuation from the study," and at the time point, the change in serum VEGF levels showed trends different from those earlier in some of the patients. Therefore, it is considered appropriate to use the results of analysis in which missing data were imputed using values measured at a scheduled visit immediately before entering the long-term open-label period before Week 24 or immediately before discontinuation from the study.

PMDA asked the applicant to explain the efficacy of thalidomide in relation to the clinical symptoms selected as secondary endpoints.

The applicant's explanation:

- Manual muscle strength testing: in the double-blind period of Study JPOST-10, no marked differences were noted between the thalidomide and placebo groups based on the prespecified assessment by muscle group. However, in a total score assessment, which was an additional assessment, the total score (least squares mean ± standard error) was 81.1 ± 1.16 (11 subjects) in the placebo group and 84.1 ±

0.95 (13 subjects) in the thalidomide group, with the between-group difference and the 95% confidence interval (CI) being 3.0 [0.03, 5.99] (an MMRM analysis assuming compound symmetry for the correlation structure, with treatment group, baseline values, visit, treatment group-by-visit interaction as factors), showing a trend towards an increase after treatment with thalidomide. Change from baseline in the score of each muscle group in Study JPOST-10 (double-blind period) is summarized in Table 5, and that in Study JPOST-10 (long-term open-label period) and Study JPOST-13 (Japanese phase II study, CTD 5.3.5.2.1) in Table 6. In both sets of data, manual muscle strength tended to be either maintained or improved in the thalidomide group. In the upper limbs, muscle strength tended to be maintained, while in the lower limbs, muscle strength tended to be either maintained or improved, suggesting that the results are of clinical significance in POEMS syndrome, which is characterized by a significant deterioration in the muscles of the lower limbs.

Table 5. Change from baseline in the manual muscle strength score (mean of right and left) of each muscle group at the end of treatment, at the time of discontinuation from the study, or entering the long-term open-label period before Week 24
(Study JPOST-10 [double-blind period], FAS)

Category		Placebo (N = 11)			Thalidomide (N = 12[a)])		
		No change	Decreased	Increased	No change	Decreased	Increased
Proximal upper limb	Deltoid	8	3	0	11	1	0
	Biceps brachii	8	2	1	11	0	1
Distal upper limb	Wrist extensor	9	2	0	11	1	0
	Finger extensors	10	1	0	9	2	1
Proximal lower limb	Iliopsoas muscle	8	3	0	8	1	3
	Quadriceps femoris	10	1	0	11	0	1
	Biceps femoris	8	3	0	7	1	4
Distal lower limb	Tibialis anterior	8	3	0	9	2	1
	Gastrocnemius	9	1	1	10	0	2

a) One subject was excluded from the analysis due to missing data at the time of discontinuation from the study

Table 6. Change from baseline in the manual muscle strength score (mean of right and left) of each muscle group at the end of treatment or at the time of discontinuation from the study
(Study JPOST-10 [long-term open-label period] and Study JPOST-13, FAS)

Category		Long-term open-label period in Study JPOST-10 (N = 20[a)])			Study JPOST-13 (N = 10)		
		No change	Decreased	Increased	No change	Decreased	Increased
Proximal upper limb	Deltoid	18	1	1	9	0	1
	Biceps brachii	18	1	1	8	0	2
Distal upper limb	Wrist extensor	15	2	3	8	0	2
	Finger extensors	13	2	5	6	1	3
Proximal lower limb	Iliopsoas muscle	15	3	2	3	1	6
	Quadriceps femoris	17	1	2	6	0	4
	Biceps femoris	15	1	4	5	0	5
Distal lower limb	Tibialis anterior	16	2	2	6	0	4
	Gastrocnemius	15	2	3	5	0	5

a) Three subjects were excluded from the analysis due to missing data at the time of discontinuation from the study

- Grip strength: in the double-blind period of Study JPOST-10, no marked differences were noted between the thalidomide and placebo groups, while slight increases were noted in the long-term open-label period in Study JPOST-10, with the median values being 21.5 kg at baseline vs 24.3 kg at the end of treatment (mean of right and left); and in Study JPOST-13, with the median values being 15.5 kg (left) and 17.0 kg (right) at baseline, vs 18.5 kg (left) and 20.5 kg (right) at the end of treatment or discontinuation. Overall neuropathy limitation scale: in the double-blind period of Study JPOST-10, no marked differences were noted between the thalidomide and placebo groups; however, total scores tended to be improved in the long-term open-label period in Study JPOST-10, with the median values being 4.0 at baseline vs 2.0

at the end of treatment, and in Study JPOST-13, with the median values being 5.5 at baseline vs 4.0 at the end of treatment or discontinuation.

- Median nerve (right and left) amplitudes of compound muscle action potential, motor nerve conduction velocity, and F-wave latencies: in the double-blind period of Study JPOST-10, no marked differences were noted between the thalidomide and placebo groups for any of the indicators. In the long-term open-label period in Study JPOST-10, there were trends towards an increase (improvement) in the median nerve amplitudes of compound muscle action potential (median values; right, from 4.50 mV to 4.90 mV; left, from 4.10 mV to 5.80 mV) and in motor nerve conduction velocity (median values; right, from 35.0 m/s to 38.5 m/s; left, from 34.0 m/s to 38.0 m/s), and there was a trend towards a decrease (improvement) in F-wave latency (median values; right, from 42.9 ms to 37.8 ms; left, from 41.9 ms to 38.1 ms). In Study JPOST-13, there were trends towards an increase (improvement) in the median nerve amplitudes of compound muscle action potential (median values; from 4.70 mV to 5.30 mV) and in motor nerve conduction velocity (median values; from 32.5 m/s to 40.0 m/s), and there was a trend towards a decrease (improvement) in F-wave latency (median values; from 48.0 ms to 39.4 ms).
- Pleural fluid volume: in the double-blind period in Study JPOST-10, no marked differences were noted between the thalidomide and placebo groups. Table 7 shows changes in pleural fluid volume based on categorical evaluation (none, small, moderate, or large) in Study JPOST-10 (double-blind and long-term open-label periods) and Study JPOST-13 from baseline to the end of treatment (including data at the time of discontinuation or entering the long-term open-label period before Week 24 in Study JPOST-10). Compared with the placebo group, a decrease in pleural fluid volume occurred in more subjects in the thalidomide group, and an increase in pleural fluid volume occurred in only few subjects.

Table 7. Change from baseline in pleural fluid volume at the end of treatment (Studies JPOST-10 and JPOST-13, FAS)

Baseline	At the end of treatment (including data at the time of discontinuation or entering the long-term open-label period before Week 24 in Study JPOST-10)															
	Double-blind period of Study JPOST-10								Long-term open-label period of Study JPOST-10				Study JPOST-13			
	Placebo				Thalidomide											
	None	Small	Moderate	Large	None	Small	Moderate	Large	None	Small	Moderate	Large	None	Small	Moderate	Large
None	6	1	1	0	7	2	0	0	14	1	0	0	5	0	0	0
Small	0	1	1	0	1	1	0	0	2	1	1	0	4	1	0	0
Moderate	0	0	0	1	1	0	0	0	0	0	1	1	0	0	0	0
Large	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0

Number of subjects

- QOL assessed by the SF-36[9)] score: in the double-blind period of Study JPOST-10, 3 of the 8 subscales of SF-36 (BP, RE, and MH) either improved or remained unchanged, and the remaining 5 subscales (PF, RP, GH, VT, and SF) decreased, all by a greater degree, in the placebo group; in contrast, 6 of the 8 subscales of SF-36 (BP, GH, VT, SF, RE, and MH) either improved or remained unchanged, and the remaining 2 subscales (PF and RP) decreased, both by a relatively small degree, in the thalidomide group. In the long-term open-label period in Study JPOST-10, only the scores of subscale BP remained unchanged; however, the scores of the remaining 7 subscales improved. The results of Study JPOST-13 showed improvements in all 8 subscales.
- The above results indicated that clinical symptoms established as endpoints improved or remained unchanged in many subjects in Study JPOST-10 (double-blind and long-term open-label periods) and Study JPOST-13.

7.R.1.2 Progression-free survival and overall survival

Since POEMS syndrome is related to multiple myeloma, the most likely goal of its treatment is prolonged survival; therefore, PMDA considered that the efficacy of thalidomide should also be evaluated based on data including overall survival, and asked the applicant to present the results for these efficacy indices.

The applicant's explanation:

- Progression-free survival and overall survival were evaluated in 25 patients (12 in the placebo and 13 in the thalidomide groups) who were registered in Study JPOST-10 using data from Study JPOST-10 and its extension study, JPOST-12.[10)] Study JPOST-10 was not designed to evaluate progression-free survival or overall survival; therefore, it was decided that "subacute exacerbation" or "death" events that occurred during the study period were to be retrieved afterwards and handled as events. The progression-free survival analysis continued up to the day medication was discontinued while overall survival analysis continued up to the final observation day. One subject in the placebo group who violated GCP was censored at the time of registration to Study JPOST-10. The results of progression-free survival and overall survival analyses are shown below.
- The Kaplan-Meier plot for progression-free survival is shown in Figure 1. The median follow-up period was 7.7 months, the median progression-free survival was 4.3 months in the placebo group[11)] and 71.8 months in the thalidomide group. The hazard ratio between groups with its 95% CI was 0.418 [0.110–1.586].

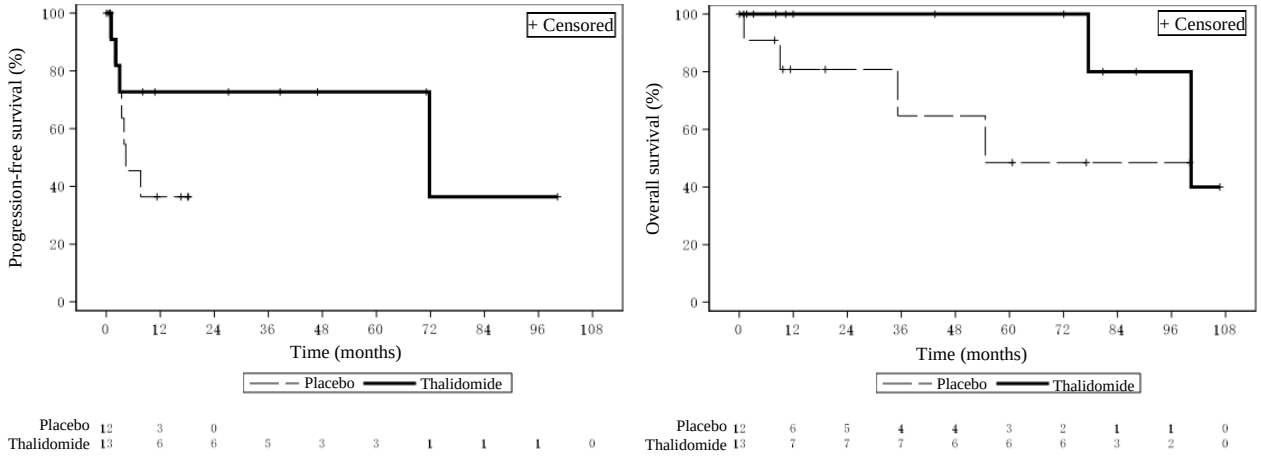

Figure 1. Kaplan-Meier plots for progression-free survival (left) and overall survival (right) (Studies JPOST-10 and JPOST-12, FAS)

- Figure 1 shows the Kaplan-Meier plot for the overall survival. The median follow-up period was 19.1 months. During the follow-up period, 4 of 12 subjects died in the placebo group (exacerbation of primary disease [2 subjects], acute myeloid leukaemia [1 subject], and ischaemic heart disease [1 subject]); and 2 of 13 subjects died in the thalidomide group (exacerbation of primary disease [1 subject] and

10) Study JPOST-12 was conducted in patients who had completed Study JPOST-10 to provide opportunities to receive thalidomide treatment up to the time of approval of new indication for thalidomide and to evaluate the long-term safety and efficacy of thalidomide.
11) The placebo group was established only in the double-blind period of Study JPOST-10. In the long-term open-label period of Study JPOST-10 and thereafter, all patients were treated with thalidomide.

cholangiocarcinoma [1 subject]). The median overall survival was 54.6 months in the placebo group and 100.4 months in the thalidomide group. The hazard ratio between groups with its 95% CI was 0.185 [0.022–1.540].

- Placebo-treated subjects started thalidomide treatment after entering the long-term open-label period before Week 24 due to subacute exacerbation or completion of the double-blind period. Despite the fact that subjects in the placebo group received thalidomide as a post-treatment therapy, there was a difference in prognosis between groups, suggesting that early initiation of thalidomide treatment in patients with POEMS syndrome is meaningful.

