Report on the Deliberation Results

March 8, 2018

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Rapalimus Gel 0.2%
Non-proprietary Name	Sirolimus (JAN*)
Applicant	Nobelpharma Co., Ltd.
Date of Application	October 20, 2017

Results of Deliberation

In its meeting held on March 1, 2018, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council. The product is not classified as a biological product or a specified biological product, and the re-examination period is 10 years. The drug product is classified as a powerful drug.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to further understand the characteristics of patients treated with the product and collect data on the safety and efficacy of the product as soon as possible, thereby taking necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

February 16, 2018
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Rapalimus Gel 0.2%
Non-proprietary Name	Sirolimus
Applicant	Nobelpharma Co., Ltd.
Date of Application	October 20, 2017
Dosage Form/Strength	Topical gel: Each gram of gel contains 2 mg of sirolimus.
Application Classification	Prescription drug, (3) Drug with a new route of administration
Items Warranting Special Mention	*Sakigake*-designated product (*Sakigake* Drug Designation No. 1 of 2015 [*27 yaku*]; Notification No. 1027-1 dated October 27, 2015, issued by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare), and orphan drug designated product (Orphan Drug Designation No. 369 of 2015 [*27 yaku*]; Notification No. 1218-1 dated December 18, 2015, issued by the Evaluation and Licensing 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 product has efficacy in the treatment of tuberous sclerosis complex-associated skin lesions, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication

Tuberous sclerosis complex-associated skin lesions

Dosage and Administration

Usual dosage: Apply an appropriate amount of Rapalimus Gel to the affected skin areas twice daily.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to further understand the characteristics of patients treated with the product and collect data on the safety and efficacy of the product as soon as possible, thereby taking necessary measures to ensure proper use of the product.

Attachment

Review Report (1)

January 15, 2018

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

Product Submitted for Approval	
Brand Name	Rapalimus Gel 0.2%
Non-proprietary Name	Sirolimus
Applicant	Nobelpharma Co., Ltd.
Date of Application	October 20, 2017
Dosage Form/Strength	Topical gel: Each gram of gel contains 2 mg of sirolimus.
Proposed Indication	Tuberous sclerosis complex-associated skin lesions
Proposed Dosage and Administration	Usual dosage for adults and children: Apply an appropriate amount of Rapalimus Gel to the affected skin areas twice daily. The dosage should be adjusted according to the symptoms.

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List of Abbreviations

See Appendix.

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

Tuberous sclerosis complex (TSC) is an autosomal dominant disease characterized by systemic hamartomas. TSC has been designated for the Rare/Intractable Disease Research Project in Japan. TSC involves the *TSC1* and/or *TSC2* genes. Mutations in the *TSC1* or *TSC2* gene lead to constitutive activation of the downstream mammalian target of rapamycin (mTOR) pathway that promotes cell proliferation and other cellular functions, resulting in the development of hamartomas in the skin, brain, lungs, heart, kidneys, bones, etc. (Diagnostic Criteria and Treatment Guideline for Tuberous Sclerosis Complex 2008. The Japanese Dermatological Association ed. [TSC treatment guideline 2008]).

Major TSC-associated skin lesions include facial angiofibromas and fibrous cephalic plaques. Laser therapy, liquid nitrogen cryotherapy, surgical therapy, and other therapies are used to treat these skin lesions, but all of these therapies are highly invasive.

Rapalimus Gel is a topical gel formulation containing sirolimus as the active ingredient (sirolimus gel), and it inhibits the activity of the mTOR, thereby suppressesing cell proliferation and other cellular functions. In Japan, an oral formulation of sirolimus, "Rapalimus Tablets 1 mg," was approved for the indication of lymphangioleiomyomatosis in July 2014. A topical formulation, sirolimus gel, was developed because it would allow for the noninvasive treatment of TSC-associated skin lesions.

Claiming that the efficacy and safety of sirolimus gel in patients with TSC-associated skin lesions such as angiofibromas were confirmed in a Japanese phase III study, the applicant has filed a marketing application for sirolimus gel.

Sirolimus gel received the *Sakigake* designation with the intended indication of "tuberous sclerosis complex-associated angiofibromas" on October 27, 2015 (*Sakigake* Designation No. 1 of 2015 [*27 yaku*]) and the orphan drug designation on December 18, 2015 (Drug Designation No. 369 of 2015 [*27 yaku*]).

Sirolimus gel has not been approved in any country as of October 2017.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

A Drug Master File (DMF) for the drug substance sirolimus has been registered [redacted].

