Report on the Deliberation Results

December 11, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Rapalimus Tablets 1 mg, Rapalimus Granules 0.2%
Non-proprietary Name	Sirolimus (JAN*)
Applicant	Nobelpharma Co., Ltd.
Date of Application	April 24, 2023

Results of Deliberation

In its meeting held on December 8, 2023, the First Committee on New Drugs concluded that the partial change application for Rapalimus Tablets 1 mg and the product application for Rapalimus Granules 0.2% may be approved, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

Rapalimus Granules 0.2% is not classified as a biological product or specified biological product, and the drug product is classified as a powerful drug. The re-examination period for both Rapalimus Tablets 1 mg and Rapalimus Granules 0.2% is 10 years.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of limited experiences in Japanese patients, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the products to compile data from a certain number of cases for an understanding of patient characteristics, collect product safety and efficacy data promptly, and take necessary measures to ensure the proper use of the products.

**Japanese Accepted Name (modified INN)*

Review Report

November 22, 2023
Pharmaceuticals and Medical Devices Agency

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

Brand Name	(a) Rapalimus Tablets 1 mg, (b) Rapalimus Granules 0.2%
Non-proprietary Name	Sirolimus
Applicant	Nobelpharma Co., Ltd.
Date of Application	April 24, 2023
Dosage Form/Strength	(a) Sugar-coated tablets, each containing 1 mg of sirolimus (b) Granules, containing 2 mg of sirolimus per gram
Application Classification	(a) Prescription drug (4) Drug with a new indication, (6) Drug with a new dosage (b) Prescription drug (4) Drug with a new indication, (6) Drug with a new dosage, (8) Drug in an additional dosage form
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 491 of 2020 [R2 *yaku*]; PSEHB/PED Notification No. 1125-9, dated November 25, 2020, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the products have efficacy in the treatment of refractory vascular tumors and refractory vascular malformations (lymphangioma [lymphatic malformations], lymphangiomatosis, Gorham's disease, lymphangiectasia, hemangioendothelioma, tufted angioma, venous malformations, blue rubber bleb nevus syndrome, combined vascular malformations, and Klippel-Trenaunay-Weber syndrome), and that the products have acceptable safety in view of their benefits (see the Attachment).

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

Indications

(a) Rapalimus Tablets 1 mg

- Lymphangioleiomyomatosis
- The following refractory ~~lymphatic diseases~~ vascular tumors and refractory vascular malformations; lymphangioma (lymphatic malformations), lymphangiomatosis, Gorham's disease, lymphangiectasia, hemangioendothelioma, tufted angioma,
  venous malformations, blue rubber bleb nevus syndrome,
  combined vascular malformations, Klippel-Trenaunay-Weber syndrome

(b) Rapalimus Granules 0.2%

- The following refractory vascular tumors and refractory vascular malformations;
  lymphangioma (lymphatic malformations), lymphangiomatosis, Gorham's disease, lymphangiectasia, hemangioendothelioma, tufted angioma,
  venous malformations, blue rubber bleb nevus syndrome,
  combined vascular malformations, Klippel-Trenaunay-Weber syndrome

(Underline denotes additions. Strikethrough denotes deletions.)

Dosage and Administration

(a) Rapalimus Tablets 1 mg

Lymphangioleiomyomatosis

The usual adult dosage is 2 mg of sirolimus administered orally once daily. The dose may be adjusted according to the patient's condition. However, the dose should not exceed 4 mg once daily.

Refractory ~~lymphatic diseases~~ vascular tumors and refractory vascular malformations

The usual starting dose is 2 mg (body surface area $\geq$1.0 m^2) or 1 mg ((body surface area <1.0 m^2) of sirolimus administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed 4 mg once daily.

(b) Rapalimus Granules 0.2%

Refractory vascular tumors and refractory vascular malformations

The usual starting dose is 2 mg (body surface area $\geq$1.0 m^2) or 1 mg (body surface area $\geq$0.6 and <1.0 m^2) of sirolimus administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed 4 mg once daily.

For patients with a body surface area <0.6 m^2, the starting dose is determined based on their age in months as shown below, and administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed the maximum dose indicated below.

Age in months	Starting daily dose (≤1 mg)	Maximum daily dose (≤4 mg)
<3 months	0.02 mg/kg	0.08 mg/kg
≥3 months to <6 months	0.04 mg/kg	0.16 mg/kg
≥6 months to <12 months	0.06 mg/kg	0.24 mg/kg
≥12 months	0.08 mg/kg	0.32 mg/kg

(Underline denotes additions. Strikethrough denotes deletions.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of limited experiences in Japanese patients, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the products to compile data from a certain number of cases for an understanding of patient characteristics, collect product safety and efficacy data promptly, and take necessary measures to ensure the proper use of the products.

Attachment

Review Report (1)

October 17, 2023

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

Product Submitted for Registration

Brand Name	(a) Rapalimus Tablets 1 mg, (b) Rapalimus Granules 0.2%
Non-proprietary Name	Sirolimus
Applicant	Nobelpharma Co., Ltd.
Date of Application	April 24, 2023
Dosage Form/Strength	(a) Sugar-coated tablets, each containing 1 mg of sirolimus (b) Granules, containing 2 mg of sirolimus per gram

Proposed Indications

(a) Rapalimus Tablets 1 mg

- Lymphangioleiomyomatosis
- The following refractory ~~lymphatic diseases~~ vascular tumors and refractory vascular malformations; lymphangioma (lymphatic malformations), lymphangiomatosis, Gorham's disease, lymphangiectasia, hemangioendothelioma, tufted angioma, venous malformations, blue rubber bleb nevus syndrome, combined vascular malformations, Klippel-Trenaunay-Weber syndrome

(b) Rapalimus Granules 0.2%

- The following refractory vascular tumors and refractory vascular malformations; lymphangioma (lymphatic malformations), lymphangiomatosis, Gorham's disease, lymphangiectasia, hemangioendothelioma, tufted angioma, venous malformations, blue rubber bleb nevus syndrome, combined vascular malformations, Klippel-Trenaunay-Weber syndrome

(Underline denotes additions. Strikethrough denotes deletions.)

Proposed Dosage and Administration

(a) Rapalimus Tablets 1 mg

Lymphangioleiomyomatosis

The usual adult dosage is 2 mg of sirolimus administered orally once daily. The dose may be adjusted according to the patient's condition. However, the dose should not exceed 4 mg once daily.

Refractory ~~lymphatic diseases~~ *vascular tumors and refractory vascular malformations*

The usual starting dose is 2 mg (body surface area ≥1.0 m^2) or 1 mg (body surface area <1.0 m^2) of sirolimus administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed 4 mg once daily.

(b) Rapalimus Granules 0.2%

Refractory vascular tumors and refractory vascular malformations

For adults and children aged ≥1 year

The usual starting dose is 1.6 mg (body surface area ≥1.0 m^2) or 0.8 mg (≥1 year-old and body surface area <1.0 m^2) of sirolimus, administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed 3.2 mg once daily.

For infants aged <1 year

The usual starting dose is determined based on the patient's age in months as shown below, and administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed 4 times the age (in months)-based starting dose.

Age in months	Starting daily dose
<3 months	0.02 mg/kg
≥3 months to <6 months	0.04 mg/kg
≥6 months to <12 months	0.06 mg/kg

(Underline denotes additions. Strikethrough denotes deletions.)

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List of Abbreviations

See the Appendix.

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

Vascular tumors and vascular malformations mainly occur in childhood, manifesting as dysplasia of blood vessels or lymphatic vessels. These diseases include lymphatic dysplasia (hereinafter referred to as "lymphatic diseases"), blood vessel dysplasia, and a combined type of dysplasia affecting multiple vascular components.

Surgical resection, sclerotherapy, radiotherapy, etc. are currently used to address various symptoms of vascular tumors and vascular malformations, such as swelling, pain, ulceration, functional impairment, organ damage, and cosmetic problems. However, these treatments are infeasible or less effective depending on the location and size of the lesion ("Japanese Clinical Practice Guidelines for Vascular Anomalies 2022" edited by the Group for "Research on Refractory Hemangioma, Vascular Malformations, Blood Vessel Malformations, Lymphangioma, Lymphangiomatosis, and Other Related Diseases," the Research Project for Intractable Disease supported by the Health and Labour Sciences Research Grant, Fiscal Years 2020 to 2022 [hereinafter referred to as the "Clinical Practice Guidelines 2022"]).

Sirolimus is an inhibitor of the mammalian target of rapamycin (mTOR), developed by US Wyeth-Ayerst (now Pfizer Inc.). In Japan, sirolimus was approved as tablets (Rapalimus Tablets 1 mg) for the treatment of "lymphangioleiomyomatosis" in July 2014, and for "lymphangioma (lymphatic malformations), lymphangiomatosis, Gorham's disease, and lymphangiectasia," which are "vascular tumors and refractory vascular malformations" categorized as "refractory lymphatic diseases," in September 2021. A sirolimus-eluting stent, a medical device to treat ischemic heart disease developed by Johnson & Johnson K.K., was approved in 2004, while a topical formulation of sirolimus, developed by the applicant, was approved in March 2018 for the indication of "tuberous sclerosis complex-associated skin lesions." In Japan, no drugs have been approved for the indication of vascular tumors and refractory vascular malformations other than lymphatic diseases.

From June 2020, a clinical study was conducted using sirolimus tablets and the applicant's newly developed product, sirolimus granules (Rapalimus Granules 0.2%) in patients with refractory vascular tumors and refractory vascular malformations at Gifu University Hospital. It was an investigator-initiated study as a part of the Project Promoting Clinical Trials for Development of New Drugs led by the Japan Agency for Medical Research and Development. Among the target diseases of the investigator-initiated study, excluding the previously approved lymphatic diseases, giant venous malformations (cervical, oral, and oropharyngeal diffuse lesions) (Notification No. 279) and Klippel-Trenaunay-Weber syndrome (Notification No. 281) are designated intractable diseases (dated July 1, 2015; Ministry of Health, Labour and Welfare).

Recently, the applicant has filed an application for partial change approval for sirolimus tablets and a marketing application for sirolimus granules, based on their conclusion that the investigator-initiated study had demonstrated the efficacy and safety of the drug product in the mentioned dosage forms against refractory vascular tumors and refractory vascular malformations.

As of March 2023, sirolimus has been approved in 110 countries or regions outside Japan, but has not been approved for refractory vascular tumors or refractory vascular malformations in any countries or regions.

Sirolimus has been designated as an orphan drug with the intended indication of "refractory vascular tumors and refractory vascular malformations" (Orphan Drug Designation No. 491 of 2020 [R2 *yaku*], dated November 25, 2020).

2. Quality and Outline of the Review Conducted by PMDA

The present application pertains to a new indication and new dosage regimens of sirolimus tablets and sirolimus granules as additional dosage form. Therefore, quality-related data were submitted. PMDA conducted a review on a drug in an additional dosage form, found no particular issues on the additional dosage form, and concluded that the quality of sirolimus granules was adequately controlled.

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

Although the present application is intended for a new indication and new dosages, no new data on non-clinical pharmacology have been submitted. The non-clinical pharmacology of sirolimus was evaluated during the review for the initial approval and the approval for refractory lymphatic diseases (Review Reports for "Rapalimus Tablets 1 mg," dated May 15, 2014 and August 6, 2021).

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

Although the present application pertains to a new indication and new dosages, no new data on non-clinical pharmacokinetics have been submitted. The non-clinical pharmacokinetics of sirolimus was evaluated in the process of the review for the initial approval (Review Report for "Rapalimus Tablets 1 mg," dated May 15, 2014).

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application pertains to a new indication and new dosages, no new data regarding the toxicity of sirolimus have been 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

The applicant submitted the results of a bioequivalence study of sirolimus tablets and granules, as data relating to biopharmaceutic studies.

In a Japanese clinical study submitted as evaluation data for the present application, sirolimus granules used were identical to the proposed commercial formulation, and sirolimus tablets used were the commercial formulation.

Whole blood sirolimus concentrations were measured via liquid chromatography and tandem mass spectrometry (LC-MS/MS), with a lower limit of quantification of either 0.5 or 1.0 ng/mL.[1)]

In this report, the doses and whole blood concentrations of sirolimus tablets and sirolimus granules are described as the concentrations of sirolimus.

6.1.1 Bioequivalence study (CTD 5.3.4.1-1, Study No. NPC-12T-1, November to December 2018)

A randomized, open-label, 2-treatment, 2-period crossover study was conducted to evaluate the bioequivalence between sirolimus granules and sirolimus tablets in 10 healthy Japanese adults.

The subjects received a single oral dose of sirolimus granules 2 mg or sirolimus tablets 2 mg in the fasting state, with a washout period of ≥14 days.[2)]

Table 1 shows the pharmacokinetic (PK) parameters of sirolimus. The 90% confidence intervals for the geometric mean ratios of C_{max} and $AUC_{0\text{-last}}$ values of sirolimus granules to those of sirolimus tablets were outside the range from 0.8 to 1.25, failing to demonstrate bioequivalence between these dosage forms. The C_{max} and $AUC_{0\text{-last}}$ values of sirolimus granules were higher than those of sirolimus tablets.

Table 1. PK parameters of sirolimus administered as a single oral dose of sirolimus granules or sirolimus tablets

Dosage Form	N	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-last}}$ (ng·h/mL)	$t_{1/2}$ (h)	Geometric mean ratio to tablets [90% CI]	
						C_{max}	$AUC_{0\text{-last}}$
Granules	10	16.2±5.45	1.8 [1.0, 2.0]	165±39.7	56.8±19.9	2.30 [1.90, 2.78]	1.48 [1.22, 1.80]
Tablets	10	6.89±1.75	2.0 [1.5, 4.0]	111±23.7	46.5±19.9	-	-

Mean ± standard deviation
a) Median [minimum, maximum]

The safety analysis revealed no adverse events.

6.2 Clinical pharmacology

6.2.1 Investigator-initiated study (the CVA study) (CTD 5.3.5.2-1, Study No. NPC-12T-CVA, June 2020 to February 2022)

Trough whole blood sirolimus concentrations following multiple oral doses of sirolimus tablets or granules were determined in patients with refractory vascular tumors or refractory vascular malformations.

For patients weighing ≥30 kg, the starting dose was 2 mg-sirolimus tablets or 1.4 mg-sirolimus granules administered orally once daily. Patients weighing <30 kg received sirolimus granules orally once daily[3)] at the starting dose as per Table 2, based on their age in months. Subsequent doses were adjusted to maintain trough whole blood sirolimus concentrations within the target range of 5 to 15 ng/mL [see Section 7.1 for an overview of the study and the efficacy and safety results].