PMDA asked the applicant to explain the clinical course of censored patients in the progression-free survival and overall survival analyses including the reasons for censoring.

The applicant's explanation:

- A total of 14 subjects (5 in the placebo and 9 in the thalidomide groups) were censored in the progression-free survival analysis, with the reasons for censoring being "adverse events" in 6 subjects, "remission" in 3 subjects, "insufficient effectiveness" in 1 subject, "patient's request for withdrawal" in 1 subject, "treatment being inappropriate" in 1 subject, "continuation not possible" in 1 subject, and "data were not used due to GCP violation" in 1 subject (Table 8). A total of 19 subjects (8 in the placebo and 11 in the thalidomide groups) were censored in the overall survival analysis, with the reasons for censoring being "final observation day" in 16 subjects, "lost to follow-up" in 1 subject, "patient's request for withdrawal" in 1 subject, and "data were not used due to GCP violation" in 1 subject.

Table 8. List of subjects censored in the progression-free survival analysis (excluding 1 subject whose data were not used due to GCP violation)

Assigned treatment in the double-blind period in Study JPOST-10	Reason for censoring	Clinical course[a)]
Thalidomide	Insufficient effectiveness	Approximately 8 months after a dose increase to thalidomide 300 mg/day, the patient was determined as "insufficient effectiveness" and thalidomide was discontinued to initiate a chemotherapy regimen (no detailed information).
Thalidomide	Adverse events	After a dose increase to thalidomide 200 mg/day, the dose was decreased to thalidomide 100 mg on alternate days due to an adverse event. On the 21st day after the dose reduction, thalidomide treatment ended due to "an adverse event (peripheral sensory neuropathy)."
Placebo	Adverse events	On the first day the patient started Study JPOST-12, thalidomide treatment was discontinued due to "an adverse event (cardio-respiratory arrest), with the thalidomide dose on the previous day being the last dose.
Thalidomide	Remission	Approximately 3 years and 11 months after the start of thalidomide treatment, thalidomide treatment ended due to "remission."
Thalidomide	Adverse events	After a dose increase to thalidomide 200 mg/day, the dose was decreased to thalidomide 100 mg/day due to an adverse event. On the 21st day after the dose reduction, thalidomide treatment ended due to "an adverse event (peripheral sensory neuropathy)."
Placebo	Adverse events	Thalidomide treatment was discontinued due to "an adverse event (pneumonia)," which occurred approximately 5 months after a dose increase to thalidomide 200 mg/day.
Thalidomide	Adverse events	The dose was increased to thalidomide 100 mg/day, and then decreased to thalidomide 100 mg on alternate days due to an adverse event. Subsequently, thalidomide treatment was discontinued due to "an adverse event (neutrophil count decreased)."
Thalidomide	Patient's request for withdrawal	Two days after a dose increase to thalidomide 200 mg/day, thalidomide treatment ended due to "patient's request for withdrawal."
Thalidomide	Adverse events	Twelve days after a dose increase to thalidomide 200 mg/day, thalidomide treatment was discontinued due to "an adverse event (cardiac arrest)."
Placebo	Remission	The dose was increased to thalidomide 200 mg/day, and then decreased to thalidomide 100 mg/day. On the 27th day after the dose reduction, thalidomide treatment ended due to "remission."
Placebo	Treatment being inappropriate	The dose was increased to thalidomide 200 mg/day, and then decreased to thalidomide 100 mg on alternate days due to an adverse event. Approximately in the fifth month after dose reduction, the patient needed to start a different therapy, as determined by the investigator and other healthcare professionals due to being refractory to thalidomide. Thalidomide treatment ended because "the treatment was inappropriate" for the patient.
Thalidomide	Continuation not possible	The dose was increased to thalidomide 200 mg/day, and then decreased to thalidomide 100 mg/day. In the 6th year after the dose reduction, the patient died of intrahepatic bile duct cancer. Thalidomide treatment ended due to "continuation not possible."
Thalidomide	Remission	Approximately 4 years 11th months after the start of thalidomide treatment, the treatment ended due to "remission."

a) Adverse events are those that had been developed at the time of censoring

PMDA recognized the possible risk of overestimating the efficacy of thalidomide if subjects in the thalidomide group were censored for study drug discontinuation due to adverse events, insufficient effectiveness, patient's request for withdrawal, or continuation not possible, and the possible risk of underestimating the efficacy of thalidomide if subjects in the thalidomide group were censored for study drug discontinuation due to remission. PMDA therefore asked the applicant to present additional analysis results based on the definition of censoring as an event for patients in whom efficacy was likely to have been overestimated, and to explain the efficacy of thalidomide taking the results into account.

The applicant's explanation:

- In the progression-free survival analysis, based on the clinical course from the start of Study JPOST-10 to the final observation day, it was considered that censoring of 3 subjects (2 subjects who died and 1 subject who had increased pleural fluid volume and was assessed as subacute exacerbation) could lead to underestimation of the incidence of the events. In Study JPOST-12, it was difficult to evaluate the effect of post-treatment therapies on the efficacy of the study drug because collection of information on post-treatment therapies administered between the discontinuation of thalidomide treatment and the final observation day had not been specified. For this reason, a sensitivity analysis was performed after excluding 3 subjects censored due to remission and 1 subject whose data were not used due to GCP

violation. After defining the censoring as an event, this additional analysis included 10 subjects who had been censored in the previous analysis (3 and 7 subjects assigned to the placebo and thalidomide groups, respectively, in the double-blind period in Study JPOST-10). Figure 2 shows the Kaplan-Meier plot for progression-free survival. The median progression-free survival was 4.3 months in the placebo group[11)] and 10.8 months in the thalidomide group. The hazard ratio between groups with its 95% CI was 0.533 [0.201–1.415].

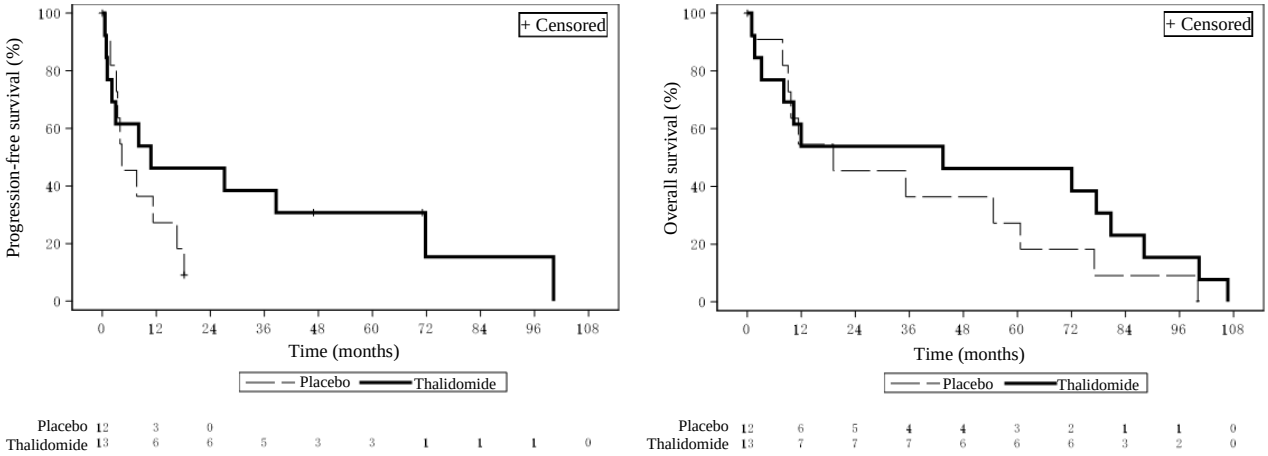

Figure 2. Kaplan-Meier plots for progression-free survival (left) and overall survival (right) in the sensitivity analysis in which some censored data were counted as events (Studies JPOST-10 and JPOST-12, FAS)

- In the overall survival analysis, the censoring time point was defined as the final observation day. Since there were no new events, there will be no effects on the incidence of events. A sensitivity analysis was performed after excluding 1 subject whose data were not used due to GCP violation. After defining the censoring as an event, the analysis included 18 subjects who had been censored in the previous analysis (7 and 11 subjects assigned to the placebo and thalidomide groups, respectively, in the double-blind period in Study JPOST-10). Figure 2 shows the Kaplan-Meier plot for overall survival. The median overall survival was 19.1 months in the placebo group and 43.5 months in the thalidomide group. The hazard ratio between groups with its 95% CI was 0.630 [0.267–1.483].
- Although there were a certain number of censored cases that may affect the evaluation of progression-free survival and overall survival in Studies JPOST-10 and JPOST-12, each censored case was closely examined, and an additional sensitivity analysis was performed by defining the censoring that may lead to overestimation of the efficacy of thalidomide as events. As a result of the additional analysis, progression-free survival and overall survival tended to be prolonged in the thalidomide group than in the placebo group. Thus, the efficacy of thalidomide is expected in patients with POEMS syndrome.

PMDA's view on the efficacy of thalidomide based on the discussions in Sections 7.R.1.1 and 7.R.1.2:

- Although the decrease in serum VEGF levels, the primary endpoint, may not always lead to clinically meaningful improvement of symptoms, given that POEMS syndrome is a rare disease exhibiting a wide variety of clinical manifestations, and thus difficult to evaluate by selecting a specific symptom as a primary endpoint, it was reasonable to conduct the clinical study using an approach that allowed a

comprehensive evaluation of efficacy by selecting serum VEGF levels as the primary endpoint and clinical symptoms as the secondary endpoints.

- In the analysis for the primary endpoint, the analysis method was modified after database lock and unmasked without clarifying the definition for missing data imputation by LOCF in advance. This raises the concern that data may have been evaluated arbitrary and was not appropriate when performing efficacy evaluation. Nevertheless, VEGF is thought to be involved in POEMS syndrome, and published literature (e.g., *Blood.* 2011;118:4663-5, *Blood.* 2018;131:2173-6) have reported the correlation between serum VEGF level and clinical symptoms. Besides LOCF, other sensitivity analyses for imputation show trends towards a decrease in VEGF in thalidomide-treated subjects compared with placebo.
- The applicant explained that various clinical manifestations of POEMS syndrome tended to improve in Study JPOST-13. Given that the results were obtained in an exploratory discussion conducted unmasked by comparing data before and after thalidomide treatment, and that a trend towards improvement was observed only in limited categories of clinical symptoms in the double-blind period in Study JPOST-10, it is difficult to clearly determine whether clinical manifestations of POEMS syndrome have improved as a result of thalidomide treatment. Meanwhile, the manual muscle strength test showed that muscle strength tended to be maintained or improve in the long-term open-label period of Study JPOST-10 and Study JPOST-13, after long-term treatment with thalidomide, compared with muscle strength in the double-blind period in Study JPOST-10. It has been also suggested that other clinical symptoms, such as pleural fluid volume, showed some trend towards improvement. In Studies JPOST-10 and JPOST-13, pleural fluid volume at the end of the study or discontinuation remained unchanged or improved compared with baseline in many thalidomide-treated subjects.
- In the double-blind period in Study JPOST-10, improvement in patients' QOL was not indicated in subscales PF and RP. However, the scores of BP, the extent of pain or limitation of activity in life due to pain, and GH, rating of current health status, tended to improve or remain unchanged. In Study JPOST-13, all subscales of the SF-36 tended to improve.
- There were trends towards a decrease in the serum VEGF levels, the primary endpoint, and data also suggest some trends towards improvement in clinical symptoms, the secondary endpoints. These findings as well as the above trends indicate that symptoms may improve after long-term treatment with thalidomide.
- Since POEMS syndrome is considered to be related to multiple myeloma, the most likely goal of its treatment is prolonged survival. Therefore, it is not appropriate to evaluate the efficacy of thalidomide based only on these endpoints, and a comprehensive evaluation should be performed including overall survival data.
- The analysis for progression-free survival and overall survival in patients who registered in Study JPOST-10 (Figure 1) was not planned in advance, but rather, it was an exploratory evaluation. Taking into account various factors including the handling of censoring, which could have had an effect on efficacy evaluation results, evaluating efficacy based solely on the results is difficult. However, sensitivity analysis results based on the most cautious estimate (Figure 2) suggest that progression-free survival and overall survival tended to be prolonged in the thalidomide group compared with the placebo group.

- Taken together, thalidomide is expected to have a certain level of efficacy; however, given the limitations in the evaluation of endpoints, a final decision on the efficacy of thalidomide will be made, taking account of comments from the Expert Discussion.