2.1.1 Characterization

The drug substance is a white to off-white powder. The general properties of the drug substance have been determined, including description, melting point, solubility, and partition coefficient.

Its chemical structure has been elucidated by infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (NMR) (^{1}H-NMR and ^{13}C-NMR), mass spectrometry, elemental analysis, and X-ray powder

diffraction. In solution, sirolimus interconverts between 3 isomers: A, B, and C. Sirolimus exists primarily as isomer B in solution.

2.1.2 Manufacturing process

See attachment.

2.1.3 Control of drug substance

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

2.1.4 Stability of drug substance

The primary stability studies of the drug substance are shown in Table 1. The photostability data showed that the drug substance is photolabile. After the stability studies were conducted, the specification limit for [redacted] was tightened. [redacted] batches in the long-term testing (48 months), [redacted] batch in the long-term testing (36 months), and [redacted] batches in the accelerated testing met the current [redacted] specification. There were no changes over time under the long-term or accelerated testing conditions.

Table 1. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	6 commercial-scale batches	5°C	–	Polyethylene bags ([redacted]) + aluminum bag ([redacted]) + fiber drum	48 months (5 batches) 36 months (1 batch)
Accelerated	4 commercial-scale batches	25°C	60%RH		6 months

Based on the above, a retest period of 36 months has been proposed for the drug substance when stored in [redacted] polyethylene bags and [redacted] aluminum bag placed in a fiber drum at 2°C to 8°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a topical gel. Each gram of gel contains 2 mg of sirolimus. The excipients used are carboxyvinyl polymer, anhydrous ethanol, triethanolamine, and purified water.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of dissolution, gelling, filling, packaging, testing, and storage. [redacted] and [redacted] have been defined as critical steps.

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (ultraviolet-visible spectrophotometry [UV]), pH, purity (related substances [HPLC]), and assay (HPLC).

2.2.4 Stability of drug product

The primary stability studies on the drug product are shown in Table 2. The results of the accelerated testing fell outside the specification for related substances. The drug product was found to be sensitive to heat. The photostability data showed that the drug product is photolabile.

Table 2. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	5°C	–	Aluminum tube	12 months
Accelerated		25°C	60%RH		3 months

Based on the above, a shelf life of 12 months has been proposed for the drug product when stored in an aluminum tube at 2°C to 8°C. The long-term testing will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data and other information, PMDA concluded that the quality of the drug substance and drug product is adequately controlled. The DMF registrant had submitted its DMF for sirolimus, and PMDA reviewed the information contained in the DMF. The results of the review are shown in attachment.

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

A primary pharmacodynamic study was conducted to investigate inhibition of tumor growth by topical sirolimus. Although the present application is intended for a new route of administration, no new safety pharmacology data have been submitted. The effects of sirolimus on the central nervous, respiratory, and cardiovascular systems and other organs had been assessed in safety pharmacology studies submitted for a marketing application for "Rapalimus Tablets 1 mg" which contains the same active ingredient as that of sirolimus gel (see the Rapalimus Tablets 1 mg Review Report [May 15, 2014]). Sirolimus-containing ointments were used in the primary pharmacodynamic study.

3.1 Primary pharmacodynamics

3.1.1 Inhibition of tumor growth by *Tsc2*-deficient cells in mice (CTD 4.2.1.1-1 [Reference data], *BMC Dermatol*. 2008;8: 1)

Nude mice were injected subcutaneously with NTC/T2 null cells derived from *Tsc2*-deficient mouse embryonic fibroblasts. Animals began treatment when their tumor volume reached approximately 200 mm^3, and a 0.4% or 0.8% sirolimus ointment or vehicle (petrolatum) was applied to the skin 3 times a week. On Day 29, tumors were measured to calculate tumor volumes (Table 3).

Tumor volume assessment showed that 0.4% and 0.8% sirolimus ointments significantly reduced tumor growth, compared with vehicle control.