1) 0.5 ng/mL in Study NPC-12T-1; 1.0 ng/mL in Study NPC-12T-CVA and the specified clinical study (Study SRL-CVA-01)
2) The day the study drug was administered was the day when the washout period started.
3) Each patient was allowed to take sirolimus either in the fasting or fed state, which however had to be remained fixed throughout the study.

Table 2. Starting doses of sirolimus granules in patients weighing <30 kg

Age in months	Starting dose of sirolimus granules
<3 months	0.02 mg/kg
≥3 months to <6 months	0.04 mg/kg
≥6 months to <12 months	0.06 mg/kg
≥12 months	0.08 mg/kg (≤1.4 mg)

Table 3 are PK data showing trough whole blood sirolimus concentrations through Week 52.

Table 3. Trough whole blood sirolimus concentrations (ng/mL)

Dosage Form	Body weight, BSA, age	Week 1	Week 2	Week 4	Week 12	Week 24	Week 36	Week 52
Total		5.55±2.38 (N = 13)	5.71±1.74 (N = 13)	5.76±2.05 (N = 13)	6.57±3.00 (N = 13)	6.64±1.52 (N = 12)	7.33±3.08 (N = 12)	7.82±3.56 (N = 13)
Tablets	≥30 kg	5.70±1.11 (N = 4)	6.23±1.02 (N = 4)	6.00±1.13 (N = 4)	6.48±1.02 (N = 4)	6.63±1.80 (N = 3)	8.00±3.08 a) (N = 4)	9.73±5.05 a) (N = 4)
Granules	≥30 kg	2.90 (N = 1)	3.40 (N = 1)	4.10 (N = 1)	5.30 (N = 1)	8.80 (N = 1)	9.20 a) (N = 1)	7.70 a) (N = 1)
	<30 kg and BSA ≥0.6 m^2	6.40±4.08 (N = 3)	6.20±2.54 (N = 3)	6.70±2.82 (N = 3)	6.80±4.14 (N = 3)	5.73±0.75 (N = 3)	7.03±2.29 (N = 3)	9.67±2.18 (N = 3)
	≥1 year and BSA <0.6 m^2	5.48±2.69 (N = 4)	5.80±1.87 (N = 4)	4.75±2.39 (N = 4)	7.15±4.67 (N = 4)	6.68±1.86 (N = 4)	6.70±5.27 (N = 3)	5.23±1.50 (N = 4)
	<1 year	5.30 (N = 1)	4.10 (N = 1)	7.70 (N = 1)	5.20 (N = 1)	7.10 (N = 1)	5.60 (N = 1)	5.10 (N = 1)

Mean ± standard deviation (n); BSA, body surface area

a) Patients who switched the dosage form at Week 24 (1 patient from the tablets to the granules, 1 patient from the granules to the tablets) were counted in the latter.

6.2.2 Population pharmacokinetic analysis (CTD 5.3.3.5-1)

A population pharmacokinetic (PPK) analysis (NONMEM, version 7.4.3) was performed using a non-linear mixed effects model, based on whole blood sirolimus concentration data (1282 timepoints, 215 subjects) from a bioequivalence study in healthy adults (Study NPC-12T-1); an investigator-initiated study in patients with refractory vascular tumors or refractory vascular malformations (the CVA study); an investigator-initiated study in patients with refractory lymphatic diseases (the LM study[4)]); a specified clinical study in patients with refractory vascular tumors and refractory vascular malformations (Study SRL-CVA-01[5)]); a clinical study in patients with refractory lymphatic diseases (Study 0403[6)]); an investigator-initiated study in patients with focal cortical dysplasia type II (Study FCDS-01[7)]); a specified clinical study in patients with focal cortical dysplasia type II (Study FCDS-02 [8)]); and, an investigator-initiated study in patients with

4) An investigator-initiated study in patients with refractory lymphatic diseases who had body surface area (BSA) ≥0.6 m^2 (see the Review Report for "Rapalimus Tablets 1 mg," dated August 6, 2021): Patients received sirolimus tablets orally once daily. The starting dose was 2 mg for patients with BSA ≥1.0 m^2 and 1 mg for those with BSA <1.0 m^2. Subsequent doses were adjusted to <4 mg/day to maintain trough whole blood sirolimus concentrations within the target range of 5 to 15 ng/mL.

5) A specified clinical study in patients with refractory vascular tumors and refractory vascular malformations aged ≥0 years conducted with the following dosage regimens:
Sirolimus tablets; The starting dose, i.e., 2 mg for patients with BSA ≥1.0 m^2 or 1 mg for those with BSA <1.0 m^2, was administered orally once daily. Subsequent doses were adjusted to maintain trough whole blood sirolimus concentrations within the target range of 5 to 15 ng/mL.
Sirolimus granules; The starting dose, i.e.,0.02 mg/kg for patients aged <3 months,0.04 mg/kg for patients aged ≥ 3 to <6 months, 0.06 mg/kg for patients aged ≥6 to <12 months, or 0.08 mg/kg for patients aged ≥12 months (<1.4 mg), was administered orally once daily. Subsequent doses were adjusted to maintain trough whole blood sirolimus concentrations within the target range of 5 to 15 ng/mL.

6) A clinical study in patients with lymphatic diseases aged ≥0 years using sirolimus tablets. The starting dose, i.e., 0.1 mg/kg for patients aged <6 months, 1.6 mg/m^2 for patients aged ≥6 months to <20 years, or 2 mg for patients aged ≥20 years, was administered orally once daily. Subsequent doses were adjusted to <4 mg/day to maintain trough whole blood sirolimus concentrations within the target range of 5 to 15 ng/mL.

7) An investigator-initiated study in patients with focal cortical dysplasia type II aged ≥6 years using sirolimus tablets. The starting dose, i.e., 2 mg for patients weighing ≥40 kg or 1 mg for patients weighing <40 kg, was administered orally once daily. Subsequent doses were adjusted to <4 mg/day, to maintain trough whole blood sirolimus concentrations within the target range of 5 to 15 ng/mL.

8) A specified clinical study in patients with focal cortical dysplasia type II aged ≥2 years using sirolimus tablets. Sirolimus was administered once daily at a dose (0.5 to 4 mg) that was equivalent to the dose taken at the completion of Study FCDS-01 or the preceding clinical study.

lymphangioleiomyomatosis (the MLSTS [9] study). The PK of sirolimus was described by a 2-compartment model with first-order absorption.

Covariates[10] were explored for CL/F, Vc/F, Vp/F, Q/F, Ka, and F. The final model incorporated the following covariates: body weight,[11] age,[12] concomitant use of a CYP3A4 inducer, sample storage condition before delivery to the laboratory for drug concentrations measurement (frozen versus refrigerated), and baseline hemoglobin for CL/F; body weight[11] for Vc/F, Vp/F, and Q/F; the administration of sirolimus granules for Ka; and, the administration of a simple suspension of sirolimus tablets and the administration of sirolimus granules for F. The steady-state trough whole blood sirolimus concentration and AUC following the administration of sirolimus granules were estimated to be 1.23-fold [90% CI; 1.09, 1.37] and 1.27-fold [90% CI; 1.12, 1.41], respectively, those following the administration of sirolimus tablets.

A simulation of drug concentrations using the final model indicated that the concentration had reached a steady state within 7 to 14 days of treatment, regardless of the dosage form. Table 4 shows the estimated trough whole blood sirolimus concentrations following the administration of sirolimus tablets and sirolimus granules at each dose based on body surface area (BSA).

Table 4. Steady-state trough whole blood sirolimus concentrations following the administration of sirolimus tablets and sirolimus granules (estimated values)

BSA	Dose of sirolimus	Granules	Tablets
		Trough whole blood sirolimus concentration (ng/mL)[a]	Trough whole blood sirolimus concentration (ng/mL)[a]
<0.6 m^2	1 mg/day	13.0 [4.75, 68.7]	10.6 [3.98, 55.8]
	2 mg/day	26.1 [9.49, 137]	21.3 [7.95, 112]
≥0.6 to <1.0 m^2	1 mg/day	6.28 [2.72, 13.2]	5.16 [2.26, 10.7]
	2 mg/day	12.6 [5.43, 26.4]	10.3 [4.53, 21.4]
≥1.0 to <1.5 m^2	1 mg/day	3.85 [1.75, 7.50]	3.13 [1.45, 6.07]
	2 mg/day	7.70 [3.50, 15.0]	6.26 [2.89, 12.1]
	3 mg/day	11.5 [5.25, 22.5]	9.39 [4.34, 18.2]
≥1.5 m^2	1 mg/day	2.81 [1.18, 5.26]	2.29 [0.97, 4.25]
	2 mg/day	5.63 [2.36, 10.5]	4.58 [1.95, 8.50]
	3 mg/day	8.44 [3.54, 15.8]	6.87 [2.92, 12.8]

a) Median [90% prediction interval]

Table 5 shows the estimated trough whole blood sirolimus concentrations following the administration of sirolimus granules by age (in months)-based dose.

9) An investigator-initiated study in patients with lymphangioleiomyomatosis aged ≥18 years (see the Review Report for "Rapalimus Tablets 1 mg," dated May 15, 2014) using sirolimus tablets. The starting dose was 2 mg administered orally once daily. Subsequent doses were adjusted to <4 mg/day to maintain trough whole blood sirolimus concentrations within the target range of 5 to 15 ng/mL.

10) Covariates examined included age, sex, body weight, disease, laboratory values (hemoglobin, red blood cell count, AST, ALT), concomitant use of a CYP3A4 inducer, dosage form (tablets, crushed tablets, simple suspension of tablets, granules), and sample storage condition before delivery to the laboratory for drug concentrations measurement (frozen versus refrigerated).

11) Based on allometric scaling in which CL/F, Q/F, Vc/F, and Vp/F were proportional to powers of body weight, allometric coefficients was 0.75 for CL/F and Q/F, and 1 for Vc/F and Vp/F, and the change over time in body weight was taken into account.

12) Postmenstrual age calculated based on an assumed gestational age of 40 weeks, with the change over time in age taken into account.

Table 5. Steady-state trough whole blood sirolimus concentrations following the administration of sirolimus granules (estimated values), by age (in months)-based dose

Age in months	Dose of sirolimus	Trough whole blood sirolimus concentration (ng/mL)[a)]
<3 months	0.02 mg/kg	7.23 [3.68, 12.4]
≥3 months to <6 months	0.04 mg/kg	10.1 [5.02, 17.5]
≥6 months to <12 months	0.06 mg/kg	10.1 [4.71, 18.9]
≥12 months (and BSA <0.6 m^2)[b)]	0.08 mg/kg	9.56 [4.01, 18.9]

a) Median [90% prediction interval]
b) Using the standard height and body weight in Japanese children, trough whole blood sirolimus concentrations were estimated in children with BSA<0.6 mg^2 (height, 70 to 95 cm; body weight, 8 to 14 kg).

6.R Outline of the review conducted by PMDA

6.R.1 Food effect on sirolimus granules

The applicant's explanation about the effects of food intake on the PK of sirolimus granules:

The effects of a high-fat meal on the PK of sirolimus oval tablets[13)] or liquid were assessed. The geometric mean ratios [90% CIs] of the PK parameters of sirolimus oval tablets administered after a high-fat meal to those administered in the fasting state were 1.65 [1.50, 1.82] for C_{max}, 1.23 [1.14, 1.33] for $AUC_{0-\infty}$, and 1.32 [1.04, 1.66] for t_{max} (Study 172-US[14)]). As sirolimus is lipophilic, the high-fat meal may have promoted the elution and dissolution of sirolimus in oval tablets and increased its absorption from the gastrointestinal tract. With the sirolimus liquid formulation, the geometric mean ratios [90% CIs] of the PK parameters of sirolimus administered after the high-fat meal to those administered in the fasting state were 0.66 [0.61, 0.71] for C_{max}, 1.35 [1.26, 1.45] for $AUC_{0-\infty}$, and 3.54 [2.97, 4.22] for t_{max} (Study 127-US[15)]). Because sirolimus has been already dissolved in the liquid formulation, a high-fat meal could have decreased the gastric emptying rate, slowed the distribution of sirolimus to the absorption sites, consequently reducing the C_{max}. The slowed distribution to the absorption sites could have prevented the saturation of absorption mechanism which in turn increased systemic absorption ($AUC_{0-\infty}$). Thus, both sirolimus oval tablets and liquid are affected by food intake, albeit through different mechanisms.

Although not been assessed in a study, sirolimus granules is also expected to be affected by food, in view of the observed food effect on sirolimus oval tablets and liquid. Furthermore, in the CVA study, each patient was allowed to choose a dose timing, i.e., whether to take sirolimus in the fasting or fed state, which however had to remain fixed throughout the study, for efficacy and safety evaluations of sirolimus granules [see Section 7.1]. Therefore, patients should remain on a fixed dose timing, either fasting or fed, to obtain stable blood sirolimus concentrations during the treatment with sirolimus granules. This precaution should be offered via the package insert.

PMDA's view:

13) The commercial formulation and proposed formulation of sirolimus tablets are both triangular tablets.
14) A randomized, open-label, 2-period crossover study in 24 non-Japanese healthy adults (see the Review Report, "Rapalimus Tablets 1 mg" dated May 15, 2014): The effect of food intake (a high-fat meal) after a single oral dose of sirolimus oval tablets 10 mg was assessed.
15) A randomized, open-label, 2-period crossover study in 22 non-Japanese healthy adults: Food effect (a high-fat meal) after a single oral dose of sirolimus liquid 15 mg was assessed.

No studies have been conducted on the food effect on sirolimus granules, precluding adequate assessment on the level of food effect on the PK of sirolimus granules. However, food effect was observed in sirolimus oval tablets and sirolimus liquid, and presumably the same holds true for sirolimus granules. In the CVA study, each patient received sirolimus granules either in the fed or fasting state, while their trough whole blood sirolimus concentrations were maintained within the target range of 5 to 15 ng/mL by dose adjustment, and the study demonstrated the efficacy and safety of sirolimus granules [see Sections 7.R.1 and 7.R.2.1]. According to the dosing conditions in the CVA study, sirolimus granules should be administered at a fixed timing, either fasting or fed, as practiced with sirolimus tablets or other forms, so as to minimize intra-individual variability of blood sirolimus concentration due to food effect and stabilize it. This precaution should be offered in "Precautions Concerning Dosage and Administration" section of the package insert.