7.R.2 Safety

7.R.2.1 Differences in safety profiles between patients with multiple myeloma and patients with POEMS syndrome

PMDA asked the applicant to explain the safety profiles of thalidomide in patients with POEMS syndrome, and how those profiles differ from the safety profiles of patients with multiple myeloma, for which thalidomide has already been approved.

The applicant's explanation:

- Table 9 shows the incidence of adverse events in Japanese clinical studies in patients with POEMS syndrome (CTD 5.3.5.1.1, 5.3.5.1.2, Study JPOST-10; CTD 5.3.5.2.1, Study JPOST-13) and clinical studies in patients with relapsed or refractory multiple myeloma (Study FPF300-02-01 [data for initial application for approval of Thaled Capsules 100, CTD 5.3.5.1] and Study FPF300-02-02[12]). Sinus bradycardia occurred more commonly in patients with POEMS syndrome than in patients with multiple myeloma.
- Table 10 shows the incidence of adverse events that had not been reported in Studies FPF300-02-01 and FPF300-02-02, but were reported in Study JPOST-10 or JPOST-13. Adverse events classified as serious include arrhythmia and cardiovascular-related adverse events.

12) A long-term extension study for FPF300-02-01 participants

Table 9. Incidence of adverse events in Japanese clinical studies in patients with POEMS syndrome or multiple myeloma (safety analysis set)

	POEMS syndrome				Multiple myeloma
	Double-blind period in Study JPOST-10		Double-blind and long-term open-label periods in Study JPOST-10 (N = 25)	Study JPOST-13 (N = 10)	Studies FPF300-02-01 and FPF300-02-02 (N = 37)
	Placebo (N = 11)	Thalidomide (N = 13)			
All adverse events	11 (100.0)	13 (100.0)	25 (100.0)	10 (100.0)	37 (100.0)
Adverse events for which a causal relationship to the study drug could not be ruled out	8 (72.7)	10 (76.9)	23 (92.0)	10 (100.0)	37 (100.0)
Death	0	0	2 (8.0)	0	2 (5.4)
Serious adverse events other than death	2 (18.2)	3 (23.1)	13 (52.0)	3 (30.0)	11 (29.7)
Adverse events leading to treatment discontinuation	0	1 (7.7)	7 (28.0)	1 (10.0)	25 (67.6)
Adverse events occurring in ≥2 subjects in the thalidomide group in the Japanese clinical study conducted in patients with POEMS syndrome					
Pneumonia	0	1 (7.7)	5 (20.0)	0	5 (13.5)
Anaemia	0	1 (7.7)	3 (12.0)	2 (20.0)	1 (2.7)
Hyponatraemia	0	1 (7.7)	2 (8.0)	0	1 (2.7)
Decreased appetite	0	0	2 (8.0)	0	11 (29.7)
Insomnia	0	2 (15.4)	3 (12.0)	1 (10.0)	3 (8.1)
Headache	1 (9.1)	1 (7.7)	2 (8.0)	0	10 (27.0)
Peripheral sensory neuropathy	0	0	5 (20.0)	0	1 (2.7)
Somnolence	1 (9.1)	3 (23.1)	4 (16.0)	2 (20.0)	24 (64.9)
Sinus bradycardia	0	7 (53.8)	11 (44.0)	5 (50.0)	6 (16.2)
Hypertension	0	2 (15.4)	3 (12.0)	0	2 (5.4)
Constipation	4 (36.4)	8 (61.5)	16 (64.0)	9 (90.0)	25 (67.6)
Diarrhoea	0	0	3 (12.0)	1 (10.0)	18 (48.6)
Dyspepsia	0	1 (7.7)	1 (4.0)	2 (20.0)	10 (27.0)
Vomiting	1 (9.1)	1 (7.7)	2 (8.0)	0	7 (18.9)
Dry skin	0	4 (30.8)	9 (36.0)	1 (10.0)	2 (5.4)
Pruritus	0	0	2 (8.0)	0	10 (27.0)
Urticaria	0	2 (15.4)	2 (8.0)	1 (10.0)	2 (5.4)
Back pain	0	0	0	2 (20.0)	8 (21.6)
Oedema peripheral	0	1 (7.7)	2 (8.0)	0	5 (13.5)
Pain	0	0	2 (8.0)	0	2 (5.4)
Pyrexia	4 (36.4)	3 (23.1)	4 (16.0)	1 (10.0)	6 (16.2)
ALT increased	1 (9.1)	2 (15.4)	2 (8.0)	1 (10.0)	14 (37.8)
AST increased	1 (9.1)	2 (15.4)	2 (8.0)	1 (10.0)	13 (35.1)
Blood cholesterol increased	1 (9.1)	0	0	2 (20.0)	14 (37.8)
Blood immunoglobulin G decreased	1 (9.1)	0	1 (4.0)	2 (20.0)	2 (5.4)
Eosinophil count increased	0	2 (15.4)	3 (12.0)	0	20 (54.1)
Neutrophil count decreased	1 (9.1)	2 (15.4)	4 (16.0)	0	24 (64.9)
White blood cell count decreased	0	2 (15.4)	2 (8.0)	0	20 (54.1)
Contusion	2 (18.2)	1 (7.7)	2 (8.0)	0	1 (2.7)

n (incidence, %)

Table 10. Incidence of adverse events that had not been reported in the studies in patients with multiple myeloma (Studies FPF300-02-01 and FPF300-02-02) but were reported in Study JPOST-10 or JPOST-13 (safety analysis set)

	Double-blind period in Study JPOST-10		Double-blind and long-term open-label periods in Study JPOST-10 (N = 25)	Study JPOST-13 (N = 10)
	Placebo (N = 11)	Thalidomide (N = 13)		
Main adverse events (adverse events occurring in ≥2 subjects in any group)				
Upper respiratory tract infection	1 (9.1)	2 (15.4)	5 (20.0)	0
POEMS syndrome	2 (18.2)	1 (7.7)	8 (32.0)	0
Disseminated intravascular coagulation	0	0	2 (8.0)	0
Hyperglycaemia	0	2 (15.4)	3 (12.0)	1 (10.0)
Hyperkalaemia	1 (9.1)	3 (23.1)	4 (16.0)	1 (10.0)
Hypertriglyceridaemia	1 (9.1)	0	0	2 (20.0)
Cerebral infarction	0	0	2 (8.0)	1 (10.0)
Pneumonitis	0	0	3 (12.0)	1 (10.0)
Dermatitis acneiform	0	1 (7.7)	2 (8.0)	0
Rash maculo-papular	0	1 (7.7)	3 (12.0)	1 (10.0)
Serious adverse events (adverse events occurring in ≥1 subject in the thalidomide group)				
Lipoma	0	0	1 (4.0)	0
POEMS syndrome	0	0	7 (28.0)	0
Cerebral infarction	0	0	2 (8.0)	1 (10.0)
Syncope	0	0	1 (4.0)	1 (10.0)
Cardiac arrest	0	1 (7.7)	1 (4.0)	0
Cardiac failure	0	1 (7.7)	1 (4.0)	0
Cardio-respiratory arrest	0	0	1 (4.0)	0
Prinzmetal angina	0	0	1 (4.0)	0
Sinus arrest	0	0	1 (4.0)	0
Pleural effusion	0	0	1 (4.0)	0
Ileus	1 (9.1)	0	1 (4.0)	0
Inguinal hernia	0	0	1 (4.0)	0
Intestinal obstruction	0	0	1 (4.0)	0
Acute kidney injury	0	0	0	1 (10.0)

n (incidence, %)

The applicant also considers that peripheral nerve disorders, which are recognized as a symptom of POEMS syndrome, are likely to occur at a high frequency in patients on long-term thalidomide treatment. In the long-term open-label period in Study JPOST-10, peripheral sensory neuropathy occurred in 5 subjects (21.7%), and 3 of them were able to continue treatment following dose reduction of thalidomide or by receiving appropriate treatment (pregabalin, duloxetine). Therefore, the applicant considers that peripheral nerve disorders can be managed with dose reduction or appropriate treatment.

In addition, based on the safety profiles of thalidomide, the applicant evaluated individual adverse events, namely, arrhythmia and cardiovascular-related adverse events.[13)]

7.R.2.2 Arrhythmia and cardiovascular-related adverse events

Sinus bradycardia has occurred more frequently in the clinical studies in patients with POEMS syndrome, compared with thalidomide-treated patients with multiple myeloma.

The applicant's explanation about the incidence of arrhythmia and cardiovascular-related adverse events:

- In the double-blind period in Study JPOST-10, the incidence of sinus bradycardia was 0% (0 of 11) of subjects in the placebo group and 53.8% (7 of 13) of subjects in the thalidomide group.
- Table 11 shows the incidence of arrhythmia and cardiovascular-related adverse events in the thalidomide group in Studies JPOST-10 and JPOST-13, and in the thalidomide group in the clinical studies

13) MedDRA/J SOC "cardiac disorders" and PT "syncope"

in patients with relapsed or refractory multiple myeloma (Study FPF300-02-01 [data for initial application for approval of Thaled Capsules 100, CTD 5.3.5.1] and Study FPF300-02-02). The incidence of arrhythmia and cardiovascular-related adverse events tended to be higher in the clinical studies in patients with POEMS syndrome than that in the clinical studies in patients with multiple myeloma.

Table 11. Incidence of arrhythmia and cardiovascular-related adverse events (Studies JPOST-10 and JPOST-13, safety analysis set)

	POEMS syndrome		Multiple myeloma
	Double-blind and long-term open-label periods in Study JPOST-10 (N = 25)	Study JPOST-13 (N = 10)	Studies FPF300-02-01 and FPF300-02-02 (N = 37)
All adverse events	14 (56.0)	5 (50.0)	6 (16.2)
Adverse events for which a causal relationship to the study drug could not be ruled out	13 (52.0)	5 (50.0)	5 (13.5)
Individual adverse events			
Sinus bradycardia	11 (44.0)	5 (50.0)	6 (16.2)
Syncope	1 (4.0)	1 (10.0)	0
Cardiac arrest	1 (4.0)	0	0
Cardio-respiratory arrest	1 (4.0)	0	0
Sinus arrest	1 (4.0)	0	0
Prinzmetal angina	1 (4.0)	0	0
Cardiac failure	1 (4.0)	0	0

n (incidence, %)

- In Studies JPOST-10 and JPOST-13, 23 events of arrhythmia and cardiovascular-related adverse events occurred in 19 subjects in the thalidomide group. All these events, except for sinus bradycardia were classified as serious adverse events, and a causal relationship could not be ruled out for all events except for cardio-respiratory arrest in the long-term open-label period in Study JPOST-10 and syncope in Study JPOST-13.
- Details of subject who developed a serious adverse event are as follows. The 3[redacted] year-old male patient who developed cardiac arrest: 12 days after a dose increase to thalidomide 200 mg/day in Cycle 1 in the double-blind period of Study JPOST-10, this patient experienced a loss of consciousness, with queasiness and cold sweat. Sinus arrest lasting for 9 seconds was suspected based on the electrocardiogram monitoring data during the time period. The patient regained consciousness in seconds and improved without any sequelae. However, the patient was assessed to be eligible for permanent pacemaker implantation and was therefore discontinued from the clinical study. The baseline demographic data show that the patient had had valvular disease and pericardial effusion.
- The 6[redacted] year-old male patient who experienced a cardio-respiratory arrest: at a scheduled visit at the end of the long-term open-label period in Study JPOST-10 (end of Cycle 12), the patient had a loss of consciousness. Immediately after that, cardio-respiratory arrest was confirmed, and cardiac massage was started. Because ventricular fibrillation was detected by electrocardiogram monitoring, defibrillation was performed. Following the return of spontaneous circulation, tracheal intubation was performed, and circulatory and respiratory management was performed in the intensive care unit. Subsequently, the level of consciousness gradually improved, the circulatory and respiratory management became unnecessary, and the patient recovered. The baseline demographic data did not indicate that the patient had had heart disease or electrocardiographic abnormalities.
- The 4[redacted] year-old male patient who experienced sinus arrest/Prinzmetal angina: the patient had subacute exacerbation of primary disease and entered the long-term open-label period in Study JPOST-10. In Cycle

1, approximately 1 month after the dose was increased to thalidomide 300 mg/day, the patient had a loss of consciousness, and sinus arrest and high-grade atrioventricular block were detected by electrocardiogram monitoring. An external pacemaker was attached immediately. However, sporadic pacing waveforms were detected thereafter, the study drug was interrupted, and permanent pacemaker was implanted. In a provocation test with acetylcholine, coronary spasm was detected. The patient was diagnosed as having coronary spastic angina, and treatment with diltiazem hydrochloride and isosorbide mononitrate was started. Approximately 2 weeks later, treatment resumed at thalidomide 100 mg/day, and then the dose was increased to 200 mg/day. Thereafter, there were no subjective symptoms of coronary spastic angina while pacing waveforms were detected at nighttime. The baseline demographic data did not indicate that the patient had had heart disease or electrocardiographic abnormalities.