Table 3. Tumor volumes on Day 29 in mice injected with *Tsc2*-deficient cells

Treatment group	n	Tumor volume on Day 29 [a] (mm^3)
Vehicle	12	2736 ± 321
0.4% sirolimus	15	1568 ± 155*
0.8% sirolimus	13	1212 ± 118***

a) Mean ± standard error (SE)
*: $P < 0.01$, ***: $P < 0.0001$ (vs. vehicle control, t-test)

3.R Outline of the review conducted by PMDA

The applicant's explanation about the pharmacological effects of topical sirolimus:
TSC involves *TSC1* and *TSC2*, and *TSC1* and *TSC2* encode hamartin and tuberin, respectively. Hamartin and tuberin form a complex that controls the activation of mTOR, which is involved in the regulation of cell proliferation and differentiation (*Oncogene*. 2006;25: 6347-6360). When mutations occur in *TSC1* or *TSC2*, the hamartin-tuberin complex does not function properly and the mTOR pathway is constitutively activated. This leads to increased cell proliferation and differentiation, resulting in the development of hamartomas such as angiofibromas in the skin (Frontiers of Diagnosis and Treatment of Tuberous Sclerosis Complex. The Japanese Society of Tuberous Sclerosis Complex ed. SHINDAN TO CHIRYO SHA Inc. 2016).

Sirolimus should be effective in the treatment of TSC-associated hamartomas in the skin, on the following grounds: (i) Sirolimus forms a complex with mTOR, thus inhibiting its activity (see the Rapalimus Tablets 1 mg Review Report [May 15, 2014]) and (ii) it reduced tumor growth in mice injected with *Tsc2*-deficient cells [see Section 3.1.1].

PMDA's view:
Based on the primary pharmacodynamic data submitted with the present application and other data, topical sirolimus, an mTOR inhibitor, should be effective in the treatment of TSC-associated hamartomas in the skin.

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

The pharmacokinetics of sirolimus gel following repeated dermal applications in rats, monkeys, and mice were determined based on toxicokinetics in toxicity studies. Whole blood concentrations of unchanged sirolimus in rats and monkeys were determined by liquid chromatography/tandem mass spectrometry (LC/MS/MS), and the lower limit of quantification (LLOQ) was 0.1 ng/mL for both. Skin concentrations of unchanged sirolimus in mice were determined by LC/MS/MS, and the LLOQ was 1 ng/mg tissue.

Unless otherwise specified, male and female animals were used in studies. Ethanol-containing aqueous gel formulations, as with the proposed commercial formulation, were used in all of these studies.

The distribution, metabolism, and excretion of sirolimus had been evaluated for a marketing application for "Rapalimus Tablets 1 mg" which contains the same active ingredient as that of sirolimus gel (see the Rapalimus Tablets 1 mg Review Report [May 15, 2014]).

4.1 Absorption

4.1.1 Rat repeated-dose study (CTD 4.2.3.2-1, Study [redacted])

Rats were treated dermally with 0.01%, 0.05%, 0.2%, or 0.8% sirolimus gel twice daily for 13 weeks.[1)] The pharmacokinetic parameters of unchanged sirolimus in whole blood in rats are shown in Table 4. The C_{max} and $AUC_{0\text{-}24h}$ increased with increasing dose, and tended to be higher in males than in females.

Table 4. Pharmacokinetic parameters of unchanged sirolimus in whole blood in rats after 13-week dermal applications

Sex	Sirolimus concentration (%)	Day 1			Week 13 (Day 91)		
		C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
Male	0.01	BLQ	NC	NC	0.2	3	2.8
	0.05	BLQ	NC	NC	0.4	1	6.2
	0.2	BLQ	NC	NC	1.0	1	17.8
	0.8	0.1	24	0.7	1.4	7	23.2
Female	0.01	BLQ	NC	NC	0.2	7	3.7
	0.05	BLQ	NC	NC	0.2	9	4.7
	0.2	BLQ	NC	NC	0.5	1	9.7
	0.8	BLQ	NC	NC	0.9	1	16.5

Each parameter was calculated from the mean blood concentration of 4 animals per time point.

4.1.2 Monkey repeated-dose studies (CTD 4.2.3.2-3 and 4.2.3.2-4, Studies [redacted] and [redacted])

Monkeys were treated dermally with 0.01%, 0.05%, 0.2%, or 0.8% sirolimus gel twice daily for 13 weeks[2)] and 0.05%, 0.2%, or 0.8% sirolimus gel twice daily for 39 weeks.[2)] The pharmacokinetic parameters of unchanged sirolimus in whole blood in monkeys are shown in Table 5 (13 weeks) and Table 6 (39 weeks). In both studies, the C_{max} and $AUC_{0\text{-}24h}$ increased with increasing dose.