6.R.2 Therapeutic drug monitoring of sirolimus for patients with refractory vascular tumors and refractory vascular malformations

The applicant's explanation about the appropriateness of designing therapeutic drug monitoring (TDM) with sirolimus for patients with refractory vascular tumors and refractory vascular malformations by modeling on that for patients with refractory lymphatic diseases:

Patients with refractory vascular tumors and refractory vascular malformations have various factors potentially affecting the PK of sirolimus, such as multiple underlying diseases and high prevalence in children, which are the contributory factors to the PK of sirolimus with likely large intra-individual variability. Therefore, in the CVA study, the dose of sirolimus was adjusted so as to maintain trough whole blood sirolimus concentrations within the target range of 5 to 15 ng/mL, as in the LM study in patients with refractory lymphatic diseases (see the Review Report for "Rapalimus Tablets 1 mg," dated August 6, 2021). Target trough whole blood sirolimus concentrations were measured at Weeks 1 and 2, every 4 weeks between Weeks 4 and 24, and every 8 weeks between Weeks 28 and 52. Although 1 patient had a trough whole blood sirolimus concentration of >15 ng/mL,[16)] the adverse events[17)] reported from the patient around the time when the concentration exceeded 15 ng/mL were all non-serious, and sirolimus was continued. Among the 4 patients who had a trough whole blood sirolimus concentration of <5 ng/mL within 1 month before the efficacy assessment, 3 patients had partial response. Although it should be noted that the CVA study involved only a limited number of patients, most of the observed trough whole blood sirolimus concentrations fell within the target range of 5 to 15 ng/mL [see Section 6.2.1]. Thus, sirolimus was expected to have efficacy in these patients, including those who had trough whole blood sirolimus concentrations outside the target range. The CVA study revealed no safety tendencies that would pose major problems [see Sections 7.R.1 and 7.R.2.1].

In conclusion, patients with refractory vascular tumors or refractory vascular malformations do not need to undergo periodic measurement of trough whole blood sirolimus concentration as frequently as did those with refractory lymphatic diseases on sirolimus in the clinical study. However, as patients with refractory vascular tumors or refractory vascular malformations have many factors potentially affecting the PK of sirolimus with

16) The patient switched from sirolimus granules 4.1 mg to sirolimus tablets 6 mg, and had a trough whole blood sirolimus concentration of 16 ng/mL at 4 weeks post-switch.

17) The patients reported pyrexia (Grade 1), abdominal pain upper (Grade 1), and lymphopenia (Grade 3), all of which were categorized as adverse drug reactions.

possible large intra-individual variability, whole blood sirolimus concentration should be checked when a steady state is reached at Days 7 to 14 after the start of treatment with sirolimus tablets or granules, and the dose should be adjusted to maintain sirolimus concentrations below 15 ng/mL. After that, blood sirolimus concentrations should be measured after dose increase, at the onset of a suspected adverse drug reaction, or in any circumstances potentially affecting blood sirolimus concentrations (inevitable long-term concomitant use of a drug that may affect CYP3A4, or patients with hepatic impairment, etc.) to adjust the dose. This advice should be offered in the package insert.

PMDA' view:

Based on the results from the CVA study and the applicant's explanation, the requirements proposed for patients with refractory vascular tumors and refractory vascular malformations, i.e., trough whole blood sirolimus concentration measurement at Weeks 1 to 2 after the start of treatment with sirolimus, dose adjustment to maintain sirolimus concentrations below 15 ng/mL, trough whole blood sirolimus concentrations measurement following dose increase or onset of a suspected adverse drug reaction, etc., as practiced for patients with refractory lymphatic diseases, are appropriate. Given the extremely small sample size of the CVA study, the description of the advice on blood concentration measurement should be reviewed as necessary, when any new concern emerges in the post-marketing setting.

Meanwhile, Study NPC-12T-1 failed to demonstrate bioequivalence between sirolimus tablets and sirolimus granules. Physicians must be advised to check trough whole blood sirolimus concentration after a change in dosage form needed [see Section 7.R.5.3].

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from 1 investigator-initiated study (Table 6).

Table 6. Outline of efficacy and safety evaluation data

Phase	Study identifier	Target diseases	Study design	Duration of treatment	N	Primary efficacy endpoint
III	NPC-12T-CVA	Refractory vascular tumors and refractory vascular malformations	Open-label, uncontrolled	52 weeks	13 patients	Target lesion response rate at Week 24

7.1 Investigator-initiated study (the CVA study (CTD 5.3.5.2-1, Study No. NPC-12T-CVA, June 2020 to February 2022)

A multicenter, open-label, uncontrolled study was conducted at 4 sites in Japan to assess the efficacy and safety of sirolimus in patients with refractory vascular tumors and refractory vascular malformations (Table 7) (target sample size ≥10 patients[18)]).

[18)] Of 72 patients identified in "the Refractory Vascular/Lymphatic Disease Registry" (complied by the group for "the Research on the Number of Cases of Lymphangiomatosis in Japan and the Development of Diagnostics and Treatments," Research Project on Measures for Intractable Diseases supported by the Health and Labour Sciences Research Grant, and "the Study for the Establishment of Sirolimus Therapy for Patients with Intractable Lymphatic Anomalies," a Project Promoting Clinical Researches and Trials for the Development of New Drugs and Medical Devices, by the Japan Agency for Medical Research and Development), none experienced lesion shrinkage at 6 or 12 months. In "the Lymphangioma Registry" (complied by the group for "the Research on the Number of Cases of Lymphangiomatosis in Japan and the

Table 7. Key inclusion and exclusion criteria

Key inclusion criteria • **Corrected[a] age ≥1 month** • **Confirmed diagnosis of any of the following diseases:** **Vascular tumors: kaposiform hemangioendothelioma, tufted angioma** **Venous malformations: venous malformations, blue rubber bleb nevus syndrome** **Combined vascular malformations: combined vascular malformations, Klippel-Trenaunay-Weber syndrome** **Lymphatic diseases: lymphangioma, lymphangiomatosis, Gorham's disease** • **≥1 measurable target lesion on MRI** • **Any of the following severe impairments or intractable symptoms associated with the target disease** **Hemorrhage, chronic pain, chronic cellulitis (≥3 episodes per year), skin ulcer, organ invasion (lung, heart, liver, spleen, etc.), bone invasion, or impaired important organs (e.g., eye, airway, ear), or suspected such conditions**
Key exclusion criteria • **Use of mTOR inhibitors (e.g., everolimus) or other drugs targeting mTOR pathway-related molecules (e.g., tyrosine kinase inhibitors) within 8 weeks** • **Ongoing infection requiring systemic therapy** • **Any of the following comorbidities:** **Uncontrolled diabetes, hypertension, or hyperlipidemia; interstitial lung disease, chronic liver disease, chronic renal disease** • **Ongoing long-term (≥ 4 weeks) treatment with immunosuppressive agents (e.g., cyclosporine, tacrolimus) or systemic steroids at the time of enrollment**

a) Calculated by subtracting the difference between the expected delivery date and the actual delivery date (in weeks and days) from the actual age in months (in weeks and days), for patients who were born earlier than the expected delivery date (40 weeks and 0 days)

Patients weighing ≥30 kg received the starting dose of sirolimus tablets 2 mg or sirolimus granules 1.4 mg orally once daily. Patients weighing <30 kg received the starting dose of sirolimus granules orally once daily, as per Table 2 according to their age in months.[3)] Subsequent doses were adjusted to maintain trough whole blood sirolimus concentrations within the target range of 5 to 15 ng/mL (Table 8). The study treatment continued for ≤52 weeks.

Table 8. Dose adjustment procedure

Timing to measure trough whole blood sirolimus concentration[a]	Trough whole blood sirolimus concentration	Tablets	Granules	
		≥30 kg body weight	≥30 kg body weight	<30 kg body weight
Week 1 (Days 6 to 10)	≤15 ng/mL	No change	No change	No change
	>15 ng/mL	Reduce to 1 mg at Week 2 (next adjustment at Week 8)	Reduce to 0.7 mg at Week 2 (next dose adjustment at Week 8)	Reduce by 30% at Week 2 (next dose adjustment at Week 8)
Week 2 (Days 13 to 17)	<5 ng/mL	Increase by 1 mg at Week 4	Increase by 0.7 mg at Week 4	Increase by 30% at Week 4
	>5 to ≤15 ng/mL	No change	No change	No change
	>15 ng/mL	Reduce by 1 mg at Week 4	Reduce by 0.7 mg at Week 4	Reduce by 30% at Week 4
The third and subsequent measurement[b]	<5 ng/mL	Increase by 1 mg at next visit	Increase by 50% at next visit	Increase by 30% at next visit
	>5 to ≤15 ng/mL	No change	No change	No change
	>15 ng/mL	Reduce by 1 mg at next visit. If the current dose is 1 mg, change to alternate-day dosing	Reduce by 50% at next visit	Reduce by 30% at next visit
When patients do not response adequately to the reduced dose, the dose may be increased within the range that allows the trough whole blood sirolimus concentration to remain ≤15 ng/mL. **In case of any adverse event, etc., the dose may be reduced as needed, regardless of whether trough whole blood concentration is <5 ng/mL.**				

a) Measurement of trough whole blood sirolimus concentration and dose adjustment were performed at specified visits or between the specified visits as necessary.

b) Visits were scheduled every 4 weeks between Weeks 4 and 24, and every 8 weeks between Weeks 28 and 52. Trough whole blood sirolimus concentration was measured at every visit.

Development of Diagnostics and Treatments," a Research Project on Measures for Intractable Diseases supported by the Health and Labour Sciences Research Grant), 1 of 19 patients experienced lesion shrinkage. Based on these results, the threshold response rate was conservatively determined at 5%. The expected response rate was set at 60%, based on the results from the LM study in patients with refractory lymphatic diseases and other findings. Accordingly, a sample size of 7 patients would ensure the lower limit of the 95% confidence interval (Clopper-Pearson method) for the response rate exceeding the threshold response rate of 5%, with a power of 90%. Considering the potential unevaluable cases due to discontinuation, etc., and possible multiple diseases registered for the same patient, the target sample size was set at ≥10 patients.

The switch of dosage form was allowed, if requested by patients, at the ratio of 1 sirolimus tablet to 0.7 sirolimus granules after Week 25 (Table 9). After the switch, trough concentrations were checked 2 weeks later, 4 weeks later, and every 8 weeks afterward, to adjust the dose according to "The third and subsequent measurement" in Table 8.

Table 9. Daily doses at the switch between sirolimus tablets and sirolimus granules

From tablets to granules		From granules to tablets	
Dose in tablets pre-switch	Dose in granules post-switch	Dose in granules pre-switch	Dose in tablets post-switch
1 mg	0.7 mg	≥0.6 mg to <1.0 mg	1 mg
2 mg	1.4 mg	≥1.0 mg to <1.6 mg	2 mg
3 mg	2.1 mg	≥1.6 mg to <2.4 mg	3 mg
4 mg	2.8 mg	≥2.4 mg to <3.2 mg	4 mg
5 mg	3.5 mg	≥3.2 mg to <4.0 mg	5 mg
6 mg	4.2 mg	≥4.0 mg to <4.6 mg	6 mg

All 13 treated patients were included in the safety analysis set and defined as the full analysis set (FAS), which was the main efficacy analysis population. No patients withdrew from the study after the start of treatment.

The primary efficacy endpoint was "the target lesion[19] response rate (the proportion of patients with a complete response [CR] or partial response [PR]) at Week 24," as assessed centrally according to Table 10Table 10. The results are shown in Table 11. The lower limit of the 95% confidence interval for the target lesion response rate exceeded the prespecified threshold response rate of 5% ($P < 0.001$; binomial test with a one-sided significance level of 2.5%).

Table 10. Therapeutic effect at the target lesion

Judgment	MRI findings
Complete response (CR)	Disappearance of all target lesions
Partial response (PR)	A ≥20% decrease in the volume of the target lesion from baseline
Stable disease (SD)	The shrinkage is not sufficient to be rated as PR, and the increase in volume is not sufficient to be rated as PD as compared with the smallest volume observed after the start of treatment
Progressive disease (PD)	A ≥20% increase in the volume of the target lesion compared with the smallest volume observed after the start of treatment
Response	CR or PR

Table 11. Target lesion response at Week 24 (centrally assessed) (FAS)

Judgment	% (n) (N = 13)
CR	0% (0)
PR	53.8% (7)
SD	30.8% (4)
PD	15.4% (2)
Response rate [95% CI][a)] *P*-value[b)]	53.8 [25.1, 80.8] % (7) *P* < 0.001

a) Calculated using the Clopper-Pearson method
b) Binomial test with a one-sided significance level of 2.5%

A safety analysis revealed that all 13 patients experienced both adverse events and adverse drug reactions. Table 12 shows the adverse events and adverse drug reactions reported in ≥2 patients.

19) If a patient had multiple lesions, the largest lesion was selected as the target lesion, as a general rule. If the largest lesion did not fit in a single MRI image, the central assessment committee selected one of the lesions appearing on the image as the target lesion.

Table 12. Adverse events and adverse drug reactions reported in ≥2 patients (safety analysis set)

Event terms	Sirolimus (N = 13)		Event terms	Sirolimus (N = 13)	
	Adverse events	Adverse drug reactions		Adverse events	Adverse drug reactions
All events	100 (13)	100 (13)	Headache	15.4 (2)	15.4 (2)
Stomatitis	76.9 (10)	76.9 (10)	Rhinorrhoea	15.4 (2)	15.4 (2)
Pyrexia	69.2 (9)	61.5 (8)	Abdominal pain	15.4 (2)	15.4 (2)
Diarrhoea	30.8 (4)	23.1 (3)	Nausea	15.4 (2)	15.4 (2)
Acne	23.1 (3)	23.1 (3)	Malaise	15.4 (2)	15.4 (2)
Neutrophil count decreased	23.1 (3)	23.1 (3)	Nasopharyngitis	23.1 (3)	7.7 (1)
RS virus infection	23.1 (3)	15.4 (2)	Otitis media	15.4 (2)	0
Upper respiratory tract inflammation	23.1 (3)	15.4 (2)	Pharyngitis	15.4 (2)	0
Upper respiratory tract infection	15.4 (2)	15.4 (2)	Dry skin	15.4 (2)	0

Incidence % (n), MedDRA/J ver. 25

There were no deaths. Serious adverse events occurred in 30.8% (4 of 13) of patients (RS virus infection/bronchitis/upper respiratory tract inflammation, RS virus infection, bacterial infection, and lower gastrointestinal haemorrhage in 1 patient each). All events except lower gastrointestinal haemorrhage were identified as adverse drug reactions. All of these serious adverse events resolved, and the patients continued with the study treatment. There were no adverse events that led to drug discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant's explanation about the design of the investigator-initiated study in patients with refractory vascular tumors and refractory vascular malformations (the CVA study), and the efficacy of sirolimus observed in the study:

Although the etiologies of vascular tumors and vascular malformations remain unclear, abnormal activity of the PI3K/AKT/mTOR pathway leading to the overgrowth of vascular endothelial cells, lymphatic endothelial cells, etc. are possible cause of the diseases (the Clinical Practice Guidelines 2022). Sirolimus is an mTOR inhibitor. Binding to mTOR that regulates the division, proliferation, survival, etc. of cells, sirolimus inhibits mTOR activation, and thereby suppresses cell proliferation and exhibits antiangiogenic and antilymphangiogenic effects. Based on this mechanism, sirolimus is expected to suppress the growth of vascular tumors and vascular malformations. Many articles have reported about sirolimus's efficacy and good tolerability (e.g., *Pediatrics.* 2016;137:e20153257, *Orphanet J Rare Dis.* 2018;13:191). In Japan, an investigator-initiated study in patients with refractory lymphatic diseases (the LM study) began in 2017, and sirolimus tablets was approved in September 2021 for the treatment of refractory lymphatic diseases. When the CVA study was at the planning stage, sirolimus tablets had not been approved for the treatment of refractory lymphatic diseases. However, the study design and efficacy evaluation method in the CVA study were determined by following the preceding LM study.