- The 5[redacted] year-old female patient who developed cardiac failure: in Cycle 3 in the double-blind period in Study JPOST-10, the patient visited a hospital after experiencing difficulty breathing and leg oedema. On the basis of the test results, the patient was diagnosed as having cardiac failure accompanying pulmonary hypertension, and was hospitalized for treatment. The symptoms resolved after treatment for cardiac failure, and approximately 1 month later the patient was discharged from the hospital. The baseline demographic data indicated that the patient had had pulmonary hypertension.
- The 6[redacted] year-old male patient who had syncope in Study JPOST-10: due to subacute exacerbation of POEMS syndrome, the patient entered the long-term open-label period approximately 4 months after the start of treatment with placebo. After the dose was increased to thalidomide 200 mg/day, the patient had subacute exacerbation again, and the dose was increased to thalidomide 300 mg/day (Cycle 1). After the dose increase, the patient's pulse rate was 50 to 60/minute in the morning, indicating a trend towards bradycardia. After coadministration with Predonine 20 mg, symptoms improved, and the patient was discharged from the hospital. Approximately 1 month after the dose increase to 300 mg/day, the patient had abdominal pain due to constipation at night and an episode of loss of consciousness within a minute. Although possible vasovagal reflex was suspected, the dose was decreased to thalidomide 200 mg/day because a causal relationship could not be ruled out. The baseline demographic data did not indicate that the patient had had heart disease or electrocardiographic abnormalities.
- The 3[redacted] year-old male patient who had syncope in Study JPOST-13: the patient had a total of 3 episodes of syncope on Days 10, 21, and 26 (Cycle 1) while receiving thalidomide 100 mg/day after the initiation of the study drug treatment. The electrocardiographic findings suggested cardiogenic syncope was unlikely. The patient was diagnosed as having reflex syncope from the findings of autonomic nerve function testing. The patient complained of abdominal pain immediately after recovery from the first episode of syncope and a large amount of fecal mass was observed in the large intestine. Because syncope may have been induced by abdominal pain associated with constipation caused by thalidomide treatment, the dose was not increased, and thalidomide treatment continued at 100 mg/day. The baseline demographic data did not indicate that the patient had had heart disease or electrocardiographic abnormalities.

In Studies JPOST-10 and JPOST-13, arrhythmia and cardiovascular-related adverse events occurred frequently, in particular, arrhythmia-related adverse events such as sinus bradycardia. PMDA asked the applicant to provide details on the risk control measures to be implemented.

The applicant explained the results obtained from a nested case-control study (see CTD 5.3.5.4.1, JPOST_NCC study) which was conducted to explore the risk factors for the development of arrhythmia in patients with POEMS syndrome.

- A nested case-control study was conducted to explore the risk factors for the development of arrhythmia in patients with POEMS syndrome, in participants of the clinical studies of thalidomide[14)] and patients who had not participated in the clinical studies but had started treatment around the same time as well as patients for whom study drug treatment was made available for compassionate purposes.[15)]
- Of the 79 patients from whom informed consent for participation in the study was obtained (30 patients who were participants of the clinical studies[14)] and 49 patients who had not participated in the clinical studies, including who received study drug treatment made available[15)]), 6 patients[16)] who did not meet the inclusion criteria[17)] were excluded, and the remaining 73 subjects were included in the analysis set.
- Arrhythmia events[18)] were assessed by cardiologists. Arrhythmia events occurred in 18 subjects and did not occur in 55 subjects.
- In addition to the prespecified possible risk factors of "sex," "age," and "overall neuropathy limitation scale," "subacute exacerbation" and "heart disease or electrocardiographic abnormalities[19)]" were selected after consultation with cardiologists and other experts on the results of preliminary analysis,[20)] univariate

14) Patients enrolled in any of the following studies at [redacted]: Study JPOST-10, JPOST-12, or JPOST-13.
15) Patients enrolled in Study JPOST-15 (a clinical study to make thalidomide treatment available to patients who were not able to participate in Study JPOST-10, JPOST-12, or JPOST-13).
16) The reasons for exclusion: the initial treatment started before January 20[redacted] (5 patients); and the initial day of treatment is unknown (1 subject).
17) The inclusion criteria:
• Patients who were diagnosed as having Crow-Fukase syndrome according to the diagnostic criteria;
• Participants of any of the following studies: Study JPOST-10, JPOST-12, or JPOST-13, or patients who started treatment between January 20[redacted] and December 20[redacted] at [redacted] and participants of Study JPOST-15, a study aiming to provide opportunities for thalidomide treatment;
• Patients from whom informed consent was obtained or who did not reject participation in the study.
18) Events were to be assessed by independent cardiologists. Events were those that are listed below and must be assessed as arrhythmia by the cardiologist. In addition, among these events, the event that occurred the earliest in each of (1) and (2) was selected.
(1) Events with the highest severity requiring risk management
Sinus arrest with a severity that is accompanied by syncope and other symptoms; severe bradycardia accompanied by fatigue, etc. or CTCAE v4.0 Grade ≥2 severity; life-threatening arrhythmia and cardiac arrest; events that required a pacemaker
(2) Atrioventricular block; orthostatic hypotension requiring medical therapy or hospitalization; arrhythmia-related adverse events leading to treatment intervention (except for the use of a pacemaker) or treatment discontinuation of the study drug
19) According to the definition, electrocardiographic abnormalities are "present" if any of the following conditions is met, and "absent" for all other cases:
QRS width ≥0.10 seconds; PQ interval ≥0.20 seconds; valvular disease, present; ischaemic heart disease, present; pericardial effusion, present; other heart diseases, present; chest pain, present.
20) • Baseline demographic data were gathered and the data of the patient group with events were compared with those without events.
• Data were sorted according to thalidomide treatment vs no thalidomide treatment at baseline, and the incidence of events was calculated for each group. The incidence of the thalidomide-treated group was compared with that of the no thalidomide-treated group.
• A diagram was created and details on individual patients who developed an event were described to show changes in clinical and therapeutic course from baseline up to onset of event.
• The number of days from baseline to the time of event onset was calculated for patients who developed an event.

analysis,[21] and multivariate analysis.[22] An analysis was performed using a multivariate conditional logistic model incorporating these factors.

- The odds ratio of thalidomide treatment was >1.0 for the following factors: "sex_male," "age_≥65 years," "subacute exacerbation_present," and "heart disease or electrocardiographic abnormalities_present." On the basis of the point estimates of odds ratio and other information, "subacute exacerbation_present" and "heart disease or electrocardiographic abnormalities_present" among the 4 factors were considered as risk factors for the development of arrhythmia events when using thalidomide, although it is difficult to conclude that "sex" and "age" are risk factors at present.

Then the applicant explained that following are appropriate control measures when using thalidomide.

- The package insert and other information materials will include cautionary statement to the effect that before using thalidomide the risk of arrhythmia and cardiovascular-related events must be thoroughly explained and informed consent must be obtained in writing.
- Cautionary statement will be provided to the following effect: before administering thalidomide to patients with POEMS syndrome for the first time, the past history of heart disease, presence of complications (chest pain symptoms, valvular disease, ischaemic heart disease, pericardial effusion, and other heart disease), presence of electrocardiographic abnormalities (prolonged QRS width, prolonged PQ interval), and presence of subacute exacerbation of primary disease must be verified prior to the use of thalidomide regardless of the patient's risk factors, and whether the patient can be treated with thalidomide should be carefully determined, taking account of cardiovascular risks assessed by cardiologists.
- For a specified period after the start of thalidomide treatment, cardiovascular risk assessment by cardiologists will be required regardless of the patient's risk factors. In principle, immediately after the start of treatment, patients with risk factors will receive treatment as inpatients.
- In Studies JPOST-10 and JPOST-13, treatment was to start at thalidomide 100 mg dosing on alternate days, the dose was to be increased after an interval of at least 1 week to 100 mg/day, and another week to 200 mg/day (maximum of 28 days from the start of treatment to dose increase). After the start of thalidomide treatment, patients were to receive treatment on an inpatient basis for ≥3 weeks in principle. The time from the start of treatment to dose increase in individual patients ranged from 12 to 26 days. Sinus bradycardia occurred in 5 of 16 subjects within 1 week of the start of treatment, 7 of 16 subjects within 2 weeks, 9 of 16 subjects within 3 weeks, and 9 of 16 subjects within 4 weeks.
- Table 12 shows the time of onset of arrhythmia events[18] in 17 thalidomide-treated subjects in the JPOST_NCC study. Arrhythmia events occurred in 3 of 17 subjects within 1 week of the start of treatment, 7 of 17 subjects within 2 weeks, 9 of 17 subjects within 3 weeks, and 12 of 17 subjects within 4 weeks, indicating that more than half of the reported events occurred within 3 weeks of the start of treatment.
- Taking the above into account, patients with risk factors should receive thalidomide on an inpatient basis for at least 3 weeks from the start of thalidomide treatment, which is the dose increase phase, and

21) An analysis was performed using a univariate conditional logistic model to investigate the relationship between the occurrence of the initial event and with/without thalidomide treatment, or each risk factor, and odds ratio for each risk factor was calculated.

22) Taking into account the comments on the results of the preliminary analysis and univariate analysis provided by cardiologists and other experts, "sex," "age," "overall neuropathy limitation scale," "hypothyroidism," "subacute exacerbation," "sinus bradycardia," and "heart disease or electrocardiographic abnormalities" were selected as possible risk factors to be included in multivariate analyses. An analysis was performed using a multivariate conditional logistic model incorporating these factors and the odds ratio for each risk factor was calculated.

cautionary statement should be provided to ensure that electrocardiography and other tests are performed during that time. After being discharged from hospital, tests including electrocardiography should be performed once a month for 6 months after the start of thalidomide treatment, and thereafter, on a regular basis during treatment.

Table 12. Time to onset of event (days) (JPOST NCC study)

Patient	Age	Sex	Event	Number of days from the start of thalidomide treatment	Number of days from the last dose increase
Patient 1	4	Male	Sinus arrest	50	36
Patient 2	6	Female	Sinus bradycardia	5	5
Patient 3	6	Male	Syncope	54	35
Patient 4	6	Male	Atrial fibrillation paroxysmal, sinus bradycardia	4	4
Patient 5	6	Male	Cardio-respiratory arrest	338	324
Patient 6[a)]	6	Female	Sinus arrest	16	9
Patient 7[a)]	4	Female	Sinus arrest	29	21
Patient 8	3	Male	Cardiac arrest	27	13
Patient 9	3	Male	Sinus bradycardia	14	7
Patient 10	6	Male	Sinus bradycardia, cardiac arrest[b)]	16	9
Patient 11	3	Male	Syncope	11	4
Patient 12	6	Female	Syncope	68	54
Patient 13	5	Male	Syncope	11	5
Patient 14	7	Female	Ventricular tachycardia	8	8
Patient 15	6	Male	Atrioventricular block, sinus bradycardia	25	11
Patient 16	3	Male	Sinus bradycardia	5	5
Patient 17	7	Female	Syncope	28	14

a) The patient received a thalidomide formulation that is different from Thaled capsule
b) The event occurred 90 days after the completion of thalidomide treatment (263 days after the start of thalidomide treatment)

- Immediately after the start of treatment, if necessary, patients without risk factors should also be considered for treatment on an inpatient basis. Tests including electrocardiography should be performed once a month for 6 months after the start of thalidomide treatment, and thereafter, on a regular basis during treatment.

During treatment with thalidomide, a patient had been taking a calcium channel blocker as an antihypertensive. After stopping the calcium channel blocker, the patient had coronary spasm. PMDA asked the applicant if discontinuation of thalidomide treatment should be considered when dose reduction or discontinuation of calcium channel blocker becomes necessary, and whether it is necessary to include a cautionary statement that coronary spasm may occur after discontinuation of calcium channel blockers.