Table 5. Pharmacokinetic parameters of unchanged sirolimus in whole blood in monkeys after 13-week dermal applications

Sex	Sirolimus concentration (%)	Day 1			Week 13 (Day 93)		
		C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
Male	0.01	BLQ	NC	NC	0.1 ± 0.1	9.3 ± 12.7	1.9 ± 2.0
	0.05	BLQ	NC	NC	0.3 ± 0.0	24.0 ± 0.0	5.0 ± 0.8
	0.2	BLQ	NC	NC	0.6 ± 0.3	9.3 ± 10.1	11.1 ± 5.7
	0.8	0.5 ± 0.2	16.5 ± 8.7	6.7 ± 3.0	2.7 ± 2.2	14.3 ± 11.3	45.2 ± 31.3
Female	0.01	BLQ	NC	NC	0.1 ± 0.1	7.7 ± 1.2	1.1 ± 1.2
	0.05	BLQ	NC	NC	0.2 ± 0.1	4.3 ± 2.8	3.9 ± 1.0
	0.2	BLQ	NC	NC	0.5 ± 0.2	6.8 ± 0.5	6.3 ± 1.1
	0.8	BLQ	NC	NC	1.3 ± 0.9	3.8 ± 3.2	16.5 ± 11.2

Mean ± standard deviation (SD), n = 4

Table 6. Pharmacokinetic parameters of unchanged sirolimus in whole blood in monkeys after 39-week dermal applications

Sex	Sirolimus concentration (%)	Week 4 (Day 27)		Week 13 (Day 90)		Week 39 (Day 272)	
		C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)
Male	0.05	0.6 ± 0.2	12.5 ± 4.2	0.6 ± 0.3	10.9 ± 4.7	0.4 ± 0.1 [a)]	7.7 ± 1.7 [a)]
	0.2	2.0 ± 0.7	39.8 ± 13.8	1.9 ± 0.7	33.4 ± 3.8	2.5 ± 0.3	48.9 ± 3.3
	0.8	7.5 ± 3.1	135.8 ± 43.9	4.3 ± 0.7 [a)]	78.9 ± 20.9 [a)]	7.3 ± 1.7 [a)]	129.1 ± 47.5 [a)]
Female	0.05	1.2 ± 1.3	8.0 ± 3.1	0.6 ± 0.2	10.8 ± 4.2	0.4 ± 0.1	9.1 ± 2.9
	0.2	1.0 ± 0.2	16.3 ± 3.2	1.6 ± 0.5	28.6 ± 4.0	1.5 ± 0.2 [a)]	27.1 ± 1.6 [a)]
	0.8	2.4 ± 0.4 [a)]	40.9 ± 7.5 [a)]	5.3 ± 2.1	87.2 ± 25.4	4.9 ± 1.6	93.6 ± 26.8

Mean ± SD, n = 4
a) n = 3

[1)] 0.5 g/kg per application
[2)] 0.25 g/kg per application

4.1.3 Distribution to skin in mice (CTD 4.2.3.4-1 [Reference data], Study [redacted])

Male mice were treated dermally with 0.2% or 0.8% sirolimus gel once daily for 4 weeks.[3)] Skin concentrations of unchanged sirolimus in mice after the last dose are shown in Table 7. The skin concentration of unchanged sirolimus increased with increasing dose.

Table 7. Skin concentrations of unchanged sirolimus after the last dose in mice treated dermally for 4 weeks (ng/mg tissue)

Sirolimus concentration (%)	2 hours post-dose	8 hours post-dose	24 hours post-dose
0.2	183.4 ± 51.3	133.4 ± 103.4	244.5 ± 94.2
0.8	950.9 ± 600.8	853.0 ± 437.3	700.4 ± 458.9

Mean ± SD, n = 3

4.R Outline of the review conducted by PMDA

The applicant's explanation about percutaneous absorption of sirolimus gel:

Mice were treated dermally with 0.2% sirolimus gel once daily for 4 weeks. The skin concentration of unchanged sirolimus in mice ranged from 183 to 245 ng/mg tissue, showing that sirolimus migrates into the skin.

In the study in which rats were treated dermally with 0.01% to 0.8% sirolimus gel twice daily for 13 weeks, unchanged sirolimus was detected in whole blood at Week 13. The whole blood concentration of unchanged sirolimus remained almost constant throughout 24 hours, and there were no apparent changes in its concentration that may have represented the absorption or elimination phase. Also in the study in which monkeys were treated dermally with 0.05% to 0.8% sirolimus gel twice daily for 39 weeks, from Week 4 onward, the whole blood concentrations of unchanged sirolimus were independent of treatment duration and remained almost constant. There were no apparent changes in its concentration that may have represented the absorption or elimination phase.