As with the LM study, the CVA study was designed as an open-label, uncontrolled study using no control group, in view of the absence of drugs indicated for vascular tumors or vascular malformations, no standard treatments that could serve as control, limited number of Japanese patients with the target diseases, and the difficulty in using a placebo group because of the intractability and relatively serious nature of the diseases. Because

vascular tumors and vascular malformations mainly affect children, the CVA study targeted patients (corrected[20]) aged ≥1 month and used sirolimus granules that could be taken by young children, in addition to sirolimus tablets. The target diseases selected with reference to clinical reports from Japan and overseas were kaposiform hemangioendothelioma, tufted angioma, venous malformations, blue rubber bleb nevus syndrome, combined vascular malformations, Klippel-Trenaunay-Weber syndrome, and lymphatic diseases (lymphangioma, lymphangiomatosis, and Gorham's disease), for which an association with mTOR has been suggested. As with the LM study, the primary efficacy endpoint of the CVA study was the target lesion response rate (Table 11) assessed by the central assessment committee based on the change in the volume of the target lesion measurable by MRI (Table 10). Response to the treatment was defined as improved symptoms with a ≥20% decrease in the volume of the target lesion, which is considered a clinically relevant change based on the outcomes of a Japanese clinical study, in which improvement of symptoms was observed in patients who achieved a ≥20% decrease in lesion volume (*Orphanet J of Rare Dis.* 2019;14:141). In the LM study, a certain degree of efficacy was indicated by the change in the shrinkage rate of the target lesion as early as Week 12. However, in the CVA study, the primary assessment was scheduled at Week 24 to assess the response over a longer term (see the Review Report for "Rapalimus Tablets 1 mg," dated August 6, 2021). The threshold for efficacy was conservatively determined at 5%, because 1.1% (1 of 91 patients) of patients experienced spontaneous lesion shrinkage according to the Refractory Vascular/Lymphatic Disease Registry[21] and the Lymphangioma Registry.[22]

The primary endpoint of Week 24 centrally-assessed target lesion response rate [95% CI] was 53.8 (7 of 13 patients) [25.1, 80.8]%, and the lower limit of the 95% confidence interval exceeded the prespecified threshold of 5% (Table 11). The response rates at Weeks 12 and 52 were both 61.5% (8 of 13 patients) (Table 13), indicating the effect of sirolimus noticeable at Week 12 and sustained through Week 52.

Table 13. Responses of the target lesion to sirolimus (as centrally assessed) (FAS)

Judgment	Week 12 (N = 13)	Week 24 (N = 13)	Week 52 (N = 13[b])
CR	0% (0)	0% (0)	0% (0)
PR	61.5% (8)	53.8% (7)	61.5% (8)
SD	30.8% (4)	30.8% (4)	15.4% (2)
PD	7.7% (1)	15.4% (2)	15.4% (2)
Response rate [95% CI][a]	61.5% (8) [31.6, 86.1]	53.8% (7) [25.1, 80.8]	61.5% (8) [31.6, 86.1]

% (n)
a) Calculated using the Clopper-Pearson method
b) One patient who could not undergo an MRI test at Week 52 was regarded as "no result/non-responder."

Table 14 shows the target lesion response rates by patient characteristics at Week 24. Although the limited number of patient in each subgroup precluded precise evaluation, all subgroups had ≥1 responder.

20) Calculated by subtracting the difference between the estimated date of birth and the actual date of delivery (in weeks and days) from the actual age in months (in weeks and days), for patients who were born earlier than the estimated date of birth (40 weeks and 0 days)
21) In "the Refractory Vascular/Lymphatic Disease Registry" (compiled by the group for "the Research on the Number of Cases of Lymphangiomatosis in Japan and the Development of Diagnostics and Treatments," a Research Project on Measures for Intractable Diseases supported by the Health and Labour Sciences Research Grant, and "the Study for the Establishment of Sirolimus Therapy for Patients with Intractable Lymphatic Anomalies," a Project Promoting Clinical Researches and Trials for the Development of New Drugs and Medical Devices, by the Japan Agency for Medical Research and Development), all of the 72 patients who underwent follow-up and imaging assessment for ≥1 year, except for those with inadequate data, had an SD at Months 6 and 12.
22) In "the Lymphangioma Registry" (compiled by the group for "the Research on the Number of Cases of Lymphangiomatosis in Japan and the Development of Diagnostics and Treatments," a Research Project on Measures for Intractable Diseases supported by the Health and Labour Sciences Research Grant), 1 of 19 untreated patients experienced lesion shrinkage.

Table 14. Target lesion response rates at Week 24 by patient characteristics (FAS)

Baseline patient characteristics		N	Response rate % (n)
Age	<1 year	1 [a)]	100.0% (1)
	1 to 3 years	4	75.0% (3)
	4 to 11 years	4	25.0% (1)
	≥12 years	4	50.0% (2)
BSA	<0.6 m^2	5	60.0% (3)
	≥0.6 to <1.0 m^2	3	66.7% (2)
	≥1.0 m^2	5	40.0% (2)
Body weight	<10 kg	3	66.7% (2)
	≥10 kg to <30 kg	5	60.0% (3)
	≥30 kg	5	40.0% (2)
Gender	Male	6	50.0% (3)
	Female	7	57.1% (4)
Disease group	Vascular tumors	1	100.0% (1)
	Venous malformations	3	66.7% (2)
	Combined vascular malformations	5	60.0% (3)
	Lymphatic diseases	4	25.0% (1)

a) [redacted] months old

The assessment by disease group showed a lower response rate in patients with lymphatic diseases, an approved indication of sirolimus. However, in view of the following outcomes, the efficacy of sirolimus observed in the treatment of lymphatic diseases in the LM study is not denied:

- Week 12 response rate in patients with lymphatic diseases was 75.0% (3 of 4 patients), indicating response to sirolimus.
- Of the 3 responders at Week 12, 2 patients had no response at Week 24. In one of these patients, the percent change in the target lesion volume was -29.0% at Week 12, but improvement in skin lesions contributed to the stop of lymphatic leakage, consequently pooled lymph fluid increased the target lesion volume by roughly 10% after Week 24 as compared with that at the start of treatment. In the other patient, who underwent a tracheostomy for a lesion in the cervical region, had persistent hemorrhage and lymphorrhea from the oral cavity and tongue, and suffered repetitive infection. Week 12 percent change in the volume of the target lesion was -32.4%, showing a response to sirolimus. However, before Week 24 assessment, intracystic hemorrhage occurred and caused the target lesion volume to increase by roughly 10% from that at the start of treatment. At Week 52, the patient had respiratory tract infection, which precluded Week 52 MRI test due to the risk of possible respiratory depression posed by sedatives for the MRI test. Nevertheless, the lesion size decreased.

The following describes results of the secondary endpoints, including non-target skin lesions, hemorrhage, pain, pleural effusion, and ascites.

Non-target skin lesions were identified in 12 patients at the start of treatment. Improvement[23)] after Week 24 was "improved" in 6 patients and "no change" in 5 patients, indicating that non-target skin lesions improved in nearly half of the patients (1 patient had no data). Hemorrhage at any site was found in 5 patients (WHO bleeding scale Grade 1 in 3 patients and Grade 2 in 2 patients) at the start of treatment, and in 2 patients (Grades 1 and 2 in 1 patient each) at Week 24. One patient who had gastrointestinal hemorrhage at the start of treatment

23) The change from the start of treatment was assessed by the investigator as follows: markedly improved, improved, slightly improved, unchanged, slightly deteriorated, or deteriorated. Patients with a lesion assessed as "markedly improved," "improved," or "slightly improved" were counted as "improvement."

experienced no hemorrhage after the start of treatment. Pain was assessed using a visual analogue scale (VAS) in 8 patients. The score (mean ± standard deviation) was 23.9 ± 32.7 (8 patients) at the start of treatment and 35.1 ± 37.3 (7 patients, excluding 1 patient with no data) at Week 24. No patients had pleural effusion or ascites at the start of treatment.

Table 15 shows the patient characteristics, doses, and efficacy results at Week 24 for individual patients.

Table 15. Patient characteristics and efficacy results at Week 24 for individual patients (FAS)

Disease group	Disease	Age	BSA (m^2)	Body weight (kg)	Dosage Form[a)]	Starting dose (mg)	Dose at Week 24 (mg)	Response of target lesion at Week 24	Percent change in Week 24target lesion volume
Vascular tumors	Kaposiform hemangioendothelioma	≤1 year	[redacted]	[redacted]	Granules	[redacted]	0.87	PR	-64.0
Venous malformations	Venous malformations	10 to 19 years	1.57	52.4	Tablets	2	2	PR	-43.1
	Blue rubber bleb nevus syndrome	6 to 10 years	0.83	21.0	Granules	1.40	3.08	PR	-28.8
		10 to 19 years	1.16	32.6	Tablets	2	2	SD	-4.5
Combined vascular malformations	Combined vascular malformations	Adults	1.87	69.7	Tablets	2	4	PR	-45.4
		≤1 year	[redacted]	[redacted]	Granules	[redacted]	1.22	PR	-48.3
	Klippel-Trenaunay-Weber syndrome	≤1 year	[redacted]	[redacted]	Granules	[redacted]	1.03	PR	-22.4
		1 to 5 years	0.55	12.6	Granules	1.00	1.7	SD	-13.9
		6 to 10 years	1.08	31.0	Tablets	2	2	SD	-16.1
Lymphatic diseases	Lymphangioma	1 to 5 years	0.61	14.2	Granules	1.15	1.5	PR	-20.7
		Adults	1.69	67	Granules	1.40	4.1	PD	13.2
		≤1 year	[redacted]	[redacted]	Granules	[redacted]	1.27	PD	10.2
	Lymphangiomatosis	6 to 10 years	0.78	19.7	Granules	1.40	1.4	SD	-1.5

a) The dosage form administered from the start of treatment to Week 24

PMDA's view on the study design and efficacy results of the CVA study:
Considering the limited numbers of patients with refractory vascular tumors and refractory vascular malformations, and the limitations in study size and duration for being an investigator-initiated study, etc., the CVA study was conducted inevitably as an open-label, uncontrolled study, as with the preceding the LM study in patients with refractory lymphatic diseases. Because of the lack of standard treatments and low spontaneous regression rates in patients, a before-after comparison is valid to some extent for efficacy evaluation. In addition, the primary endpoint and the efficacy threshold specified as 5% in the CVA study, based on the LM study and spontaneous regression rates observed in the registries, were appropriate.

Week 24 centrally-assessed target lesion response rate [95% CI] , the efficacy primary endpoint, was 53.8 (7 of 13 patients) [25.1, 80.8]%, and the lower limit of the 95% confidence interval exceeded the prespecified threshold of 5% (Table 11). More than half of the patients (7 patients) responded to sirolimus, of whom 4 patients achieved a >40% decrease in the volume of the target lesion (Table 15), suggesting a certain level of lesion shrinkage by sirolimus. These results indicate sirolimus's promising shrinkage effect on lesions in patients with refractory vascular tumors or refractory vascular malformations.

The efficacy of sirolimus by disease is further reviewed in Section "7.R.4 Indications." The efficacy by patient characteristics other than diseases and symptoms in non-target lesions are difficult to evaluate due to

the small number of improved cases, thus data collection should be further continued via the post-marketing investigation.

7.R.2 Safety

PMDA's view:

The reviews in Sections 7.R.2.1 to 7.R.2.4 did not raise no new issues that would require additional cautions or safety measures in the treatment of refractory vascular tumors and refractory vascular malformation, other than those for the approved indication of refractory lymphatic diseases. Thus, the safety of sirolimus is acceptable in the treatment of refractory vascular tumors and refractory vascular malformation, as in the treatment of refractory lymphatic diseases, where sirolimus is used by physicians with adequate knowledge and experience in the diagnosis and treatment of vascular tumors and vascular malformations and full understanding of the effects and risks of sirolimus. However, due to the extremely limited number of patients evaluated in the investigator-initiated study (the CVA study), safety data of sirolimus should be further collected via the post-marketing investigation, etc.

7.R.2.1 Summary of adverse events in the CVA study

The applicant's explanation about the adverse events reported in the CVA study:

In the CVA study, adverse events and adverse drug reactions were reported in all 13 patients. Table 12 shows the events reported in ≥2 patients. There were no deaths. A total of 6 serious adverse events were reported in 4 patients (RS virus infection/bronchitis/upper respiratory tract inflammation, RS virus infection, bacterial infection, and lower gastrointestinal haemorrhage in 1 patient each), which, other than lower gastrointestinal haemorrhage, were serious adverse drug reactions. However, the study treatment continued and all events resolved. There were no adverse events that led to study drug discontinuation.

Table 16 shows the incidences of adverse events by patient characteristics. Serious infection-related events tended to be reported more frequently in younger children, patients with BSA <0.6 m^2, and those weighing <10 kg. However, the reported events (RS virus infection, bronchitis, upper respiratory tract inflammation, and bacterial infection), generally more common in younger children, resolved without having to change the study drug. Although the limited number of patients in each subgroup precluded precise evaluation, there was no tendency posing a subgroup-specific safety issue.