The applicant's explanation:

- In Study JPOST-10, sinus arrest/Prinzmetal angina (coronary spastic angina) occurred in 1 subject in the long-term open-label period. In the double-blind period in Study JPOST-10, this patient had started receiving a calcium channel blocker after a dose increase of the study drug (placebo) to 200 mg/day; however, 2 months later, all oral medications were suspended due to intestinal obstruction. One week later, treatment was resumed with a starting dose of thalidomide 100 mg on alternate days. Approximately 1 month after a dose increase to thalidomide 300 mg/day, the subject had a loss of consciousness, and sinus arrest and high-grade atrioventricular block were detected by electrocardiogram monitoring. Study drug treatment was interrupted, and permanent pacemaker was implanted. A provocation test with acetylcholine indicated that the patient had coronary spastic angina, and pharmacotherapy was started.

Approximately 2 weeks later, thalidomide treatment was resumed at thalidomide 100 mg/day, followed by a dose increase to 200 mg/day. Subsequently, while pacing waveforms were detected at nighttime, the patient did not have subjective symptoms of coronary spastic angina.

- Coronary spastic angina was reported in 3 patients with POEMS syndrome in 3 case reports.[23)] Of the 3 patients, 2 patients developed coronary spastic angina concurrently with the onset or exacerbation of POEMS syndrome, paralleling the disease condition, and the other patient developed coronary spastic angina 4 months after the diagnosis with POEMS syndrome. According to the report on one of the patients in whom coronary spasm coincided with POEMS syndrome, treatment for POEMS syndrome was effective for coronary spasm, and cardiovascular risks such as hypertension and hyperlipidaemia were not detected. None of these patients were treated with thalidomide. Coronary spasm observed in patients with POEMS syndrome may be attributable to an exacerbation of POEMS syndrome.
- The above findings suggest that coronary spasm may be caused by an exacerbation of POEMS syndrome, and currently, the relationship between thalidomide and coronary spasm is not clear. Therefore, it is not necessary to provide cautionary statement regarding coronary spasm in the package insert.

PMDA's view on the safety of thalidomide:

- Sinus bradycardia occurred more frequently in the clinical studies in patients with POEMS syndrome (Studies JPOST-10 and JPOST-13) than in the clinical studies in patients with relapsed or refractory multiple myeloma (Studies FPF300-02-01 and FPF300-02-02), suggesting that the safety profiles in patients with POEMS syndrome tend to differ from those in patients with multiple myeloma.
- Many events of arrhythmia and cardiovascular-related adverse events occurred in Studies JPOST-10 and JPOST-13, including some life-threatening events. As stated by the applicant, before starting treatment with thalidomide in patients with POEMS syndrome, the risk of arrhythmia and cardiovascular-related events must be thoroughly explained, and informed consent must be obtained in writing. There is no particular problem with the applicant's proposal that cautionary statement should be included in the package insert and information materials to the effect that whether the patient can be treated with thalidomide should be carefully determined, taking account of cardiovascular risks assessed by cardiologists. However, "subacute exacerbation" and "heart disease or electrocardiographic abnormalities" were identified as risk factors for arrhythmia in the JPOST_NCC study; therefore, the package insert should include a cautionary statement to the effect that there is potential increased risk for arrhythmia in patients with these risk factors.
- Peripheral nerve disorders are events of particular interest in thalidomide treatment. In the long-term open-label period in Study JPOST-10, peripheral sensory neuropathy occurred in 5 subjects (21.7%), 3 of whom were able to continue treatment following dose reduction of thalidomide or by receiving appropriate treatment (pregabalin, duloxetine). There is no particular problem with the applicant's explanation that peripheral nerve disorders can be managed with dose reduction or appropriate treatment.
- According to the applicant's proposed risk control measures to be implemented in the early phase of treatment with thalidomide, only patients with risk factors for arrhythmia identified in the results of the

23) *Am Heart J.* 1992;124:505-7, *Eur Neurol.* 1994;34:110, and *Acta Neurol (Napoli).* 1994;16:170-6

JPOST_NCC study, i.e., "subacute exacerbation" and "heart disease or electrocardiographic abnormalities" will be required to receive treatment on an inpatient basis for 3 weeks after the start of administration of thalidomide, in principle, while hospitalization on an as-needed basis would be sufficient for patients without these risk factors.

- However, the findings shown below indicate that all patients should receive thalidomide on an inpatient basis. It is also appropriate to provide cautionary statement to the effect that patients should be monitored for electrocardiogram, pulse rate, and symptoms such as chest pain and syncope on an inpatient basis for at least 4 weeks after the start of treatment so that suitable measures to minimize cardiovascular risks associated with thalidomide treatment are taken for all patients including those without the risk factors.
  - Serious arrhythmia or cardiovascular-related adverse events for which a causal relationship to thalidomide could not be ruled out occurred in 5 subjects in Study JPOST-10. The baseline demographic data did not indicate that the patients had had heart disease or electrocardiographic abnormalities, and a number of patients had not experienced subacute exacerbation.
  - In the JPOST_NCC study, a considerable amount of data was missing, and only 18 patients had arrhythmia events; therefore, it is difficult to determine whether the risk factors have been fully identified.
  - The data on the onset of arrhythmia events in 17 patients who had been treated with thalidomide (Thaled capsules or other formulations) in the JPOST_NCC study show that arrhythmia events occurred in 3 of 17 subjects within 1 week of the start of treatment, 7 of 17 subjects within 2 weeks, 9 of 17 subjects within 3 weeks, and 12 of 17 subjects within 4 weeks, indicating that arrhythmia events occurred ≥3 weeks after the start of treatment in several patients (Table 12).
- There is no problem with the details of the applicant's risk control measures to be implemented 1 month after the start of thalidomide treatment and beyond. Patients are to be monitored (e.g., electrocardiogram) once a month for the first 6 months, and on a regular basis thereafter throughout the treatment period; in addition, cardiovascular risk assessment by cardiologists will be required for a certain period of time after the start of treatment.
- As mentioned above, since it is difficult to determine whether the risk factors have been fully identified, the applicant should continue to collect and evaluate data on risk factors in post-marketing settings.
- While the applicant's explanation that coronary spasm occurring after thalidomide treatment may be attributable to an exacerbation of POEMS syndrome is understandable, 2 subjects in clinical studies of thalidomide experienced coronary spasm or suspected coronary spasm after stopping the calcium channel blocker, and both patients had a serious clinical course. Healthcare professionals should be informed to be cautioned for coronary spasm during thalidomide treatment of patients who have been taking a calcium channel blocker and require dose reduction or discontinuation of calcium channel blocker.
- A final conclusion on the details of cautionary statement on arrhythmia and cardiovascular-related adverse events and appropriateness of risk control measures discussed above will be made, taking account of comments from the Expert Discussion.

7.R.3 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of thalidomide.

The applicant's explanation:

- POEMS syndrome is a rare disease, and no drugs have been approved for the indication of POEMS syndrome in Japan or other countries. Patients with POEMS syndrome have been treated with treatment regimens similar to those for multiple myeloma, which is also a plasma cell proliferative disorder. No other drugs have been evaluated in a randomized study in Japan or other countries. No standard of care has been established.
- In the Japanese Society of Hematology (JSH) *Practical Guidelines for Hematological Malignancies*, 2018 (hereinafter referred to as "Japanese clinical practice guidelines"), high-dose chemotherapy with autologous PBSCT is defined as the mainstream approach for transplant-eligible patients, and thalidomide plus dexamethasone is recommended as the initial remission induction regimen based on the data from the clinical studies of thalidomide (CTD 5.3.5.1.1, 5.3.5.1.2, Study JPOST-10) using a randomized, double-blind design. For patients who are refractory to thalidomide, short-term lenalidomide plus dexamethasone therapy or bortezomib therapy should be considered. Therapies recommended for transplant-ineligible patients or patients with relapsed or refractory POEMS syndrome include melphalan plus dexamethasone, thalidomide plus dexamethasone, lenalidomide plus dexamethasone, and bortezomib plus dexamethasone. Radiation therapy is considered effective for single bone lesions.
- Although no clinical practice guidelines for POEMS syndrome exist in countries outside Japan, several studies (e.g., *Am J Hematol.* 2019;94:812-27, *J Neurol.* 2019;266:268-77) have reported that radiation therapy is generally recommended for patients who do not have bone marrow involvement and have ≤3 bone lesions, and systemic therapy is recommended for patients who have bone marrow involvement and/or >3 bone lesions. Systemic treatment options include high-dose chemotherapy with autologous PBSCT for transplant-eligible patients, and melphalan plus dexamethasone or lenalidomide plus dexamethasone for transplant-ineligible patients (*Leukemia.* 2018;32:1883-98). In the published literature mentioned above, thalidomide is listed as one of the treatment options for patients ineligible for high-dose chemotherapy with autologous PBSCT, melphalan plus dexamethasone, or lenalidomide plus dexamethasone. However, thalidomide is not recommended as first-line treatment, or should be used with caution due to increased risk of peripheral nerve disorders (e.g., *Am J Hematol.* 2019;94:812-27, *Leukemia.* 2018;32:1883-98).
- The risk of peripheral nerve disorders caused by thalidomide can be controlled through dose reduction of thalidomide or suitable treatment based on the following findings [see Section 7.R.2.1]. In the long-term open-label period in the clinical study of thalidomide (CTD 5.3.5.1.1, 5.3.5.1.2, Study JPOST-10), peripheral sensory neuropathy occurred in 5 of 23 subjects (21.7%), 3 of whom were able to continue treatment following dose reduction of thalidomide or by receiving appropriate treatment (pregabalin, duloxetine).
- High-dose chemotherapy with autologous PBSCT is the mainstream approach for transplant-eligible patients; however, older patients or patients with complications may not be eligible for transplant; in addition, there are a certain number of patients who choose not to undergo transplant in view of the risk of transplant-related death.

- It is considered that thalidomide can be used regardless of the eligibility of the patient for transplant for the following reasons: the incidence of myelosuppression in thalidomide-treated patients is lower than that in patients treated with melphalan or lenalidomide (*Blood.* 2011;117:6445-9, *Am J Hematol.* 2013;88:207-12); and urinary excretion of unchanged thalidomide is <1% (*J Pharmacol Exp Ther.* 1970;173:265-9), thus not requiring dose adjustment for patients with renal impairment.
- As described above, among patients who are ineligible for radiation therapy, thalidomide offers a treatment option, specifically, pretransplant remission induction therapy for those eligible for transplant, or treatment for those ineligible for transplant.

PMDA's view:

- According to the literature and clinical practice guidelines published in Japan and other countries, radiation therapy is effective in patients with single bone lesions. In the Japanese clinical practice guidelines, high-dose chemotherapy with autologous PBSCT is defined as the mainstream approach for transplant-eligible patients, and thalidomide plus dexamethasone is recommended as the initial remission induction regimen. Thalidomide plus dexamethasone is also recommended for transplant-ineligible patients or patients with relapsed or refractory POEMS syndrome. On the other hand, several literatures published outside Japan (e.g., *Am J Hematol.* 2019;94:812-27, *Leukemia.* 2018;32:1883-98) recommend other treatments but not thalidomide, and state that thalidomide is not recommended as first-line treatment.
- The efficacy data suggest that thalidomide can be expected to improve not only serum VEGF levels but also clinical symptoms, progression-free survival, and overall survival [see Section 7.R.1], while arrhythmia and cardiovascular-related adverse events occurred more in clinical studies in patients with POEMS syndrome than in clinical studies in patients with multiple myeloma [see Section 7.R.2].
- Therefore, before using thalidomide, whether thalidomide can be administered to the patient should be carefully determined based on the risks and benefits of thalidomide to individual patients, and appropriate risk control measures should be implemented.
- Treatment options for patients with POEMS syndrome ineligible for radiation therapy or high-dose chemotherapy with autologous PBSCT are extremely limited, and thalidomide is recommended in the Japanese clinical practice guidelines as an initial remission induction regimen for transplant-eligible patients and as treatment for transplant-ineligible patients or patients with relapsed or refractory POEMS syndrome. Given these circumstances, if thalidomide is determined to be efficacious in the treatment of POEMS syndrome based on the comments from the Expert Discussion, thalidomide can be defined as a treatment option for such patients.

7.R.4 Indication

The phase II/III Japanese clinical study (CTD 5.3.5.1.1, 5.3.5.1.2, Study JPOST-10) was conducted in transplant-ineligible patients with POEMS syndrome. PMDA asked the applicant to explain the appropriateness of including transplant-eligible patients in the indication of thalidomide.