In a Japanese long-term treatment study, 0.2% sirolimus gel was applied topically to skin lesions of patients with TSC twice daily. There was no trend toward increasing blood sirolimus concentration with prolonged treatment [see Section 6.R].

PMDA considers that there is no particular problem with the non-clinical pharmacokinetics of sirolimus gel.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application is intended for a new route of administration. New toxicity studies of sirolimus gel were conducted to support the present application (single-dose dermal toxicity, repeated-dose dermal toxicity, carcinogenicity, juvenile rat dermal toxicity, local tolerance [skin irritation and eye irritation], and other toxicity studies [phototoxicity, skin sensitization, and skin photosensitization studies and a toxicity study on impurities]). The systemic toxicity of sirolimus had been evaluated for the approval of "Rapalimus Tablets 1 mg" which contains the same active ingredient as that of sirolimus gel. Sirolimus gel was applied openly (a dressing was used) in all of the single-dose dermal toxicity, repeated-dose dermal toxicity, carcinogenicity, and juvenile rat dermal toxicity studies.

[3)] 15 mg per application

5.1 Single-dose toxicity

5.1.1 Single-dose dermal toxicity study in rats (CTD 4.2.3.1-1, Study [redacted])

Male and female rats were treated dermally with sirolimus gel in concentrations of 0.01%, 0.05%, 0.2%, and 0.8% (at doses of 0.1, 0.5, 2.0, and 8.0 mg/kg, respectively) or vehicle twice daily. No deaths occurred in any group, nor were there any sirolimus-related changes. The approximate lethal dose was determined to be >8.0 mg/kg.

5.2 Repeated-dose toxicity

Dermal toxicity studies were conducted in male and female rats (13 weeks) and male and female monkeys (13 and 39 weeks). The major findings of the studies were immunosuppressive effects or changes secondary to immunosuppression in rats and colitis due to stress-induced alterations in intestinal bacterial flora in monkeys. The no-observed-adverse-effect levels (NOAELs) in rats (13 weeks) and monkeys (39 weeks) were 0.1/2.0 [male/female] mg/kg/day in rats and 0.25 mg/kg/day in monkeys), respectively, and the exposures (C_{max}) at the NOAELs were 0.8/2.0-fold (male/female) and 1.7/1.8-fold (male/female) the human exposure (the mean blood concentration) at the proposed clinical dose (0.2% sirolimus gel), respectively. A 26-week dermal toxicity study in rodents was not conducted for the following reasons: (i) The toxicity of dermally applied sirolimus in the 13-week dermal toxicity study in rats was weaker than that of orally administered sirolimus. (ii) There were no differences in the toxicological profile between dermal and oral routes of administration.

5.2.1 Rat 13-week dermal toxicity study with a 4-week recovery period (CTD 4.2.3.2-1, Study [redacted])

Male and female rats were treated dermally with sirolimus gel in concentrations of 0.01%, 0.05%, 0.2%, and 0.8% (at doses of 0.1, 0.5, 2.0, and 8.0 mg/kg/day, respectively) or vehicle twice daily for 13 weeks, and the reversibility of toxicity following a 4-week recovery period was evaluated in the 0.8% sirolimus and vehicle groups. Decreased body weights were observed in males at ≥0.5 mg/kg/day and increased lung weights in males and females at 8.0 mg/kg/day. Alveolar macrophage accumulation was noted in both the sirolimus and vehicle groups, and an increase in alveolar macrophage accumulation was observed in males at ≥2.0 mg/kg/day and females at 8.0 mg/kg/day. All changes were reversible after a recovery period. The NOAELs were determined to be 0.1 mg/kg/day in males and 2.0 mg/kg/day in females.

5.2.2 Hairless rat 13-week dermal toxicity study with a 7-week recovery period (CTD 4.2.3.2-2, Study [redacted])

Male and female hairless rats were treated dermally with sirolimus gel in concentrations of 0.05%, 0.2%, and 0.8% (at doses of 0.5, 2.0, and 8.0 mg/kg/day, respectively) or vehicle twice daily for 13 weeks, and the reversibility of toxicity following a 7-week recovery period was evaluated in the 0.8% sirolimus and vehicle groups.