Table 16. Incidences of adverse events by patient characteristics (safety analysis set)

Patient characteristics		N	Serious adverse events	Serious adverse drug reactions	All infection-related events[a)]	Serious infection-related events[a)]	Gastrointestinal events[b)]
Age	<1 year	1 [c)]	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)	100.0 (1)
	1 to 3 years	4	50.0 (2)	50.0 (2)	100.0 (4)	50.0 (2)	75.0 (3)
	4 to 11 years	4	0	0	100.0 (4)	0	100.0 (4)
	≥12 years	4	25.0 (1)	0	50.0 (2)	0	100.0 (4)
BSA	<0.6 m^2	5	60.0 (3)	60.0 (3)	100.0 (5)	60.0 (3)	80.0 (4)
	≥0.6 to <1.0 m^2	3	0	0	100.0 (3)	0	100.0 (3)
	≥1.0 m^2	5	20.0 (1)	0	60.0 (3)	0	100.0 (5)
Body weight	<10 kg	3	66.7 (2)	66.7 (2)	100.0 (3)	66.7 (2)	66.7 (2)
	≥10 to <30 kg	5	20.0 (1)	20.0 (1)	100.0 (5)	20.0 (1)	100.0 (5)
	≥30 kg	5	20.0 (1)	0	60.0 (3)	0	100.0 (5)
Gender	Male	6	33.3 (2)	16.7 (1)	83.3 (5)	16.7 (1)	83.3 (5)
	Female	7	28.6 (2)	28.6 (2)	85.7 (6)	28.6 (2)	100.0 (7)
Disease group	Vascular tumors	1	0	0	100.0 (1)	0	100.0 (1)
	Venous malformations	3	33.3 (1)	0	100.0 (3)	0	100.0 (3)
	Combined vascular malformations	5	40.0 (2)	40.0 (2)	80.0 (4)	40.0 (2)	80.0 (4)
	Lymphatic diseases	4	25.0 (1)	25.0 (1)	75.0 (3)	25.0 (1)	100.0 (4)

Incidence % (n), MedDRA/J ver. 25
a) MedDRA SOC "Infections and infestations"
b) MedDRA SOC "Gastrointestinal disorders"
c) ≥ [redacted] months old

Table 17 shows the incidences of adverse events by time from the start of treatment. The incidence of all infection-related events tended to be higher at Week ≥37. However, this result was attributable to the longer data collection period and factors such as the season with high prevalence of infectious diseases. Since serious infection-related events did not tend to increase, the higher incidence of all infection-related events at Week ≥37 is not considered to be clinically relevant. There were no adverse events with a tendency for incidences increasing with the duration of treatment.

Table 17. Incidences of adverse events by time from the start of treatment (safety analysis set)

	Weeks 1 to 12 (N = 13)	Weeks 13 to 24 (N = 13)	Weeks 25 to 36 (N = 13)	Weeks 37 to 56 (N = 13)	Throughout the study (N = 13)
All adverse events	76.9 (10)	100.0 (13)	76.9 (10)	84.6 (11)	100.0 (13)
All adverse drug reactions	69.2 (9)	100.0 (13)	61.5 (8)	76.9 (10)	100.0 (13)
Serious adverse events	7.7 (1)	15.4 (2)	7.7 (1)	15.4 (2)	30.8 (4)
Serious adverse drug reactions	7.7 (1)	15.4 (2)	7.7 (1)	7.7 (1)	23.1 (3)
All infection-related events[a)]	30.8 (4)	23.1 (3)	7.7 (1)	61.5 (8)	84.6 (11)
Serious infection-related events[a)]	0 (0)	15.4 (2)	7.7 (1)	7.7 (1)	23.1 (3)
Gastrointestinal events[b)]	61.5 (8)	69.2 (9)	30.8 (4)	38.5 (5)	92.3 (12)

Incidence % (n), MedDRA/J ver. 25
a) MedDRA SOC "Infections and infestations"
b) MedDRA SOC "Gastrointestinal disorders"

In the CVA study, gastrointestinal disorders and infections were reported relatively frequently. However, the adverse events observed in patients with refractory vascular tumors or refractory vascular malformations were not largely inconsistent with the known safety profile of sirolimus.

PMDA considers as follows:

The extremely limited number of patients enrolled in the CVA study precludes adequate safety evaluation by patient characteristics or treatment duration. However, no events led to the discontinuation of study drug, or tendencies indicative of a clinically significant problem were found. Relatively common infection-related events and gastrointestinal events are separately reviewed in Section 7.R.2.3.

7.R.2.2 Summary of adverse events in the specified clinical study.

At the filing of present application, the interim results (data cutoff on December 31, 20[redacted]) of ongoing specified clinical study in patients with refractory vascular tumors or refractory vascular malformations (Study SRL-CVA-01)[5)] were submitted as reference data. In addition, adverse events reported from January 1, 20[redacted] to December 31, 20[redacted] were submitted during the review for the approval application. Meanwhile, the results of the specified clinical study up to March 31, 20[redacted] were submitted as reference data for the review for the approval application for "refractory lymphatic diseases," and evaluated (Review Report for "Rapalimus Tablets 1 mg," dated August 6, 2021). The applicant explains adverse events and the safety of sirolimus observed in the specified clinical study as follows:

As of the data cutoff for the specified clinical study on December 31, 20[redacted], 119 patients (including 3 patients who were transferred from the CVA study) were included in the safety analysis. The diseases of the patients were vascular tumors in 15 patients (12.6%), venous malformations in 13 patients (10.9%), combined vascular malformations in 17 patients (14.3%), lymphatic diseases in 66 patients (55.5%), and other diseases in 8 patients (6.7%). The duration of treatment with sirolimus was <169 days in 16 patients, ≥169 to <337 days in 25 patients, and ≥337 days (up to 1488 days) in 78 patients. The mean (youngest to oldest) age was 11.9 (0 to 71) years, with 71 patients (59.7%) aged <12 years, 27 patients (22.7%) aged ≥12 to <19 years, and 21 patients (17.6%) aged ≥20 years. BSA was <1.0 m^2 in 65 patients (54.6%) and ≥1.0 m^2 in 54 patients (45.4%).

The incidence of adverse events in the specified clinical study was 31.1% (37 of 119 patients), lower than that in the CVA study, was probably attributable to different follow-up (visit) frequency (the specified clinical study, 5 visits until Week 52 and every 24 weeks thereafter; the CVA study, 12 visits after the start of treatment). In the specified clinical study, events reported with a ≥5% incidence were stomatitis (10.1%, 12 of 119 patients), dermatitis acneiform (6.7%, 8 of 119 patients), and cellulitis (5.9%, 7 of 119 patients). A total of 4 deaths (respiratory failure, sepsis, cardiac failure, severe invasive streptococcal infection/ gastroenteritis bacterial[24)]) were reported, all of which were included in the data submitted for the approval application for refractory lymphatic diseases (data cutoff on March 31, 20[redacted]) (Review Report for "Rapalimus Tablets 1 mg," dated August 6, 2021), and no other deaths occurred since that time. Serious adverse events were reported in 14.3% (17 of 119) of patients. Events reported in ≥2 patients were cellulitis (5.9%, 7 of 119 patients) and pneumonia (1.7%, 2 of 119 patients). Adverse events led to drug discontinuation in 7.6% (9 of 119) of patients. Events that led to drug discontinuation in ≥2 patients were cellulitis and dermatitis acneiform (2 patients each).

From January 1, 20[redacted] to December 31, 20[redacted], adverse events were reported in 12 patients. Serious adverse events were reported in 4 patients (acute gastroenteritis, cellulitis, renal impairment, and lymphangitis in 1 patient each). While renal impairment did not resolve[25)] other events resolved.

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24) The terms of adverse events at the review for the approval application for "refractory lymphatic diseases" (data cutoff on March 31, 20[redacted]) were sepsis and enterocolitis, which were changed to severe invasive streptococcal infection and gastroenteritis bacterial, respectively, at the data cutoff on December 31, 20[redacted].

25) A 30-year-old man with blue rubber bleb nevus syndrome had comorbidities of coagulation disorder associated with the primary disease, myelodysplastic syndrome associated with radiotherapy during childhood, melena and anaemia associated with the primary disease and

After March 31, 20[redacted], there were no new problematic tendencies in the types, frequencies, severity, or other aspects of the adverse events reported in the specified clinical study. Furthermore, there were no major problems with the incidence of adverse events from January 1, 20[redacted] through December 31, 20[redacted], indicating generally favorable tolerability of sirolimus.

PMDA's conclusion:
No new safety concerns were identified from the information obtained by December 31, 20[redacted] since the submission of the interim report from the specified clinical study (data cutoff on March 31, 20[redacted], Review Report for "Rapalimus Tablets 1 mg," dated August 6, 2021) with the approval application for "refractory lymphatic diseases."

7.R.2.3 Relatively common adverse events

The applicant's explanation about the infection-related events (MedDRA SOC: Infections and infestations) and gastrointestinal disorders (MedDRA SOC: Gastrointestinal disorders) reported with high incidences in the CVA study by organ:

7.R.2.3.1 Infections

In the CVA study, infection-related events were reported in 84.6% (11 of 13) of patients. Of these events, the events reported in 3 patients (RS virus infection/bronchitis, RS virus infection, and bacterial infection in 1 patient each) were serious and determined as adverse drug reactions. However, the events resolved without study drug discontinuation. There were no infection-related events leading to study drug discontinuation.

In the specified clinical study [see Section 7.R.2.2], infection-related events were reported in 14.3% (17 of 119) of patients. No deaths from infections were reported by December 31, 20[redacted], except for the 2 deaths (sepsis, severe invasive streptococcal infection/gastroenteritis bacterial in 1 patient each) included in the data submitted with the approval application for "refractory lymphatic diseases" (data cutoff on March 31, 20[redacted]). Other than death, serious infection-related events were reported in 10.9% (11 of 119) of patients (cellulitis in 7 patients, gastroenteritis/pneumonia/upper respiratory tract infection, meningitis streptococcal/lymphangitis, pneumonia haemophilus, pneumonia in 1 patient each), all of which were determined as adverse drug reactions. Treatment with sirolimus was continued in 2 patients with cellulitis, but interrupted in 7 patients and discontinued in 2 patients. All events resolved, except for pneumonia in 1 patient that improved.

Most of the serious infections observed in the CVA study or the specified clinical study resolved after appropriate measures, including the interruption or discontinuation of sirolimus. However, because of its immunosuppressive effect, the use of sirolimus warrants caution against possible infections and careful observation of patient condition.

enterocolitis due to radiation, and loss of left kidney function that was probably attributable to the effect of radiotherapy (eGFR before the start of treatment with sirolimus, 57 mL/min/1.73 m^2). At Month 6 after the start of treatment, the patient's eGFR declined to 14 mL/min/1.73 m^2. This was suspected to be related to sirolimus, and sirolimus was discontinued.

PMDA's view:
In light of serious infections reported in the CVA study and the specified clinical study, due caution must be exercised against infections.

7.R.2.3.2 Gastrointestinal disorders

In the CVA study, gastrointestinal disorders were reported in 92.3% (12 of 13) of patients. Stomatitis (76.9% [10 of 13 patients]) and diarrhoea (30.8% [4 of 13 patients]) were relatively common. A serious gastrointestinal disorder was reported in 1 patient (lower gastrointestinal haemorrhage), for which a causal relationship with the study drug was ruled out, and the event resolved. There were no gastrointestinal disorders leading to study drug discontinuation.

In the specified clinical study [see Section 7.R.2.2], gastrointestinal disorders were reported in 15.1% (18 of 119) of patients. The only gastrointestinal disorder reported with a ≥2% incidence was stomatitis (10.1% [12 of 119 patients]). Serious gastrointestinal disorders were reported in 3 patients (umbilical hernia, abdominal distension, intra-abdominal bleeding in 1 patient each). Of these, the abdominal distension and intra-abdominal bleeding were identified as adverse drug reactions. Umbilical hernia resolved and abdominal distension improved, while intra-abdominal bleeding remained unresolved.[26)]

The serious events of gastrointestinal disorders reported in the CVA study and the specified clinical study were likely associated with primary diseases. Although stomatitis was reported frequently, no patients discontinued the study drug. Thus, no new safety concerns were identified as compared with the known safety profile of sirolimus.

PMDA's view:
Albeit the high incidence of stomatitis, there were no gastrointestinal events leading to the discontinuation of treatment in the CVA study, and all serious gastrointestinal disorders reported in the CVA study and the specified clinical study were presumed to be associated with primary diseases. Therefore, there are no new concerns requiring additional cautionary advice on the treatment of refractory vascular tumors or refractory vascular malformations, other than that previously offered on the approved indications.

7.R.2.3.3 Important identified risks and important potential risks

The applicant explained about the important identified risks and important potential risks in the risk management plan for sirolimus as follows [see Sections 7.R.2.3.1 and 7.R.2.3.2, respectively, for serious infections and gastrointestinal disorders]:

[26)] The patient had lymphangioma. On Day 25, intra-abdominal haemorrhage developed, probably due to the progression of the primary disease, and sirolimus was discontinued. Dehydration and hypokalaemia worsened, and on the 6th day after the discontinuation of sirolimus, arrhythmia occurred. Subsequently, the patient suffered from septic shock and died on the 10th day after the discontinuation of sirolimus (see the Review Report for "Rapalimus Tablets 1 mg," dated August 6, 2021).

7.R.2.3.3.1 Important identified risks

Interstitial pneumonia, anaphylaxis, and poor wound healing were not reported in either the CVA study or the specified clinical study.

Fluid retention was not reported in the CVA study, while chylothorax and oedema peripheral were respectively reported in 0.8% (1 of 119) of patients in the specified clinical study. Chylothorax resulted from the progression of chylous pleural effusion associated with the primary disease, and its causal relationship with sirolimus was ruled out. The event improved. The oedema peripheral was determined as adverse drug reaction and did not resolve. The patient died due to cardiac failure (Review Report for "Rapalimus Tablets 1 mg," dated August 6, 2021).

Observed dyslipidaemia included hypertriglyceridaemia in 7.7% (1 of 13) of patients in the CVA study and 1.7% (2 of 119) of patients in the specified clinical study. The event was non-serious in all these patients.

Observed renal disorder was non-serious protein urine in 7.7% (1 of 13) of patients in the CVA study. There were no renal disorders observed in the specified clinical study.

Observed skin disorders included acne in 23.1% (3 of 13), dry skin in 15.4% (2 of 13), and dermatitis and dermatitis diaper in 7.7% (1 of 13) each of patients in the CVA study, which were all non-serious. Skin disorders observed in the specified clinical study were dermatitis acneiform in 6.7% (8 of 119), and urticaria and hand dermatitis in 0.8% (1 of 119) each of patients, which were all non-serious.

These adverse events observed in patients with refractory vascular tumors and refractory vascular malformations were not largely inconsistent with the known safety profile of sirolimus.

7.R.2.3.3.2 Important potential risks

Malignant lymphoma and malignant tumors, adverse events related to reproductive hormones and bone metabolism, venous thromboembolism, thrombotic microangiopathy, alveolar proteinosis, hyperglycaemia, and developmental delay were not reported in either the CVA study or the specified clinical study.