The applicant explained that the indication should be "Crow-Fukase (POEMS) syndrome" regardless of eligibility for transplant based on the following factors:

- Since patients with POEMS syndrome are in poor general condition with decreased physical function, a high incidence of adverse events such as engraftment syndrome has been reported among patients who underwent transplant without pretransplant remission induction therapy, resulting in an increase in transplant-related toxicity (*Eur J Haematol.* 2008;80:397-406). The Japanese clinical practice guidelines states that for safe transplantation, it is desirable to introduce appropriate remission induction therapy. In addition, pretransplant remission induction therapy, including thalidomide, is an effective way to ensure safe transplant especially for those who cannot undergo transplant immediately due to serious or progressive primary disease, among transplant-eligible patients with POEMS syndrome (*Leukemia.* 2017;31:1375-81, *Neurology.* 2019;93:e975-83). It is also suggested that posttransplant prognosis is improved when serum VEGF levels are decreased by pretransplant remission induction therapy (*Blood.* 2018;131:2173-6). Taking these findings into account, thalidomide plus dexamethasone is recommended in the Japanese clinical practice guidelines as pretransplant remission induction therapy in transplant-eligible patients with POEMS syndrome.
- In the Japanese phase II study in transplant-eligible patients with POEMS syndrome (CTD 5.3.5.2.1, Study JPOST-13), it was possible to collect the peripheral blood stem cells needed[24)] for autologous PBSCT in 7 of 10 subjects. Two of the remaining 3 subjects did not achieve the target value for the following reasons: "the cells were not collected because autologous PBSCT was cancelled as a result of improved primary disease" and "the cells were not collected because the patient was withdrawn from the trial due to rash." There has been no evident adverse impact of thalidomide treatment on the collection efficiency of autologous peripheral blood stem cells. Study JPOST-10, which was conducted in transplant-ineligible patients, demonstrated the efficacy of thalidomide. A similar trend has also been observed in transplant-eligible patients [see Section 7.R.1].
- Study JPOST-13 evaluated the short-term inhibitory effect of pretransplant remission induction therapy on the progress of clinical symptoms. The study however did not evaluate the effect on long-term prognosis in transplant-eligible patients with POEMS syndrome. Therefore, it was decided to provide a cautionary statement in the Precautions Concerning Indications section to the effect that "the efficacy and safety of thalidomide in post-remission therapy or maintenance therapy have not been established in patients with Crow-Fukase (POEMS) syndrome who are eligible for high-dose chemotherapy with transplant."

PMDA's view:

- Taking into account the efficacy and safety of thalidomide as indicated by the data from Studies JPOST-10 and JPOST-13, thalidomide will not replace other treatment options recommended as standard therapy for POEMS syndrome in the Japanese clinical practice guidelines [see Section 7.R.3]. The intended patient population for thalidomide should be defined as patients for whom other standard therapies are not suitable.

24) Target value, CD34+ cells 2.0×10^6/kg

- Before starting treatment with thalidomide, the physician should carefully select patients for whom the benefits of thalidomide outweigh its risks after fully understanding the study results on the efficacy and safety of thalidomide.
- A final decision on the appropriateness of the Indications section and Precautions Concerning Indications section should be made, taking account of comments from the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Appropriateness of starting dose level, maintenance dose level, and interval between dose increases

PMDA asked the applicant to explain the rationale for the starting dose and maintenance dose levels.

The applicant explained the rationale for the starting dose and maintenance dose levels in the Japanese phase II/III study (CTD 5.3.5.1.1, 5.3.5.1.2, Study JPOST-10) and Japanese phase II study (CTD 5.3.5.2.1, Study JPOST-13).

- POEMS syndrome is considered to be related to multiple myeloma, and the dosage regimen for relapsed or refractory multiple myeloma in the "Guideline for the appropriate use of thalidomide in the treatment of multiple myeloma" (Japanese Society of Clinical Hematology) is "The usual adult dosage is 100 mg of thalidomide orally once daily at bedtime. The dose may be adjusted according to the patient's condition. The daily dose should not exceed 400 mg." In the guidelines, the maximum tolerated dose in Japanese patients is approximately 300 mg/day, and increasing the dose to ≥400 mg/day is difficult as the frequency of adverse reactions increases.
- Dosage regimens of thalidomide for POEMS syndrome reported in the literature range from 100 mg/day on alternate days to 200 mg/day, with its efficacy having been demonstrated at all the dose levels (e.g., *Am J Hematol.* 2004;76:66-8, *J Neurol Neurosurg Psychiatry.* 2008;79:1255-7).
- In the "Guideline for the appropriate use of thalidomide in the treatment of multiple myeloma," "Treatment should be initiated at an oral starting dose of thalidomide 100 mg/day. The dose should be increased to 200 mg/day 1 week later if no adverse reactions have occurred. The dose can be increased further if no serious adverse reactions have occurred."
- On the basis of the above, treatment in the double-blind period was to be started at a dose of 100 mg/day on alternate days, and the dose was allowed to be gradually increased to a maintenance dose of 200 mg/day. Patients experiencing subacute exacerbation of the primary disease were to enter the long-term open-label period, in which the dose could be increased up to 300 mg/day, with an interval of ≥1 week between each level. However, a shorter interval between dose increases was allowed for patients who entered the long-term open-label period in Study JPOST-10 before Week 24.

Then, the applicant explained the appropriateness of the starting dose and maintenance dose levels in the proposed dosage and administration:

- In Studies JPOST-10 and JPOST-13, the dose was increased to 200 mg/day in 33 of 35 subjects, many of whom continued treatment at 200 mg/day. In Study JPOST-10 with a maintenance dose of 200 mg/day, the reduction rate of serum VEGF levels at Week 24, the primary endpoint, was statistically significantly

lower in the thalidomide group than the placebo group (Table 3). In addition, clinical symptoms, progression-free survival period, and overall survival period tended to remain unchanged or improve after treatment with thalidomide [see Section 7.R.1].

- Of the 7 subjects whose dose was increased to thalidomide 300 mg/day due to subacute exacerbation, the serum VEGF levels remained unchanged or decreased in 5 subjects, and clinical symptoms tended to remain unchanged or be improved in 4 subjects.
- Except for arrhythmia and cardiovascular-related adverse events, the safety profiles of patients with POEMS syndrome in Studies JPOST-10 and JPOST-13 did not differ markedly from those of patients with multiple myeloma [see Section 7.R.2.1]. On the other hand, as shown in Table 13, reported arrhythmia and cardiovascular-related adverse events were classified as Grade 1 or 2 in severity except for 2 patients; therefore, it was concluded that the maintenance dose of 200 mg/day should be well tolerated.

Table 13. Incidence of arrhythmia and cardiovascular-related adverse events in Studies JPOST-10 and JPOST-13 by dose level at onset (Studies JPOST-10 and JPOST-13, safety analysis set)

		100 mg alternate day dosing	100 mg/day	200 mg/day	300 mg/day
N		35	34	33	7
All adverse events		7 (20.0)	5 (14.7)	5 (15.2)	2 (28.6)
Adverse events by severity	Grade 1	7 (20.0)	2 (5.9)	5 (15.2)	0
	Grade 2	0	2 (5.9)	0	0
	Grade ≥3	0	1 (2.9)	1 (3.0)	2 (28.6)

n (incidence, %)

- Table 14 shows adverse events that occurred in the 7 subjects whose dose was increased to thalidomide 300 mg/day. Serious adverse events occurred in 3 subjects (Prinzmetal angina/sinus arrest, exacerbation of POEMS syndrome, and syncope in 1 subject each), and a causal relationship to thalidomide could not be ruled out except for exacerbation of POEMS syndrome. Several subjects required dose reduction or dose interruption after a dose increase to 300 mg/day due to adverse events, and the outcome of some subjects was reported as “not resolved”; however, no irreversible adverse events occurred due to dose increase to 300 mg/day.

Table 14. Incidence of adverse events in Studies JPOST-10 and JPOST-13 by dose level at onset
(Studies JPOST-10 and JPOST-13, safety analysis set)

		Placebo (N = 11)	100 mg alternate day dosing (N = 35)	100 mg/day (N = 34)	200 mg/day (N = 33)	300 mg/day (N = 7)	After the end of thalidomide treatment (N = 35)
All adverse events		11 (100)	24 (68.6)	22 (64.7)	30 (90.9)	7 (100)	8 (22.9)
Death		0	1 (2.9)	0	0	0	1 (2.9)
Serious adverse events other than death		2 (18.2)	2 (5.7)	3 (8.8)	9 (27.3)	3 (42.9)	4 (11.4)
Adverse events leading to treatment discontinuation		0	1 (2.9)	0	4 (12.1)	0	3 (8.6)
Sinus bradycardia and arrhythmia-related adverse events		0	7 (20.0)	5 (14.7)	5 (15.2)	2 (28.6)	2 (5.7)
Adverse events by severity	Grade 1	9 (81.8)	22 (62.9)	15 (44.1)	23 (69.7)	6 (85.7)	2 (5.7)
	Grade 2	5 (45.5)	6 (17.1)	8 (23.5)	19 (57.6)	4 (57.1)	1 (2.9)
	Grade 3	3 (27.3)	5 (14.3)	5 (14.7)	8 (24.2)	4 (57.1)	4 (11.4)
	Grade 4	0	0	0	6 (18.2)	1 (14.3)	3 (8.6)
	Grade 5	0	1 (2.9)	0	0	0	1 (2.9)
Major adverse events (adverse events occurring in ≥2 subjects, which also accounts for ≥10% at any of dose level of thalidomide)							
Constipation		4 (36.4)	10 (28.6)	10 (29.4)	4 (12.1)	2 (28.6)	0
Dry skin		0	0	1 (2.9)	6 (18.2)	3 (42.9)	0
POEMS syndrome		2 (18.2)	1 (2.9)	0	2 (6.1)	3 (42.9)	3 (8.6)
Pyrexia		4 (36.4)	1 (2.9)	2 (5.9)	2 (6.1)	0	0
Sinus bradycardia		0	7 (20.0)	4 (11.8)	5 (15.2)	0	0
Pneumonitis		0	0	0	1 (3.0)	2 (28.6)	1 (2.9)
Somnolence		1 (9.1)	1 (2.9)	0	5 (15.2)	0	0
Upper respiratory tract infection		1 (9.1)	0	0	5 (15.2)	0	0
Hyperkalaemia		1 (9.1)	0	2 (5.9)	3 (9.1)	0	0
Neutrophil count decreased		1 (9.1)	1 (2.9)	1 (2.9)	3 (9.1)	0	0
Hyperglycaemia		0	2 (5.7)	0	2 (6.1)	1 (14.3)	0
Insomnia		0	3 (8.6)	0	1 (3.0)	0	0
Anaemia		0	1 (2.9)	1 (2.9)	3 (9.1)	0	1 (2.9)
White blood cell count decreased		0	0	0	2 (6.1)	0	0
Pneumonia		0	1 (2.9)	3 (8.8)	3 (9.1)	0	0

n (incidence, %)

- The data on adverse events in Studies JPOST-10 and JPOST-13 by dose level at the time of onset showed a tendency towards an increase in the incidence of dry skin and pneumonitis at high dose levels; however, due to the small number of patients assessed, clear dose-dependency was not detected (Tables 13 and 14). Meanwhile, there was a tendency towards an increase in the incidence of Grade ≥3 adverse events and sinus bradycardia and arrhythmia-related adverse events. Therefore, possible occurrence of these events should be carefully monitored when administering thalidomide 300 mg/day.
- Table 15 shows the duration from the start of treatment to the maintenance dose of 200 mg/day in Studies JPOST-10 and JPOST-13. The time taken to reach the maintenance dose varied, ranging from 12 to 25 days.

Table 15. Duration from the start of treatment to the maintenance dose of 200 mg/day

Duration to reach the maintenance dose of 200 mg/day	JPOST-10 (double-blind period, thalidomide)	JPOST-13
	13 subjects	10 subjects [a)]
<2 weeks	0 subjects	1 subject (12 days)
2 weeks	11 subjects	6 subjects
>2 weeks	2 subjects (16 and 21 days)	2 subjects (20 and 25 days)

a) 1 subject was maintained at 100 mg/day

- On the basis of the above, the dosage of thalidomide for POEMS syndrome should start at 100 mg on alternate days, and the dose should be gradually increased to the maintenance dose of 200 mg/day. The dose should be adjusted according to the patient's condition. A dose increase up to 300 mg/day is thought to be clinically meaningful for patients in whom the effect has been inadequate at 200 mg/day. There was

an increase in the incidence of more severe adverse events as well as sinus bradycardia and arrhythmia-related adverse events at 300 mg/day compared with those at 200 mg/day. However, this issue can be addressed by providing cautionary statements in the information materials for healthcare professionals. The Precautions Concerning Dosage and Administration section should also include a cautionary statement to the effect that "The starting dose is 100 mg of thalidomide on alternate days, and the dose may be gradually increased to 100 mg/day every day after an interval of approximately 1 week, and then to 200 mg/day according to the patient's condition."