Toxicity findings were as follows: increased lung weights or a trend toward increased lung weights, increased foamy macrophages in mesenteric lymph nodes, and alveolar macrophage accumulation in males and females

at ≥0.5 mg/kg/day; increased blood ALT in males at ≥0.5 mg/kg/day; increased neutrophil count or a trend toward increased neutrophil count in males at ≥0.5 mg/kg/day and females at ≥2.0 mg/kg/day; decreased body weights, an increased percentage of neutrophils or a trend toward an increased percentage of neutrophils, increases in reticulocyte and platelet counts, decreased percentages of lymphocytes and eosinophils or a trend toward decreased percentages of lymphocytes and eosinophils, increased adrenal gland weights, and decreased blood albumin and A/G ratio or a trend toward decreased blood albumin and A/G ratio in males and females at ≥2.0 mg/kg/day; decreased food consumption in males at ≥2.0 mg/kg/day and females at 8.0 mg/kg/day, increased APTT, increased foamy macrophages and Russell bodies in submandibular lymph nodes, increased macrophages in the thymus, and increased microvacuolization of the adrenal zona glomerulosa in males and females at 8.0 mg/kg/day; pale skin of the whole body, dark reddish brown stools, and decreased thymic weights in males at 8.0 mg/kg/day; and decreased ovarian weights in females at 8.0 mg/kg/day. There were wounds around the dressing on the back skin (the site of application) in both the sirolimus and vehicle groups, and its incidence was high in males and females at 8.0 mg/kg/day. All changes except for decreased body weights were reversible after a recovery period. The NOAEL was determined to be <0.5 mg/kg/day.

5.2.3 Monkey 13-week dermal toxicity study with a 4-week recovery period (CTD 4.2.3.2-3, Study [redacted])

Male and female monkeys were treated dermally with sirolimus gel in concentrations of 0.01%, 0.05%, 0.2%, and 0.8% (at doses of 0.05, 0.25, 1.0, and 4.0 mg/kg/day, respectively) or vehicle twice daily for 13 weeks, and the reversibility of toxicity following a 4-week recovery period was evaluated in the 0.8% sirolimus and vehicle groups. There were no deaths or sirolimus-related abnormalities. No abnormalities were observed after a recovery period. The NOAEL was determined to be 4.0 mg/kg/day.

5.2.4 Monkey 39-week dermal toxicity study (CTD 4.2.3.2-4, Study [redacted])

Male and female monkeys were treated dermally with sirolimus gel in concentrations of 0.05%, 0.2%, and 0.8% (at doses of 0.25, 1.0, and 4.0 mg/kg/day, respectively) or vehicle twice daily for 39 weeks. One of 4 males in the 4.0 mg/kg/day group and 1 of 4 females in the 1.0 mg/kg/day group were sacrificed moribund due to loose stools and diarrhoea, decreases in body weight and food consumption, decreased spontaneous motor activity, lateral position, etc. after Week 32. These animals had cecitis, colitis, or proctitis. The female animal also exhibited intestinal bloating caused by excess gas accumulation in the cecum and colon, and gastrointestinal changes possibly associated with the physical pressure (e.g., congestion, fibrin-like thrombi, hemorrhage, single cell necrosis in the mucosal epithelium, and desquamation of the mucosal epithelium). Thus, the applicant considered that colitis due to stress-induced alterations in intestinal bacterial flora resulted in dehydration and malnutrition associated with loose stools/diarrhoea, thereby causing deteriorated systemic condition. Toxicity findings in surviving animals were loose stools in males and females at ≥1.0 mg/kg/day, increased urine protein in males at 4.0 mg/kg/day, and reduced prothrombin time in females at 4.0 mg/kg/day. The NOAEL was determined to be 0.25 mg/kg/day.

5.3 Carcinogenicity

5.3.1 Mouse mid-term skin carcinogenesis study (CTD 4.2.3.4-2, Study [redacted])

A single application of 7,12-dimethylbenz[a]anthracene (DMBA) was followed 1 week later by 19-week once-daily applications of sirolimus gel in concentrations of 0.2% and 0.8% (at doses of 0.03 and 0.12 mg/kg, respectively), vehicle, or 12-*O*-tetradecanoylphorbol-13-acetate (TPA) 4 μg (positive control) to the back skin of male and female mice. While all animals in the TPA group developed skin tumors, no skin tumors were observed in the sirolimus or vehicle group. Sirolimus gel did not promote skin carcinogenesis in mice.