Pancytopenia/thrombocytopenia/neutropenia/anaemia, etc. observed in the CVA study were neutrophil count decreased in 23.1% (3 of 13) of patients, and lymphopenia and neutropenia 7.7% (1 of 13) each of patients, all of which were non-serious. In the specified clinical study, neutrophil count decreased was reported in 1.7% (2 of 119) of patients, and anaemia was reported in 0.8% (1 of 119) of patients, which were all non-serious.

These adverse events observed in patients with refractory vascular tumors or refractory vascular malformations were not largely inconsistent with the known safety profile of sirolimus.

PMDA's view:
Based on the applicant's explanations in Sections 7.R.2.3.3.1 and 7.R.2.3.3.2, the results from the CVA study and the specified clinical study identified no new safety concerns or event requiring additional safety measures.

7.R.2.4 Post-marketing safety information

The applicant's explanation about the post-marketing safety information on sirolimus:
As of March 20[redacted], sirolimus has been approved in 110 countries or regions. The estimated total cumulative exposure to sirolimus in the post-marketing setting is 781,430 patient-years (based on assumed daily dose of sirolimus of 3 mg). The estimated exposure to sirolimus between March 20[redacted] and March 20[redacted] was 25,639 patient-years. In Japan, 675 patients are estimated to have received sirolimus by September 14, 20[redacted] since the launch of sirolimus tablets in July 2014. According to the results from the use-results survey in patients with lymphangioleiomyomatosis and the general use-results survey in patients with refractory lymphatic diseases (data up to March 14, 20[redacted]), both conducted in Japan, the incidence of serious adverse drug reactions was 10.8% (51 of 472 patients) and the serious adverse drug reaction with a ≥1% incidence was interstitial lung disease (1.3% [6 of 472 patients]) in patients with lymphangioleiomyomatosis, while the incidence of serious adverse drug reactions was 9.52% (2 of 21 patients) (lymphangitis, meningitis, pelvic abscess, and shunt infection in 1 patient each [some patients reported multiple events]) in patients with refractory lymphatic diseases.

The post-marketing safety data currently available in and outside Japan have identified no new safety concerns of sirolimus or events that would require additional safety measures.

PMDA's view:
Based on the applicant's explanation, the currently available post-marketing safety data of sirolimus has revealed no events, etc. that require new safety measures.

7.R.3 Clinical positioning

The applicant's explanation regarding the clinical positioning of sirolimus:
In Japan, no drug has been approved for the indication of vascular tumors or vascular malformations other than lymphatic diseases. The available treatment options are as follows:

Steroids, interferons, and anticancer agents are treatment options for vascular tumors such as hemangioendothelioma and tufted angioma. However, these are not effective enough and can induce severe adverse drug reactions. While embolization and surgery are also the options, there are cases ineligible for excision or surgery, and no established surgical therapy is available. Recently, favorable results with mTOR inhibitors have been reported for the treatment of pseudomyogenic hemangioendothelioma, for which surgery is commonly indicated *(e.g., J Pediatr. Hematol Oncol.* 2017;39:e328-31, *J Pediatr. Hematol Oncol.* 2019;41:382-87). Venous malformations are treated with a combination therapy consisting of physical treatments with assistive devices or compression using elastic stockings, pharmacological conservative treatments, sclerotherapy, or surgery. Combined vascular malformation is a mixed condition of lymphatic,

venous, arteriovenous, and capillary malformations, and is treated with the mentioned treatments selected depending on the condition of vascular malformations. Many patients suffering these diseases have lesions hardly resectable by surgery, and there are cases ineligible for surgery due to patients' physical conditions. An effective therapeutic drug need to be developed.

Sirolimus, a mTOR inhibitor, is expected to have efficacy in the treatment of vascular tumors and vascular malformations, which are thought to be partly due to abnormal activity of the PI3K/AKT/mTOR pathway. The CVA study demonstrated the efficacy [see Section 7.R.1] and safety [see Section 7.R.2] of sirolimus in the treatment of vascular tumors and vascular malformations. In view that vascular tumors and vascular malformations generally develop in children, the granule form of sirolimus was developed. The CVA study enrolled infants and toddlers, while the LM study did not. Sirolimus (tablets and granules) will offer new treatment options to patients with refractory vascular tumors or refractory vascular malformations, including infants and toddlers.

PMDA's view:
In the CVA study, no patients achieved the disappearance of the target lesion (CR). However, a satisfactory level of lesion shrinkage was observed with improved symptoms in refractory vascular tumors and refractory vascular malformations [see Section 7.R.1], suggesting clinically significant efficacy of sirolimus. The safety of sirolimus is considered acceptable in view of its expected efficacy [see Section 7.R.2]. Based on these findings, sirolimus is a promising new treatment option for refractory vascular tumors and refractory vascular malformations, as it is for the approved indication of refractory lymphatic diseases. Refractory vascular tumors and refractory vascular malformations, the target diseases of sirolimus, are further reviewed in Section 7.R.4.

7.R.4 Indications

The applicant's explanation about the intended patient population, indications (draft), and advice on the intended patient population:
The ISSVA classification proposed by the International Society for the Study of Vascular Anomalies, an international academic society, classifies vascular anomalies into vascular tumors and vascular malformations. The ISSVA classification is cited in the Japanese guidelines (the Clinical Practice Guidelines 2022) as well.

The target diseases of the CVA study were the vascular anomalies that are suggested to be associated with mTOR, including vascular tumors (kaposiform hemangioendothelioma and tufted angioma), venous malformations (common venous malformations and blue rubber bleb nevus syndrome), combined vascular malformations (including Klippel-Trenaunay-Weber syndrome), and lymphatic diseases (lymphangioma, lymphangiomatosis, and Gorham's disease), for which the use of sirolimus has ever been reported. Meanwhile, the CVA study did not include (a) malignant vascular tumors, (b) high-flow vascular malformations (e.g., arteriovenous malformations), and (c) capillary malformations for the following reasons: (a) malignant diseases require a different treatment algorithm, (b) sirolimus has rarely been used for

high-flow vascular malformations, which may poorly respond to sirolimus alone, and (c) capillary malformations are localized on the skin surface, and laser therapy is selected as first-line treatment.

The CVA study involved patients with kaposiform hemangioendothelioma (1 patient), venous malformations (1 patient), blue rubber bleb nevus syndrome (2 patients), combined vascular malformations (2 patients), and Klippel-Trenaunay-Weber syndrome (3 patients), as well as those with lymphatic diseases previously approved as indications. Each disease group had responder(s), and the safety of sirolimus was also demonstrated [see Sections 7.R.1 and 7.R.2.1].

Meanwhile, no patients with tufted angioma were enrolled in the CVA study although their inclusion was intended. Furthermore, the number of enrolled patients with each target disease was limited. Thus, the diseases to be covered in the indications of sirolimus were further reviewed with reference to the specified clinical study and literature articles.

The specified clinical study (Study SRL-CVA-01) had enrolled 119 patients when interim results (data cutoff on December 31, 20[redacted]) were obtained. Of these patients, 3 had no efficacy data after the start of treatment and 1 was found to be ineligible after enrollment, and the remaining 115 patients were included in the FAS. The FAS included 15 patients with vascular tumors, 12 patients with venous malformations, and 16 patients with complex-combined vascular malformations. Table 18 is a summary of efficacy in those who had response data at Week 24. In terms of vascular tumors, the responders to sirolimus included those with tufted angioma, the population not enrolled in the CVA study, and one with pseudomyogenic hemangioendothelioma.

Table 18. Response rates at Week 24 by disease type (the specified clinical study, FAS)

	Disease	Response rate
Vascular tumors (N = 11)	Kaposiform hemangioendothelioma	100.0% (8 of 8 patients)
	Tufted angioma	100.0% (2 of 2 patients)
	Pseudomyogenic hemangioendothelioma	100.0% (1 of 1 patient)
Venous malformations (N = 8)	Venous malformations	25.0% (1 of 4 patients)
	Blue rubber bleb nevus syndrome	50.0% (2 of 4 patients)
Combined vascular malformations (N = 12)	Combined vascular malformations	57.1% (4 of 7 patients)
	Klippel-Trenaunay-Weber syndrome	60.0% (3 of 5 patients)

Pseudomyogenic hemangioendothelioma is a rare disease with limited information. Despite that, the specified clinical study enrolled 1 patient with pseudomyogenic hemangioendothelioma and the patient responded to sirolimus. Some articles have suggested the therapeutic effect of sirolimus in patients with the disease (*Pediatr Blood Cancer*. 2018;65:e26781; *J Dermatol*. 2021;48:1900-6), indicating promising efficacy of sirolimus in patients with pseudomyogenic hemangioendothelioma. Cases of hemangioendothelioma other than kaposiform or pseudomyogenic hemangioendothelioma are even rarer. There was a report that sirolimus improved symptoms of reticular hemangioendothelioma in 1 patient (*Turk J Pediatr*. 2020;62:843-50). Despite the extremely limited information on the use of sirolimus, the efficacy of sirolimus is also expected in the

treatment of hemangioendothelioma other than kaposiform hemangioendothelioma, based on its mechanism of action. Accordingly, the vascular tumors as the indications of sirolimus should include hemangioendothelioma and tufted angioma.

Venous malformations targeted in the CVA study were "common venous malformations" according to the ISSVA classification, not venous malformations in a broad sense. Therefore, the "Precautions Concerning Indications" section of the package insert will make clear the target population by noting that sirolimus is intended for patients with the common venous malformations according to the ISSVA classification.

Combined vascular malformations are diseases with ≥2 of the following conditions: capillary malformation (CM), venous malformation (VM), lymphatic malformation (LM), and arteriovenous malformation. the CVA study enrolled 1 patient with CM + LM + VM (CVLM) and 1 patient with CM + VM (CVM), while in the specified clinical study, 6 patients with CLVM and 2 patients with LM + VM (LVM) participated. The efficacy of sirolimus has not been adequately evaluated in the treatment of capillary malformations or high-flow arteriovenous malformations. Therefore, treatment with sirolimus will not be recommended for combined vascular malformations without venous or lymphatic malformation.

Klippel-Trenaunay-Weber syndrome is categorized into Klippel-Trenaunay syndrome complicated by low-flow vascular malformations and Parkes Weber syndrome complicated by high-flow vascular malformations, according to the ISSVA classification. Especially in childhood, these 2 types are difficult to differentiate from each other, and are often diagnosed as "Klippel-Trenaunay-Weber syndrome." The term "Klippel-Trenaunay-Weber syndrome" is also used as designated intractable disease or specific pediatric chronic disease, (MHLW Ministerial Announcement No. 281, dated July 1, 2015; the Information Center for Specific Pediatric Chronic Diseases, Japan, the July 5, 2019 edition). Therefore, the disease term to be used in the "Indications" should be Klippel-Trenaunay-Weber syndrome.

Based on the above, the following cautions will be provided in the package insert: The indications of sirolimus include hemangioendothelioma, tufted angioma, venous malformations, blue rubber bleb nevus syndrome, combined vascular malformations, and Klippel-Trenaunay-Weber syndrome; the term "venous malformations" refers to the common venous malformations according to the ISSVA classification; the efficacy of sirolimus has not been demonstrated in the treatment of malignant diseases or high-flow vascular malformations such as arteriovenous malformations, which were excluded from the studies; the use of sirolimus is not recommended for combined vascular malformations without venous or lymphatic malformation.

PMDA's view:
Despite the extremely limited number of patients, the CVA study suggest a certain level of efficacy of sirolimus in the treatment of the following diseases studied: vascular tumors (kaposiform hemangioendothelioma), venous malformations (common venous malformations and blue rubber bleb nevus syndrome), and combined

vascular malformations (including Klippel-Trenaunay-Weber syndrome). Tufted angioma and pseudomyogenic hemangioendothelioma were not included in the CVA study, but sirolimus is expected to have efficacy in these diseases based on the outcomes from the specified clinical study, etc. explained by the applicant and in light of sirolimus's inhibitory effect on mTOR. In view of no established pharmacotherapy for vascular tumors, it is possible to specifically mention "hemangioendothelioma" and "tufted angioma" as vascular tumors in the indications of sirolimus, on the premise that sirolimus be used by physicians with adequate knowledge and experience in the diagnosis and treatment of vascular tumors and vascular malformations, with a full understanding of the risks of sirolimus. Furthermore, the applicant's view on the cautionary advice to be offered in the package insert is reasonable, i.e., the venous malformations refers to the common venous malformations defined by the ISSVA classification, the efficacy of sirolimus has not been demonstrated in the treatment of malignant diseases or high-flow vascular malformations such as arteriovenous malformations, and treatment with sirolimus is not recommended for combined vascular malformations without venous or lymphatic malformation.

The disease terms of the refractory vascular tumors and refractory vascular malformations to be specified in the indications of sirolimus and the descriptions of patient eligibility-related cautionary advice will be finalized taking into account the comments from the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Tablets

The applicant's explanation about the dosage and administration for sirolimus tablets:

The dosage regimen for sirolimus tablets in the CVA study was determined by referring to the results from the LM study. In the LM study, the starting dose was 2 mg for patients with BSA ≥1.0 m^2 and 1 mg for those with BSA <1.0 m^2, administered orally once daily. In the CVA study, the starting dose was 2 mg administered orally once daily in patients weighing ≥30 kg, based on the estimated BSA of 1 m^2 in Japanese children weighing 30 kg. (In children weighing 30 kg, the mean heights of Japanese boys and girls are 133 cm and 136 cm, respectively, with the mean BSAs of 1.06 m^2 and 1.07 m^2, respectively.) After the start of treatment, the dose was adjusted to maintain trough whole blood sirolimus concentrations within the range of 5 to 15 ng/mL (Table 8). The results of the CVA study demonstrated the efficacy and safety of sirolimus tablets [see Sections 7.R.1 and 7.R.2.1]. The CVA study used the body weight-based dosage regimen; however, the dosage and administration proposed for the present application is a BSA-based dosage regimen, as with the approved refractory lymphatic diseases.

In the CVA study, the maximum dose was not specified, and the dose could be increased within a range so that the trough whole blood sirolimus concentration was at ≤15 ng/mL (Table 8). As a result, the maximum daily doses in 5 patients receiving sirolimus tablets (including those formerly on sirolimus granules) were 2 mg in 1 patient, 3 mg in 2 patients, 4 mg in 1 patient, and 6 mg in 1 patient. There were no tendencies toward increased or severer adverse events with dose. While the maximum daily dose was 4 mg for the approved indication of refractory lymphatic diseases, the patient who had received the daily dose of 6 mg had no major safety problems, but no lesion shrinkage was observed after dose increase. The once-daily dose of sirolimus tablet ≤4 mg is

expected to achieve a trough whole blood sirolimus concentration of 5 to 15 ng/mL, and daily doses >4 mg have not been shown to have greater efficacy. Therefore, the maximum daily dose for the treatment of refractory vascular tumors and refractory vascular malformations should be 4 mg, as with that for refractory lymphatic diseases.