PMDA's view on the dosage regimen:

- There is no particular problem with selecting a starting dose of 100 mg on alternate days and the maintenance dose of 200 mg/day.
- In the clinical studies, basically, the dose was to be increased with an interval of ≥1 week between each level. With the exception of 1 subject in Study JPOST-13, the dose was increased stepwise from 100 mg on alternate days to 200 mg/day; i.e., increased by 2 levels over ≥2 weeks. The safety of dose increase at the interval of <1 week is unknown. Therefore, the package insert should include a cautionary statement to the effect that when the dose is increased, an interval of ≥1 week should be allowed between each dose level.
- Of the 7 subjects whose dose was increased to thalidomide 300 mg/day due to subacute exacerbation, the serum VEGF levels remained unchanged or decreased in 5 subjects, and clinical symptoms tended to remain unchanged or be improved in 4 subjects. Some patients may benefit from an increased dose if a maximum dose of 300 mg/day is selected. In addition, while the incidence of adverse events of greater severity and the incidence of arrhythmia and cardiovascular-related adverse events tended to be higher at 300 mg/day compared with 200 mg/day, 2 subjects who had serious adverse events for which a causal relationship to thalidomide could not be ruled out were able to continue treatment through dose interruption or dose reduction of thalidomide. The above findings suggest that a maximum dose of 300 mg/day is acceptable.
- However, the incidence of Grade ≥3 adverse events, and the incidence of arrhythmia and cardiovascular-related adverse events tended to increase at 300 mg/day compared with the incidence at 100 mg/day or 200 mg/day (Table 14). Taking into account the factors shown below, the package insert and information materials for healthcare professionals should include a cautionary statement to the effect that when the dose is increased to 300 mg/day, the patient should be monitored for electrocardiogram, pulse rate, and symptoms such as chest pain and syncope on an inpatient basis, similar to the monitoring performed after the start of treatment.
  - In Study JPOST-10, serious arrhythmia and cardiovascular-related adverse events for which a causal relationship to thalidomide could not be ruled out were reported in 5 subjects. In 3 of the 5 subjects, adverse events occurred within 1 month of the start of treatment or dose increase [see Section 7.R.2.2].
  - The JPOST_NCC study explored risk factors for arrhythmia when using thalidomide in participants of the clinical studies of thalidomide and patients who had not participated in the clinical studies but had started treatment around the same time, as well as patients for whom study drug treatment was made available for compassionate use purposes (see CTD 5.3.5.4.1). Arrhythmia events (17

subjects) occurred in 6 of 17 subjects within 1 week of the last dose increase, 12 of 17 subjects within 2 weeks, 13 of 17 subjects within 3 weeks, and 13 of 17 subjects within 4 weeks (Table 12).

- The appropriateness of the descriptions in the Dosage and Administration section and the Precautions Concerning Dosage and Administration section should be determined, taking account of comments from the Expert Discussion.

7.R.6 Proper use of thalidomide

PMDA asked the applicant to explain the proper use of thalidomide.

The applicant's explanation:

- When administering thalidomide to patients with POEMS syndrome, the greatest attention must be paid to teratogenicity, a clinically significant adverse reaction. To prevent fetal exposure, the collaborating obstetrician-gynecologist is required to explain contraceptive methods and perform tasks as necessary for the prescribing physician as those implemented for the previously approved indications; therefore, thalidomide must be used in strict compliance with TERMS.
- POEMS syndrome is primarily a monoclonal plasma cell proliferative disorder with a principal symptom of polyneuritis; therefore, the registration requirements of physicians who are qualified to prescribe thalidomide to patients with POEMS syndrome under TERMS is limited to either a hematologist or neurologist, or physicians who can work in cooperation with these specialists.
- The package insert and information materials for healthcare professionals should include a cautionary statement to the effect that thalidomide should be administered to patients with POEMS syndrome only if collaboration with a cardiologist is feasible as a measure to control cardiovascular risks [see Section 7.R.2.2].

PMDA accepted the applicant's explanation above. However, the applicant should provide sufficient information on the intended patients of thalidomide and risks associated with the treatment, using information materials to healthcare professionals. Thalidomide should be prescribed only after the physician has thoroughly understood such information. A final decision on the details of the proper use of thalidomide will be made, taking account of comments from the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant's explanation on the post-marketing surveillance plans as outlined below:

- A specified use-results survey will be conducted to monitor the long-term safety of patients with POEMS syndrome who have received thalidomide, with a follow-up period of 3 years and a survey period of 6 years, covering all patients with POEMS syndrome who will be receiving thalidomide at medical institutions capable of providing treatment in compliance with TERMS during the registration period.
- A comparative use-results survey will be conducted to explore the risk factors for arrhythmia associated with treatment with thalidomide in clinical settings, with a follow-up period of 52 weeks and a survey period of 3 years covering all patients with POEMS syndrome at medical institutions subject to the above

specified use-results survey as of the date of approval (as a general principle, patients enrolled in the preceding JPOST_NCC study are excluded).

PMDA's view:

On the basis of the presented clinical study data, the number of patients enrolled in the studies was extremely limited, and safety profiles of thalidomide have not been adequately evaluated. Therefore, the applicant should collect data on safety and risk factors for arrhythmia associated with thalidomide treatment in the post-marketing surveillance. A final decision on the appropriateness of the post-marketing investigations will be made, taking account of comments from the Expert Discussion.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. The results showed that a sponsor-investigator modified the imputation method of missing data to perform analyses, after confirming the primary efficacy analysis results obtained by the imputation method by LOCF as specified in the statistical analysis plan, and reported the results obtained by the modified analysis method in the clinical study report of CTD 5.3.5.1.1. Although the analysis results were different before and after the modification of imputation method, the sponsor-investigator failed to report the following issues in the clinical study report: the modification to the imputation method of missing data and circumstances that led to modification, the analysis results obtained based on the method before modification, and the impact of modification on the assessment. Because the analysis results of the primary efficacy endpoint obtained by the modified imputation method differed from those obtained by the method before modification, PMDA concluded that it is appropriate to conduct its review after suitable measures are taken, such as requesting the applicant to submit, together with other documents for application, a document describing the circumstances that led to modification of the imputation method for missing data, the study results obtained by the imputation method before modification, and the impact on the assessment.

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

The new drug application data (CTD 5.3.5.1.1 through CTD 5.3.5.1.3) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that thalidomide has efficacy in the treatment of POEMS syndrome, and that thalidomide has acceptable safety in view of its benefits. Thalidomide is

clinically meaningful because it offers a new treatment option for patients with POEMS syndrome in Japan. PMDA considers that the following issues require further discussions at the Expert Discussion: the clinical positioning of thalidomide in view of its efficacy, necessity of treatment on an inpatient basis, the appropriateness of and the need for monitoring, appropriateness of the indication and dosage regimen, proper use, and appropriateness of post-marketing investigations.

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

Review Report (2)

January 15, 2021

Product Submitted for Approval

Brand Name	Thaled Capsules 25
	Thaled Capsules 50
	Thaled Capsules 100
Non-proprietary Name	Thalidomide
Applicant	Fujimoto Pharmaceutical Corporation
Date of Application	March 26, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

PMDA's view:

In the analyses for the primary endpoint for the Japanese phase II/III study (CTD 5.3.5.1.1, 5.3.5.1.2, Study JPOST-10), the primary analysis based on the LOCF method before modification showed that there was no significant difference in the change in serum VEGF levels between the groups. Therefore, it was difficult to conclude that the efficacy of thalidomide had been verified. However, taking the results for the entire study comprehensively into consideration, thalidomide can be expected to have a certain degree of efficacy for several reasons including the following: the serum VEGF levels tended to decrease as a result of thalidomide treatment based on the results of the primary analysis in which the modified LOCF method was used, as well as sensitivity analysis results; the clinical symptoms specified as secondary endpoints were also suggestive of a trend towards some improvement; progression-free survival and overall survival tended to be prolonged in thalidomide-treated patients enrolled in Study JPOST-10 compared with the placebo group [see Section 7.R.1 in Review Report (1)]. The expert advisors supported the PMDA's conclusion shown above.

1.2 Safety

Sinus bradycardia occurred more frequently in the clinical studies in patients with POEMS syndrome (Studies JPOST-10 and JPOST-13) than in the clinical studies in patients with relapsed or refractory multiple myeloma (Studies FPF300-02-01 and FPF300-02-02), suggesting that the safety profiles in patients with POEMS syndrome tend to differ from those in patients with multiple myeloma. Therefore, PMDA considered that the following actions are needed [see Section 7.R.2.2 in Review Report (1)]:

- Before starting treatment with thalidomide in patients with POEMS syndrome, the risk of arrhythmia and cardiovascular-related events must be thoroughly explained, and informed consent must be obtained in writing. Cautionary statement should be included in the package insert and information materials to the effect that whether the patient can be treated with thalidomide should be carefully determined taking into account a cardiovascular risk assessment by cardiologists. “Subacute exacerbation” and “heart disease or electrocardiographic abnormalities” were identified as risk factors for arrhythmia in the JPOST_NCC study; therefore, the package insert should contain a cautionary statement to the effect that patients with these risk factors present a potential increased risk for arrhythmia.
- The following risk control measures are appropriate in the early phase of treatment with thalidomide: all patients should receive thalidomide on an inpatient basis; cautionary advice to the effect that patients should be monitored for electrocardiogram, pulse rate, and symptoms such as chest pain and syncope on an inpatient basis for at least 4 weeks after the start of treatment so that suitable measures to minimize cardiovascular risks associated with thalidomide treatment are taken for all patients including those without the risk factors.
- The following risk control measures should be taken 1 month after the start of thalidomide treatment and beyond: from 1 month after the start of thalidomide treatment, patients should be monitored (e.g., electrocardiogram) once a month for the first 6 months, and on a regular basis thereafter throughout the treatment period; in addition, cardiovascular risk assessment by cardiologists is required for a certain period after the start of treatment.
- Coronary spasm has been reported following treatment with thalidomide. Healthcare professionals should be cautioned for possible onset of coronary spasm in patients who have been taking a calcium channel blocker during treatment with thalidomide and dose reduction or discontinuation of the calcium channel blocker becomes necessary.
- The applicant should continue to collect data on risk factors in the post-marketing surveillance and evaluate data.

The expert advisors supported the PMDA’s conclusion shown above. The expert advisors also made the following comments:

- Although there is no objection to the risk control measures in the early phase of treatment that all patients should receive thalidomide on an inpatient basis, the cardiologist should be allowed to decide the duration of inpatient stay according to the patient’s condition. Therefore, it is appropriate to provide materials containing necessary information such as general duration of inpatient stay, and the incidence of arrhythmias and other cardiovascular events reported in the clinical studies by time of onset to help determine the duration of inpatient stay.

- For a specific period after the start of treatment during which patients receive treatment on an inpatient basis, the patient should receive treatment on an inpatient basis where adequate treatment including temporary pacing can be initiated in the event of serious arrhythmia such as cardiac arrest.

On the basis of the above, PMDA instructed the applicant to include a cautionary statement in the package insert to the effect that patients should be treated on an inpatient basis for a specific period after the start of thalidomide treatment so that arrhythmia and other serious events can be adequately treated; and to provide information on the general duration of inpatient stay (3-4 weeks) and the incidence of cardiovascular events including arrhythmia reported in the clinical studies by time of onset using information materials for healthcare professionals. The applicant properly dealt with the instruction.

1.3 Indication and clinical positioning

PMDA's view:

Treatment options for patients with POEMS syndrome ineligible for radiation therapy or high-dose chemotherapy with autologous PBSCT are extremely limited, and thalidomide is recommended in the Japanese clinical practice guidelines as an initial remission induction regimen for transplant-eligible patients and as treatment for transplant-ineligible patients or patients with relapsed or refractory POEMS syndrome. Taken together, thalidomide can be defined as a treatment option for these patients [see Section 7.R.3 in Review Report (1)].

Taking into account the efficacy and safety of thalidomide as indicated by the data from Studies JPOST-10 and JPOST-13, thalidomide will not replace other treatment options recommended as standard therapy for POEMS syndrome in the Japanese clinical practice guidelines; therefore, the intended patient population of thalidomide treatment should be defined as patients for whom other standard therapies are not suitable [see Section 7.R.4 in Review Report (1)]. Furthermore, before starting treatment with thalidomide, the physician should carefully select patients for whom the benefits of thalidomide outweigh its risks after fully understanding the details of the study results on the efficacy and safety of thalidomide [see Section 7.R.4 in Review Report (1)].