5.4 Juvenile rat toxicity studies

5.4.1 Juvenile rat 4-week dermal toxicity study (CTD 4.2.3.5.4-1, Study [redacted])

Male and female juvenile rats (22 days of age) were treated dermally with sirolimus gel in concentrations of 0.01%, 0.05%, 0.2%, and 0.8% (at doses of 0.1, 0.5, 2.0, and 8.0 mg/kg/day, respectively) or vehicle twice daily for 4 weeks. Toxicity findings were as follows: increased blood AST and ALT or a trend toward increased blood AST and ALT and alveolar macrophage accumulation in males and females at ≥2.0 mg/kg/day, increases in hematocrit levels and hemoglobin concentration and increased lung weights in females at ≥2.0 mg/kg/day, decreased platelet count and decreased thymic weights in males and females at 8.0 mg/kg/day, increased hematocrit levels and increased macrophages in the thymus in males at 8.0 mg/kg/day, and an increased percentage of neutrophils and a decreased percentage of lymphocytes in females at 8.0 mg/kg/day. The NOAEL was determined to be 0.5 mg/kg/day.

5.4.2 Juvenile hairless rat 7-week dermal toxicity study (CTD 4.2.3.5.4-2, Study [redacted])

Male and female juvenile hairless rats (22 days of age) were treated dermally with sirolimus gel in concentrations of 0.05%, 0.2%, and 0.8% (at doses of 0.5, 2.0, and 8.0 mg/kg/day, respectively) or vehicle twice daily for 7 weeks. Toxicity findings were as follows: increased foamy macrophages in mesenteric lymph nodes, increased extramedullary hematopoiesis in the spleen, and microvacuolization of the adrenal zona glomerulosa in males and females at ≥0.5 mg/kg/day; decreased body weights and increased macrophages in the thymus in males at ≥2.0 mg/kg/day and females at ≥0.5 mg/kg/day; decreased food consumption, increased platelet count, changes in differential white blood cell count (number and percentage), and decreased blood albumin and A/G ratio in males and females at ≥2.0 mg/kg/day, decreased lymphocytes in the cortex of mesenteric lymph nodes in males at ≥2.0 mg/kg/day and females at 8.0 mg/kg/day, increased APTT in females at ≥2.0 mg/kg/day, increased reticulocyte count, decreased blood total protein and other changes in biochemical parameters, and increased foamy macrophages in submandibular lymph nodes in males and females at 8.0 mg/kg/day, and delayed vaginal opening, and decreased lymphocytes and lymphocyte necrosis in the thymic cortex in females at 8.0 mg/kg/day. The NOAELs were determined to be 0.5 mg/kg/day in males and <0.5 mg/kg/day in females.

5.5 Local tolerance

5.5.1 Primary skin irritation study in rabbits (CTD 4.2.3.6-1, Study [redacted])

Following a 24-hour occluded application of sirolimus gel in concentrations of 0.01%, 0.05%, and 0.2% (at doses of 0.05, 0.25, and 1 mg, respectively) or vehicle to the intact and abraded skin of male rabbits, skin

reactions were assessed. Posttreatment observations revealed no evidence of erythema or edema at the application site. Sirolimus gel was found to be non-skin irritant.

5.5.2 Primary eye irritation study in rabbits (CTD 4.2.3.6-2, Study [redacted])

Sirolimus gel in concentrations of 0.01%, 0.05%, and 0.2% (at doses of 0.01, 0.05, and 0.2 mg, respectively) or vehicle was instilled into the left eye of each of male rabbits, and the right eye remained untreated. Slight eye irritation was noted in both the sirolimus and vehicle groups. Because the eye irritation potential of sirolimus and vehicle was similar, the eye irritation noted in the sirolimus groups was considered attributable to vehicle.

5.5.3 Local tolerance study of the final drug product and its degraded product (CTD 4.2.3.6-3, Study [redacted])

Following a 24-hour occluded application of 0.2% sirolimus gel (the final drug product), its degraded product (Degradation Product A, [redacted]%; total related substances excluding Degradation Product A, [redacted]%), or vehicle to the intact or abraded skin of male rabbits, skin reactions were assessed. Posttreatment observations revealed no evidence of erythema or edema at the application site. The final drug product and its degraded product were found to be non-skin irritant.

5.6 Other toxicity studies

5.6.1 *In vitro* phototoxicity study (CTD 4.2.3.7-1, Study [redacted])

An *in vitro* Neutral Red Uptake assay with the Balb/c 3T3 mouse embryonic fibroblast cell line was performed to assess the phototoxicity potential of sirolimus gel. Results showed no differences between cell viability with and without UV (UVA [5 J/cm^2/50 minutes]) irradiation, and sirolimus gel was found not to be phototoxic.