Based on the above, the dosage regimen for the treatment of refractory vascular tumors and refractory vascular malformations has been proposed to be the same as that for the treatment of refractory lymphatic diseases.

PMDA's view:
Based on the results from the CVA study and the applicant's explanation, it is appropriate that the dosage regimen of sirolimus tablets for the treatment of refractory vascular tumors and refractory vascular malformations be the same as that for the approved indication of refractory lymphatic diseases.

7.R.5.2 Granules

The applicant's explanation about the dosage regimen of sirolimus granules:
The dosage regimen of sirolimus granules in the CVA study was determined as follows.
In the bioequivalence study of sirolimus granules and sirolimus tablets, the geometric mean ratio of $AUC_{0\text{-last}}$ for sirolimus granules to sirolimus tablets was 1.48 [see Section 6.1.1]. Thus, in the study, whereas the starting dose of sirolimus tablets was determined as 1 mg, the starting dose of sirolimus granules was determined as 0.7 mg, or 1.4 mg for patients weighing ≥30 kg. For patients weighing <30 kg, the starting dose was determined as shown in Table 2, based on the steady-state trough whole blood sirolimus concentrations estimated by age in months, using the population PK parameters[27)] of sirolimus, etc. After the start of treatment, trough whole blood sirolimus concentration was maintained within 5 to 15 ng/mL (Table 8) by dose adjustment. In the CVA study, the efficacy evaluation revealed Week 24 target lesion response rate of 55.6% (5 of 9 patients) in patients receiving sirolimus granules, and the result was comparable to that in patients receiving sirolimus tablets (50.0% [2 of 4 patients]). In the safety evaluation, the incidence of pyrexia in patients on sirolimus granules (77.8% [7 of 9 patients]) tended to be higher than that in patients on sirolimus tablets (50.0% [2 of 4 patients]). However, 77.8% (7 of 9) of patients on sirolimus granules were aged ≤6 years, while all of the patients on sirolimus tablets aged ≥6 years. The higher incidence of pyrexia is therefore likely attributable to infections, etc. that are common in younger children. Thus, there were no major problems with the efficacy and safety observed in patients receiving sirolimus granules in the CVA study.

At the same time, the dose ratio of sirolimus granules to sirolimus tablets was reassessed using a PPK analysis based on data including sirolimus concentrations in Japanese patients participated in the CVA study, the specific clinical study, etc. The trough whole blood sirolimus concentration following the administration of sirolimus granules was estimated to be 1.23-fold that following the administration of sirolimus tablets,

27) The population PK parameters from a PPK analysis in patients aged <18 years in a foreign clinical study of sirolimus in patients with vascular anomalies, including newborn infants (*Eur J Pharm Sci* 2017;109S:S124-S131), and the mean body weight by age in months in Japanese children, were used.

suggesting that sirolimus tablets 1 mg is equivalent to sirolimus granules 0.8 mg [see Section 6.2.2]. Accordingly, the dosage regimen with sirolimus granules, being modified after the CVA study, was proposed as the starting dose of 1.6 mg for patients with BSA ≥1.0 m^2 and 0.8 mg for patients aged ≥1 year with BSA <1.0 m^2. The CVA study enrolled only 1 patient aged <1 year (≥6 months to <12 months). The patient started with sirolimus at 0.06 mg/kg and had dose adjustment while trough whole blood sirolimus concentration was monitored according to Table 8. The trough whole blood sirolimus concentrations generally stayed within 5 to 15 ng/mL (Table 3). PR was maintained at Week 12 and later, and the patient continued with sirolimus with no major safety problems. In the specified clinical study[5)] which employed starting doses[28)] similar to those in the CVA study (Table 2), 9 patients aged <1 year (3 aged <3 months, 4 aged ≥3 months to <6 months, and 2 aged ≥6 months to <12 months) received sirolimus granules. None of these patients had trough whole blood sirolimus concentrations above 15 ng/mL through Week 52, and no particular safety problems were found. For younger children, the starting dose should be determined by age in months, from a safety viewpoint. Therefore, the starting doses for patients aged <1 year followed those used in the CVA study (Table 2).

In the CVA study, the maximum dose was not specified, and the dose could be increased within a range so that the trough whole blood sirolimus concentration remained ≤15 ng/mL (Table 8). The maximum daily doses in 9 patients on sirolimus granules (including those formerly on sirolimus tablets) were ≤1 mg in 1 patient, >1 mg to ≤2 mg in 6 patients, >2 mg to ≤3 mg in 1 patient, >3 mg to <4 mg in 0 patients, and ≥4 mg in 2 patients. The maximum dose of sirolimus granules was determined as 3.2 mg for patients aged <1 year, 4 times the age (in months)-based starting dose, based on the following: the maximum daily dose of sirolimus tablets for the approved indication of refractory lymphatic diseases is 4 mg, and the 4-mg sirolimus tablets is equivalent to 4-fold the starting dose (1 mg) for patients with BSA <1.0 m^2.

PMDA asked the applicant to reconsider the dosage regimen of sirolimus granules, including whether it could be standardized with sirolimus tablets. Different strengths of granules and tablets can cause confusion in clinical settings, and chronic overdose of sirolimus is unlikely to occur where the dose level is adjusted based on trough whole blood sirolimus concentration.

The applicant's explanation:
In the CVA study, among 9 patients who started the treatment with sirolimus granules, Week 2 trough whole blood sirolimus concentrations were <5 ng/mL in 4 patients and 5 to 10 ng/mL in 5 patients. No patients had a concentration above the upper limit of the target range (15 ng/mL). Subsequently, all these 9 patients underwent dose increase. In the study, 3 patients with BSA ≥0.6 to <1.0 m^2 started the treatment with >1-mg sirolimus granules. None of these patients had a trough whole blood sirolimus concentration above the upper limit of the target range (15 ng/mL), or no particular safety problems arose in these patients. In 1 patient with BSA ≥1.0 m^2 who received sirolimus granules, the treatment started at 1.4 mg; however, the trough whole blood sirolimus concentration did not reach 5 ng/mL, and the dose was subsequently increased to ≥2 mg, which did not cause any particular safety problem.

[28)] The starting doses were lower than the specified doses for the CVA study in 3 patients: 1 patient aged <3 months received 0.01 mg/kg, 1 patient aged ≥3 to <6 months received 0.02 mg/kg, and 1 patient aged ≥6 to <12 months received 0.04 mg/kg.

Sirolimus granules, when administered at an equal dose level as tablets, may increase trough whole blood sirolimus concentration as compared with tablets, which is however unlikely to lead to chronic overdose of sirolimus, where appropriate monitoring and dose adjustment according to trough whole blood sirolimus concentrations are practiced as advised in the regimen. In addition, neither the CVA study nor the studies in patients with refractory lymphatic diseases (an approved indication of sirolimus) (such as the LM study) showed a tendency for immediately or markedly increasing safety concerns at a trough whole blood sirolimus concentration above the upper limit of the target range (15 ng/mL) compared with concentrations <15 ng/mL. Therefore, the starting dose of sirolimus granules, if modified to 1 mg for patients with BSA ≥ 0.6 to <1.0 m^2 and 2 mg for patients with BSA ≥1.0 m^2, will unlikely cause clinically relevant problems immediately, and can be standardized to that of tablets. However, in patients with BSA <0.6 m^2, a starting dose of 1-mg sirolimus granules may produce trough whole blood sirolimus concentration >15 ng/mL (Table 4). Therefore, patients aged ≥1 year with BSA <0.6 m^2 and those aged <1 year should adhere to the starting dose of sirolimus granules in the CVA study (Table 2).

No major problems observed in 2 patients receiving ≥4-mg sirolimus granules in the CVA study. Because of the required dose adjustment based on trough whole blood sirolimus concentration, chronic overdose of sirolimus is unlikely to occur. Thus, the maximum dose of sirolimus granules 4 mg for patients with BSA ≥0.6 m^2 will not pose particular clinical problem. The maximum dose for patients with BSA <0.6 m^2 should not exceed 4 times the age (in months)-based starting dose.

PMDA's view:

The applicant explained their view on the starting doses of sirolimus, i.e., under appropriate monitoring by physicians with adequate knowledge and experience in the diagnosis and treatment of vascular tumors and vascular malformations, with a full understanding of the effects and risks of sirolimus, the treatment can be started with the same dose level, regardless of granules or tablets, in patients aged ≥1 year with BSA ≥0.6 m^2, while the starting dose for patients aged ≥1 year with BSA <0.6 m^2 and those aged <1 year should remain as per the CVA study (Table 2). Their viewpoint is considered reasonable. In addition, the maximum dose of sirolimus granules can be determined as 4 mg, as with sirolimus tablets, for patients with BSA ≥0.6 m^2, in view that the 2 patients receiving sirolimus granules ≥4 mg in the CVA study had no major problems, and that the dosage regimen requiring dose adjustment based on trough whole blood sirolimus concentration will prevent a risk of chronic overdose. For patients with BSA <0.6 m^2, the maximum dose should be set at ≤4 times the age (in months)-based starting dose. Furthermore, appropriate advice should be offered to healthcare professionals on blood concentration monitoring and dose adjustment in the use of sirolimus granules through the package insert and other materials, as was done for sirolimus tablets.

The dosage and administration of sirolimus granules will be finalized, taking into account the comments from the Expert Discussion.

7.R.5.3 Switching between sirolimus tablets and sirolimus granules

The applicant's explanation about switching between sirolimus tablets and sirolimus granules:
In the CVA study, the switch of dosage form was permitted after Week 25, at a tablet to granule ratio of 1:0.7 (Table 9). A switch from tablets to granules occurred in 1 patient, and vice versa in 1 patient. In both patients, no substantial changes were observed in the efficacy or safety of sirolimus before and after the switch.

In the CVA study, the measurement of trough whole blood sirolimus concentration was scheduled approximately 2 weeks after a switch of the dosage form. The trough whole blood sirolimus concentrations were measured in the 2 patients who had switched the dosage form in the CVA study. The patient who had switched from tablets 4 mg to granules 2.8 mg showed the trough whole blood sirolimus concentration of 9.1 ng/mL pre-switch and 8.7 ng/mL at 12 days post-switch, remaining stable. However, the patient who had switched from granules 4.1 mg to tablets 6 mg showed increased trough whole blood sirolimus concentration from 8.8 ng/mL pre-switch to 13.1 ng/mL at 7 days post-switch. The bioequivalence between sirolimus tablets and sirolimus granules has not been established [see Section 6.1.1], and trough whole blood sirolimus concentrations may vary by dosage form. Therefore, healthcare professionals should be advised to measure trough whole blood sirolimus concentration 1 to 2 weeks after a switch of dosage form.

PMDA's view:
The applicant's explanation is appropriate. Sirolimus tablets and sirolimus granules are not biologically equivalent. Healthcare professionals should be appropriately advised to pay due attention to a change in trough whole blood sirolimus concentration after a switch of dosage form and to check post-switch trough whole blood sirolimus concentration.

7.R.6 Post-marketing investigations

The applicant plans to conduct a general use-results survey covering all patients treated with sirolimus in the post-marketing setting, as outlined in Table 19.

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

Objective	**To evaluate the safety and efficacy of sirolimus (tablets or granules) in clinical practice**
Survey method	**Central registration system**
Population	**Patients with hemangioendothelioma, tufted angioma, venous malformations, blue rubber bleb nevus syndrome, combined vascular malformations, and Klippel-Trenaunay-Weber syndrome**
Target sample size	**All patients treated (safety analysis set, 100 patients)**
Observation period	**2 years**
Main survey items	• **Patient characteristics (age, sex, site of the target lesion, comorbidities, medical history, etc.)** • **Exposure to sirolimus (dosage regimen, dosage form, reasons for switching (if applicable), duration of treatment)** • **Prior and concomitant drugs/therapies** • **Height, body weight, general condition, presence of pleural effusion/ascites, bleeding status** • **Therapeutic effect on the target lesion, Clinical Global Impression scores for the target and non-target lesions** • **Blood sirolimus concentrations** • **Adverse events (date of onset, seriousness, outcome, continuation/discontinuation of treatment with sirolimus, causal relationship with sirolimus, etc.)** • **Laboratory values pertaining to adverse events**

PMDA's view:

Because of extremely limited number of patients enrolled in the CVA study and remaining issues to be further investigated, it is important to obtain data early from a certain number of patients in the post-marketing setting. Therefore, the post-marketing investigation should be conducted covering all patients treated with sirolimus as planned by the applicant. The applicant's survey plan is appropriate.

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

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

The new drug application data were subjected to a document-based inspection and a data integrity assessment, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the submitted application documents.

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

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the submitted application documents.

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

On the basis of the data submitted, PMDA has concluded that sirolimus has efficacy in the treatment of refractory vascular tumors and refractory vascular malformations (lymphangioma [lymphatic malformations], lymphangiomatosis, Gorham's disease, lymphangiectasia, hemangioendothelioma, tufted angioma, venous malformations, blue rubber bleb nevus syndrome, combined vascular malformations, and Klippel-Trenaunay-Weber syndrome), and that sirolimus has acceptable safety in view of its benefits. Sirolimus is clinically meaningful because it offers a new treatment option for patients with refractory vascular tumors and refractory vascular malformations.

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

Review Report (2)

November 21, 2023

Product Submitted for Registration	
Brand Name	(a) Rapalimus Tablets 1 mg, (b) Rapalimus Granules 0.2%
Non-proprietary Name	Sirolimus
Applicant	Nobelpharma Co., Ltd.
Date of Application	April 24, 2023

List of Abbreviations

See the Appendix.

1. Content of the Review

The 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 the Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008, dated December 25, 2008).

1.1. Efficacy and safety

The expert advisors generally supported the PMDA's conclusions described in the Sections "7.R.1 Efficacy" and "7.R.2 Safety" of the Review Report (1), and made the following remark.

- Although the CVA study involved patients with various types of refractory vascular tumors or refractory vascular malformations, extremely limited number of patients with each disease category allowed to provide only limited information in terms of the improvement in complicated symptoms. Therefore, the efficacy of sirolimus against respective primary diseases and associated symptoms are subject to further investigation.

PMDA's view:

Based on the comments from the expert advisors, PMDA has concluded that the post-marketing investigation should be conducted in a way that allows to confirm the efficacy of sirolimus against the respective primary diseases and associated symptoms.

1.2 Indications

The expert advisors generally supported the PMDA's conclusion described in "7.R.4 Indications" of the Review Report (1) and made the following remark.