The expert advisors supported the PMDA's conclusion shown above. The expert advisors also made the following comments:

- No standard therapy has been established for POEMS syndrome. Thalidomide is one of the treatment options recommended in the Japanese clinical practice guidelines, and it is important to increase treatment options for patients.
- Because the age of onset of POEMS syndrome is younger than that of multiple myeloma, the clinical condition of patients with POEMS syndrome is often improved by high-dose melphalan in combination with autologous PBSCT; however, autologous PBSCT may be difficult to perform in some patients due to intravascular volume depletion, and after high-dose melphalan, some patients have difficulty in expectorating sputum and may develop serious pneumonia, which sometimes requires endotracheal intubation or respiratory care. For this reason, not only transplant-ineligible patients due to age, but even transplant-eligible patients based on age will require pharmacotherapy to prevent deterioration of

subsequent stem cell collection efficiency if autologous PBSCT is difficult to perform immediately after diagnosis.

- The clinical positioning and intended patient population for thalidomide treatment would be patients ineligible for radiation therapy or high-dose melphalan in combination with autologous PBSCT, patients who are eligible for autologous PBSCT but may be at risk if autologous PBSCT were to be performed immediately due to deterioration of physical function associated with POEMS syndrome or in whom autologous PBSCT is not likely to provide a sufficient amount of stem cells, and patients with relapsed POEMS syndrome after undergoing autologous PBSCT or melphalan plus dexamethasone treatment.

On the basis of the above, PMDA instructed the applicant to include the statement shown below in the "Precautions Concerning Indications" section of the package insert, and the applicant responded appropriately.

Precautions Concerning Indications

The appropriateness of the use of thalidomide should be carefully determined based on a clear understanding of the information presented in the "17. Clinical Studies" section and of the efficacy and safety of thalidomide, and after thorough consideration of other treatment options with reference to the Japanese clinical practice guidelines.

1.4 Dosage and administration

PMDA's view:

There is no particular problem with selecting a starting dose of 100 mg on alternate days and the maintenance dose of 200 mg/day. The package insert should include a statement to the effect that when the dose is increased, an interval of ≥1 week between each level should be allowed [see Section 7.R.5 in Review Report (1)]. While a maximum dose of 300 mg/day is acceptable, the incidence of Grade ≥3 adverse events, and the incidence of arrhythmia and cardiovascular-related adverse events tended to increase at 300 mg/day compared with the incidence at 100 mg/day or 200 mg/day. Because of this and for other reasons, it is necessary to caution that the patient should be monitored for electrocardiogram, pulse rate, and symptoms such as chest pain and syncope on an inpatient basis when the dose is increased to 300 mg/day, similar to the monitoring performed after the start of treatment [see Section 7.R.5 in Review Report (1)].

The expert advisors supported the PMDA's conclusion shown above. The expert advisors also made the following comments:

- A dose increase to 300 mg/day may increase the risks for bradycardia, arrhythmia, and cardiovascular events; therefore, the patient should receive treatment on an inpatient basis for a specific period after a dose increase to 300 mg/day, similar to the treatment implemented after the start of treatment, to closely monitor the clinical course before allowing the patient to move into an outpatient setting.
- Specifying the duration of inpatient stay after a dose increase to 300 mg/day may cause a delay in the timing of dose increase, which may interfere with appropriate care for exacerbation, leading to a sudden change of the patient's condition. Therefore, the cardiologist should be allowed to determine the duration according to the patient's condition, similar to how the duration was determined after the start of treatment.

Accordingly, it is appropriate to provide information materials to help determine the duration of inpatient stay, and the materials should include necessary information such as general duration of inpatient stay, and the incidence of arrhythmias and other cardiovascular events reported after dose increase to 300 mg/day in the clinical studies by time of onset.

On the basis of the above, PMDA instructed the applicant to modify the description for the Dosage and Administration section as shown below, include the statement shown below in the Precautions Concerning Dosage and Administration section of the package insert, and use information materials for healthcare professionals to provide information on the general duration of inpatient stay and the incidence of arrhythmias and other cardiovascular events reported after dose increase to 300 mg/day in the clinical studies by time of onset. The applicant responded appropriately.

Dosage and Administration
The usual adult starting dose is 100 mg of thalidomide on alternate days. After an interval of at least 1 week, gradually increase the dose to 200 mg once daily. Thalidomide should be administered orally at bedtime. The dose should be adjusted according to the patient's condition; however, the daily dose should not exceed 300 mg.

Precautions Concerning Dosage and Administration
In the clinical studies, serious arrhythmia events were frequently reported after a dose increase to 300 mg/day. Patients should be treated with thalidomide on an inpatient basis for a specific period after a dose increase to 300 mg/day so that arrhythmia and other serious events can be appropriately treated.

1.5 Proper use

PMDA's view:
There are no particular problems with the measures the applicant plans to implement for proper use. Using information materials for healthcare professionals, the applicant should provide healthcare professionals with sufficient information regarding intended patients for thalidomide and risks associated with thalidomide treatment to ensure that thalidomide will be used only after the physician has thoroughly understood the information [see Section 7.R.6 in Review Report (1)].

The expert advisors supported the PMDA's conclusion shown above. The expert advisors also made the following comment: to ensure proper use of thalidomide, not only is cooperation between hematologists or neurologists and cardiologists important, but cooperation between hematologists and neurologists who have used thalidomide previously for the treatment of multiple myeloma is also important.

On the basis of the above, PMDA instructed the applicant to provide information using materials for healthcare professionals to ensure that thalidomide is used in cooperation of hematologists, neurologists, and cardiologists. The applicant responded appropriately.

1.6 Risk management plan (draft)

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA concluded that the risk management plan (draft) for thalidomide should include the safety specifications presented in Table 16, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 17.

Table 16. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Teratogenicity • Cerebral infarction • Cardiac failure • Neuropathy peripheral • Infection • Lethargy, somnolence • Tumour lysis syndrome • Venous thromboembolism • Ischaemic heart disease • Arrhythmia • Myelosuppression • Interstitial lung disease • Spasm • Hepatic function disorder • Gastrointestinal perforation, gastrointestinal obstruction • Hypersensitivity (e.g., oculomucocutaneous syndrome [Stevens-Johnson syndrome], toxic epidermal necrolysis [TEN])	• Secondary cancer • Pulmonary hypertension	• None
Efficacy specification[a)]		
None		

a) Only efficacy specifications relating to the present application are listed

Table 17. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)[a)]

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (Crow-Fukase [POEMS] syndrome) • Implementation of Thalidomide Education and Risk Management System (TERMS) • Specified use-results survey (Crow-Fukase [POEMS] syndrome, long-term use) • Comparative use-results survey (Crow-Fukase [POEMS] syndrome)	• Disseminate data gathered during early post-marketing phase vigilance (Crow-Fukase [POEMS] syndrome) • Implementation of Thalidomide Education and Risk Management System (TERMS) • Organize and disseminate information (through a proper use guide) for healthcare professionals (Crow-Fukase [POEMS] syndrome)

a) Only additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities relating to the present application are listed

The applicant explained that it plans to conduct post-marketing surveillance to assess the above issues: a specified use-results survey (Table 18) and comparative use-results survey (Table 19).

Table 18. Outline of specified use-results survey (draft)

Objective	To identify the safety and efficacy of long-term thalidomide treatment in patients with POEMS syndrome
Survey method	All-case surveillance
Population	Patients with POEMS syndrome who start receiving treatment with thalidomide
Observation period	3 years
Planned sample size	All patients who have been registered
Main survey items	Patient demographics (e.g., age at start of treatment, height, body weight, performance status, presence of electrocardiographic abnormalities, presence of neuropathy peripheral), status of thalidomide use, discontinuation/drop out, adverse events, serum vascular endothelial growth factor (VEGF) levels, status of survival, presence of exacerbations

Table 19. Outline of comparative use-results survey (draft)

Objective	To explore risk factors for arrhythmia in a nested case-control study in which patients with POEMS syndrome are grouped into the exposure and control groups: those who have been treated with thalidomide (Thaled capsules or other formulations) in the exposure group and thalidomide-naïve patients in the control group.
Survey method	All-case surveillance
Population	All patients with POEMS syndrome at medical institutions eligible to be surveyed as of the date of approval (as a general principle, patients enrolled in the preceding JPOST_NCC study are excluded)
Observation period	52 weeks from the date of approval (observation period can also be retrospective)
Planned sample size	All patients to be covered by the survey
Main survey items	• Patient demographics (e.g., age, height, body weight, performance status, medical history) • Treatment of POEMS syndrome (use of Thaled capsules or other treatments) • Complications (hypertension, dyslipidaemia, diabetes mellitus, hyperuricaemia, hypothyroidism, coronary spasm, ischaemic heart disease, sinus bradycardia, orthostatic hypotension, chest pain, palpitations, syncope, other heart disease [name of disease]) • Subacute exacerbation • Coadministered drugs • Arrhythmia events and adverse events

PMDA accepts the above applicant's plans. Data gathered in the surveys should be promptly provided to healthcare professionals.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications shown below, after modifying the proposed dosage and administration as shown below, with the following approval conditions. Since this application is for an orphan drug, the re-examination period for the new indication and its dosage and administration should be 10 years.

Indications

- Relapsed or refractory multiple myeloma
- Erythema nodosum leprosum
- Crow-Fukase (POEMS) syndrome

(Underline denotes additions.)

Dosage and Administration

- Relapsed or refractory multiple myeloma

The usual adult dosage is 100 mg of thalidomide orally once daily at bedtime. The dose may be adjusted according to the patient's condition. The daily dose should not exceed 400 mg.

- Erythema nodosum leprosum

Usually, thalidomide is administered orally once daily at bedtime. The adult starting dose is 50 to 100 mg of thalidomide and may be gradually increased as necessary until symptoms are alleviated. The daily dose should not exceed 400 mg. Gradually decrease the dose if symptoms improve. Control the symptoms at a lower maintenance dose.

- Crow-Fukase (POEMS) syndrome

The usual adult starting dose is 100 mg of thalidomide on alternate days. After an interval of at least 1 week, gradually increase the dose to 200 mg once daily. Thalidomide should be administered orally at bedtime. The dose should be adjusted according to the patient's condition; however, the daily dose should not exceed 300 mg.

(Underline denotes additions.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to properly comply with the Thalidomide Education and Risk Management System (TERMS) for the marketing, management, and use of the product. Any change to the procedures of the TERMS requires prior approval by the Ministry of Health, Labour and Welfare.
3. The applicant is required to take stringent and proper measures to ensure that the product will be administered only to patients identified to be appropriate to receive the treatment, under the supervision of a physician with sufficient knowledge and experience, at a medical facility capable of providing adequate emergency medical care. Prior to initiation of treatment, patients or their family members must be fully informed of its efficacy and risks in written form, and their consent must be obtained in writing.
4. Because the number of patients studied in Japan is extremely limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a specified number of patients will be collected to obtain information on the characteristics of patients treated with the product, and collect safety and efficacy data as soon as possible. The applicant is required to take necessary measures to ensure proper use of the product.

Appendix

List of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
C_{24h}	Plasma concentration at 24 hours
CD34	Cluster of Differentiation 34
CI	Confidence Interval
CT	Computed Tomography
CTCAE	Common Terminology Criteria Adverse Events
CTD	Common Technical Document
FAS	Full Analysis Set
GCP	Good Clinical Practice
HPLC	High Performance Liquid Chromatography
Japanese clinical practice guidelines	Japanese Society of Hematology (JSH) Practical Guidelines for Hematological Malignancies, 2018
LOCF	Last Observation Carried Forward
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MMRM	Mixed Model Repeated Measures
NCC	Nested case-control
PBSCT	Peripheral Blood Stem Cell Transplantation
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred Term
QOL	Quality of Life
SF-36	MOS 36-Item Short-Form Health Survey
SOC	System Organ Class
TEN	Toxic Epidermal Necrolysis
TERMS	Thalidomide Education and Risk Management System
Thaled capsules	Thaled Capsules 25, Thaled Capsules 50, Thaled Capsules 100
Thalidomide	Thalidomide
UV	Ultraviolet absorption spectroscopy
VEGF	Vascular Endothelial Growth Factor
WOCF	Worst Observation Carried Forward