- To ensure that sirolimus is administered to eligible patients, healthcare professionals should be provided with detailed information about the target diseases, i.e., refractory vascular tumors and refractory vascular malformations.

PMDA's conclusions:
Based on the comments from the expert advisors, the "Indications" and "Precautions Concerning Indications" sections should offer information as follows. Diagnostic criteria for the indications, patient condition for which sirolimus is recommended, etc. should be communicated to healthcare professionals through written materials or by other means, to ensure that sirolimus is administered to eligible patients.

Indications

(a) Rapalimus Tablets 1 mg

- Lymphangioleiomyomatosis
- The following refractory ~~lymphatic diseases~~ vascular tumors and refractory vascular malformations; lymphangioma (lymphatic malformations), lymphangiomatosis, Gorham's disease, lymphangiectasia, hemangioendothelioma, tufted angioma,
  venous malformations, blue rubber bleb nevus syndrome,
  combined vascular malformations, Klippel-Trenaunay-Weber syndrome

(b) Rapalimus Granules 0.2%

- The following refractory vascular tumors and refractory vascular malformations;
  lymphangioma (lymphatic malformations), lymphangiomatosis, Gorham's disease, lymphangiectasia, hemangioendothelioma, tufted angioma,
  venous malformations, blue rubber bleb nevus syndrome,
  combined vascular malformations, Klippel-Trenaunay-Weber syndrome

(Underline denotes additions. Strikethrough denotes deletions.)

Precautions Concerning Indications

Lymphangioleiomyomatosis

- Use the tablet form of sirolimus only. Sirolimus must be administered to patients with a confirmed diagnosis according to references including the Diagnostic Criteria for Lymphangioleiomyomatosis (LAM) provided by the Research Group on respiratory failure, a Research Project for Measures for Intractable Diseases, the Ministry of Health, Labour and Welfare.

Refractory vascular tumors and refractory vascular malformations

- Sirolimus must be administered to patients with a confirmed diagnosis according to the guidelines.
- Venous malformations to be treated with sirolimus refers to "common venous malformation" in the ISSVA classification.
- The efficacy of sirolimus has not been demonstrated against malignant diseases or high-flow vascular malformations such as arteriovenous malformations.

- Sirolimus is not recommended for the treatment of combined vascular malformations that do not include venous or lymphatic malformation.

(Underline denotes additions or changes.)

1.3 Dosage and administration

The expert advisors generally supported the PMDA's conclusion in the Section "7.R.5 Dosage and administration" of the Review Report (1) and made the following remark.

- Sirolimus granules is expected to show high inter-individual variability in blood concentrations. Thus, more appropriate dose adjustment method should be developed based on data from the post-marketing investigation, etc. and provided to clinical settings.

PMDA's conclusion:

Based on the comments from the expert advisors, the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections should be described as follows. In addition, the "Warning" section should highlight that sirolimus tablets and sirolimus granules are not biologically equivalent, with a caution that blood concentrations be checked after a switch of dosage form. Data on efficacy, safety, and blood sirolimus concentrations after a dose adjustment with sirolimus granules must be collected via the post-marketing investigation, etc. to assess the need for improvement in the current adjustment method.

Dosage and administration

(a) Rapalimus Tablets 1 mg

Lymphangioleiomyomatosis

The usual adult dosage is 2 mg of sirolimus administered orally once daily. The dose may be adjusted according to the patient's condition. However, the dose should not exceed 4 mg once daily.

Refractory ~~lymphatic diseases,~~ *vascular tumors and refractory vascular malformations*

The usual starting dose is 2 mg (body surface area $\geq$1.0 m^2) or 1 mg (body surface area <1.0 m^2) of sirolimus administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed 4 mg once daily.

(b) Rapalimus Granules 0.2%

Refractory vascular tumors and refractory vascular malformations

The usual starting dose is 2 mg (body surface area $\geq$1.0 m^2) or 1 mg (body surface area $\geq$0.6 and <1.0 m^2) of sirolimus administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed 4 mg once daily.

For patients with a body surface area <0.6 m^2, the starting dose is determined based on their age in months as shown below, and administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed the maximum dose indicated below.

Age in months	Starting daily dose (≤1 mg)	Maximum daily dose (≤4 mg)
<3 months	0.02 mg/kg	0.08 mg/kg
≥3 months to <6 months	0.04 mg/kg	0.16 mg/kg
≥6 months to <12 months	0.06 mg/kg	0.24 mg/kg
≥12 months	0.08 mg/kg	0.32 mg/kg

(Underline denotes additions. Strikethrough denotes deletions.)

Precautions Concerning Dosage and Administration (excerpt)

Refractory vascular tumors and refractory vascular malformations

- The trough blood sirolimus concentrations should be measured 1 to 2 weeks after the start of treatment with sirolimus, to adjust the dose to maintain the concentrations within the target range of ≤15 ng/mL.
- Sirolimus tablets and granules are not biologically equivalent. The steady-state trough blood sirolimus concentration following administration of sirolimus granules was 1.23-fold that following the administration of sirolimus tablets. Thus, a switch of dosage form warrants careful attention to change in blood sirolimus concentration. Trough blood sirolimus concentration should be checked at 1 to 2 weeks after the switch.

(Underline denotes additions or changes.)

Warning (excerpt)

Refractory vascular tumors and refractory vascular malformations

- Sirolimus tablets and granules are not biologically equivalent. Blood concentrations must be checked after a switch of dosage form.

(Underline denotes additions.)

1.4 Risk management plan (draft)

The expert advisors generally supported PMDA's conclusion in the Section "7.R.6 Post-marketing investigations" of the Review Report (1) and made the following remarks.

- Patients with vascular diseases, new indications of sirolimus in the present application, generally have abnormal blood coagulation. It is advisable that information about hematological tests, including those related to blood coagulation, is collected through the post-marketing investigation.
- Sirolimus is used in infants and toddlers. It is advisable that the impact of sirolimus on the development and growth of children is also investigated. In view of prolonged treatment anticipated in some patients, long-term safety and efficacy data should be collected whenever possible.
- Due to the extremely small number of patients enrolled, the CVA study failed to yield sufficient safety and efficacy data by primary disease. It is advisable that safety and efficacy against each primary disease are confirmed through the post-marketing investigation.

Based on the comments from the expert advisors, PMDA requested that the post-marketing investigation be designed to collect available clinical laboratory test (hematology, biochemistry, coagulation, etc.) data, obtain

information pertaining to the impact of sirolimus on the development and growth of children, allow a sufficient investigation period to yield data on long-term treatment, and allow safety and efficacy assessment by primary disease. In response, the applicant proposed some modifications in their post-marketing investigation plan with additional "clinical laboratory values" to the survey items, investigation of impacts of sirolimus on the development and growth of children based on height and body weight, assessment of long-term safety and efficacy in patients continuing with sirolimus from the specified clinical study (Study SRL-CVA-01), using prior treatment data including the duration of treatment with sirolimus since the first dose, and safety and efficacy assessment by primary disease (including survey items relating to disease-specific symptoms). PMDA considered that the applicant's proposal was reasonable.

PMDA view:

The current risk management plan (draft) for sirolimus should include the safety and efficacy specifications presented in Table 20, and conduct the additional pharmacovigilance activities and risk minimization activities, respectively presented in Table 22.

Table 20. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	**Important potential risks**	**Important missing information**
• **Interstitial lung disease** • **Serious infectious diseases** • **Anaphylaxis** • **Fluid retention (pericardial effusion, edema peripheral, pleural effusion, ascites)** • **Dyslipidemia** • **Poor wound healing** • **Renal disorders** • **Gastrointestinal disorders** • **Skin disorders** • **Drug interactions related to CYP3A and P-glycoprotein**	• **Malignant lymphoma and malignant tumors** • **Adverse events related to reproductive hormones and bone metabolism** • **Pancytopenia, thrombocytopenia, neutropenia, anemia, etc.** • **Venous thromboembolism (e.g., pulmonary embolism, deep vein thrombosis)** • **Thrombotic microangiopathy** • **Alveolar proteinosis** • **Hyperglycemia** • **Developmental delay**	• **None**
Efficacy specification		
• **Efficacy in clinical use**		

(No change)

Table 21. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	**Additional risk minimization activities**
• **Use-results survey (lymphangioleiomyomatosis)** • **General use-results survey (lymphangioma [lymphatic malformations]), lymphangiomatosis, Gorham's disease, and lymphangiectasia)** • **General use-results survey (hemangioendothelioma, tufted angioma, venous malformations, blue rubber bleb nevus syndrome, combined vascular malformations, and Klippel-Trenaunay-Weber syndrome)**	• **Preparation and dissemination of reference materials for healthcare professionals** • **Preparation and dissemination of reference materials for patients** • **Product web site**

(Underline denotes additions.)

Table 22. Outline of the general use-results survey (draft)

Objective	**To evaluate the safety and efficacy of sirolimus (tablets or granules) in clinical practice**
Survey method	**Central registration system**
Population	**Patients with hemangioendothelioma, tufted angioma, venous malformations, blue rubber bleb nevus syndrome, combined vascular malformations, and Klippel-Trenaunay-Weber syndrome**
Target sample size	**All patients treated (safety analysis set, 100 patients)**
Observation period	**2 years**
Main survey items	• **Patient characteristics (age, sex, site of the target lesion, comorbidities, medical history, etc.)** • **Exposure to sirolimus (dosage regimen, dosage form, reason for switching (if applicable), duration of treatment)** • **Prior and concomitant drugs/therapies** • **Height, body weight, general condition, presence of pleural effusion/ascites, bleeding status** • **Therapeutic effect on the target lesion, Clinical Global Impression scores for the target and non-target lesions** • **Clinical laboratory values (hematology, biochemistry, and coagulation tests)** • **Blood sirolimus concentrations** • **Adverse events (date of onset, seriousness, outcome, continuation/discontinuation of treatment with sirolimus, causal relationship with sirolimus, etc.)** • **Laboratory values pertaining to adverse events**

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved for the indications and dosage and administration shown below, with the following conditions. The products are an orphan drug designated with the proposed indication, "refractory vascular tumors and refractory vascular malformations." Accordingly, the re-examination period for the indication in the present application is 10 years. Sirolimus granules is not classified as a biological product or a specified biological product, and Rapalimus Granules is classified as a powerful drug.

Indications

(a) Rapalimus Tablets 1 mg

- Lymphangioleiomyomatosis
- The following refractory ~~lymphatic diseases~~ vascular tumors and refractory vascular malformations; lymphangioma (lymphatic malformations), lymphangiomatosis, Gorham's disease, lymphangiectasia, hemangioendothelioma, tufted angioma,
  venous malformations, blue rubber bleb nevus syndrome,
  combined vascular malformations, Klippel-Trenaunay-Weber syndrome

(b) Rapalimus Granules 0.2%

- The following refractory vascular tumors and refractory vascular malformations;
  lymphangioma (lymphatic malformations), lymphangiomatosis, Gorham's disease, lymphangiectasia, hemangioendothelioma, tufted angioma,
  venous malformations, blue rubber bleb nevus syndrome,
  combined vascular malformations, Klippel-Trenaunay-Weber syndrome

(Underline denotes additions. Strikethrough denotes deletions.)

Dosage and administration

(a) Rapalimus Tablets 1 mg

Lymphangioleiomyomatosis

The usual adult dosage is 2 mg of sirolimus administered orally once daily. The dose may be adjusted according to the patient's condition. However, the dose should not exceed 4 mg once daily.

Refractory ~~lymphatic diseases~~ *vascular tumors and refractory vascular malformations*

The usual starting dose is 2 mg (body surface area ≥1.0 m^2) or 1 mg (body surface area <1.0 m^2) of sirolimus, administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed 4 mg once daily.

(b) Rapalimus Granules 0.2%

Refractory vascular tumors and refractory vascular malformations

The usual starting dose is 2 mg (body surface area ≥1.0 m^2) or 1 mg (body surface area ≥0.6 and <1.0 m^2) of sirolimus, administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed 4 mg once daily.

For patients with a body surface area <0.6 m^2, the starting dose is determined based on their age in months as shown below, and administered orally once daily. Subsequent doses are adjusted according to the trough blood concentration and condition of the patient. However, the dose should not exceed the maximum dose indicated below.

Age in months	Starting daily dose (≤1 mg)	Maximum daily dose (≤4 mg)
<3 months	0.02 mg/kg	0.08 mg/kg
≥3 months to <6 months	0.04 mg/kg	0.16 mg/kg
≥6 months to <12 months	0.06 mg/kg	0.24 mg/kg
≥12 months	0.08 mg/kg	0.32 mg/kg

(Underline denotes additions. Strikethrough denotes deletions.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of limited experiences in Japanese patients, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the products to compile data from a certain number of cases for an understanding of patient characteristics, collect product safety and efficacy data promptly, and take necessary measures to ensure the proper use of the products.

Appendix

List of Abbreviations

AKT	Protein kinase B
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
Clinical Practice Guidelines 2022	"Japanese Clinical Practice Guidelines for Vascular Anomalies 2022" edited by the Group for "Research on Refractory Hemangioma, Vascular Malformations, Blood Vessel Malformations, Lymphangioma, Lymphangiomatosis, and Other Related Diseases, the Research Project for Intractable Disease supported by the Health and Labour Sciences Research Grant, Fiscal Years 2020 to 2022
CL/F	Apparent oral clearance after administration of the drug
C_{max}	Maximum observed concentration of drug
CR	Complete response
CTD	Common technical document
CVA study	Investigator-initiated study of sirolimus in patients with refractory vascular tumors and refractory vascular malformations (CTD 5.3.5.2-1, Study NPC-12T-CVA)
CYP	Cytochrome P450
F	Relative bioavailability
FAS	Full analysis set
GCP	Good clinical practice
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
ISSVA	The international society for the study of vascular anomalies
Ka	Rate constant of absorption
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LM study	Investigator-initiated study of sirolimus in patients with refractory lymphatic diseases (Study NPC-12T-LM)
MedDRA	Medical dictionary for regulatory activities
MedDRA/J	Medical dictionary for regulatory activities Japanese version
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
PD	Progressive disease
PI3K	Phosphatidylinositol 3-kinase
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Partial response
Q/F	Apparent intercompartmental clearance
SD	Stable disease
Sirolimus granules	Rapalimus Granules 0.2%
Sirolimus tablets	Rapalimus Tablets 1 mg
TDM	Therapeutic drug monitoring
t_{max}	Time to maximum concentration
VAS	Visual analogue scale
V_c/F	Apparent central volume of distribution of the drug
V_p/F	Apparent peripheral volume of distribution of the drug
WHO	World health organization