5.6.2 Skin sensitization study in guinea pigs (CTD 4.2.3.7-2, Study [redacted])

The skin sensitization potential of sirolimus gel was assessed in male guinea pigs by the adjuvant and patch test (*Contact Dermatitis*. 1981;7: 225-237). Following injection of Freund's complete adjuvant for first induction and topical application of 0.8% sirolimus gel or vehicle for second induction, the animals were challenged with 0.05%, 0.2%, or 0.8% sirolimus gel or vehicle. No skin reactions were seen in the sirolimus or vehicle group. Sirolimus gel showed no skin sensitizing potential.

5.6.3 Photosensitization studies in guinea pigs (CTD 4.2.3.7-3, 4.2.3.7-4, and 4.2.3.7-7, Studies [redacted], [redacted], and [redacted])

The skin photosensitization potential of sirolimus gel was assessed in male guinea pigs by the adjuvant and strip test (*Nishinihon J Dermatol*. 1980;42: 831-837). Following topical application of 0.8% sirolimus gel or vehicle and UV (UVA [10 J/cm^2]) irradiation as photoinduction exposure, the animals were photochallenged with 0.05% or 0.2% sirolimus gel or vehicle followed by UV (UVA [10 J/cm^2]) irradiation. Erythema was observed at the UVA-irradiated site in animals treated with 0.8% sirolimus gel as induction exposure and challenged with 0.05% or 0.2% sirolimus gel or vehicle. On the other hand, when UVA was not irradiated after the challenge exposure in animals treated with vehicle as induction exposure, erythema was not observed in

any group. When the final drug product was tested under the same condition, similar results were obtained.

The skin photosensitization potential of sirolimus gel was assessed by Kochever method without using adjuvant (*J Invest Dermatol*. 1979;73: 144-146). When animals treated with 0.8% sirolimus gel as induction exposure were challenged with 0.05% or 0.2% sirolimus gel or vehicle, or untreated (UVA irradiation only), erythema was observed at the UVA-irradiated site. In contrast, no abnormalities were observed in any group of animals treated with vehicle as induction exposure.

5.6.4 Prediction of mutagenicity of impurities present in sirolimus gel using *in silico* (Q) SAR analysis (CTD 4.2.3.7-8 [Reference data], Study [redacted])

The mutagenicity of 10 related substances (degradation products and a tautomer of sirolimus that may be present in sirolimus gel; i.e., Related Substance A, Related Substance B1, Related Substance B2, Related Substance C, Related Substance D, Related Substance E, Related Substance F1, Related Substance F2, Degradation Product A, Isomer C) was predicted using *in silico* (Q) SAR analysis ([redacted]). None showed a structural alert. These related substances were considered to be non-mutagenic.

5.R Outline of the review conducted by PMDA

The applicant's explanation about the toxicological profile of sirolimus gel:

Toxicity findings noted in dermal toxicity studies of sirolimus gel were observed also in oral toxicity studies of sirolimus (see the Rapalimus Tablets 1 mg Review Report [May 15, 2014]). No new toxicity findings were observed with dermally applied sirolimus. There were no major differences in the toxicological profile or NOAEL between adult and juvenile rats, and events unique to children are unlikely to occur.

The skin photosensitization study showed erythema occurring following UVA irradiation in guinea pigs that were treated with sirolimus gel as induction exposure, but not challenged with sirolimus gel. This suggest that sirolimus gel may induce photosensitivity-like skin reactions. The mechanism by which photosensitivity occurs even without photoallergen, as in this case, is unknown. Since the possibility that sirolimus gel might induce photosensitivity-like skin reactions in clinical studies could not be ruled out, patients were advised to avoid excessive UV exposure such as direct sunlight in Japanese clinical studies. As a result, no adverse events related to photosensitization or photosensitivity occurred in the Japanese clinical studies. Thus, the package insert should advise that patients should avoid excessive exposure to direct sunlight and other UV light sources when undergoing treatment with sirolimus gel.

PMDA's view:

On the basis of the toxicity data submitted in the present application, new toxicities are unlikely to occur with topical sirolimus. The package insert should advise that patients should avoid excessive exposure to UV radiation from direct sunlight or tanning lamps.

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

Two different formulations (both are ethanol-containing gel formulations, but some of the components of the vehicle are different) were used in clinical studies submitted as evaluation data with the present application. Formulation A (its vehicle contains [redacted]) (sirolimus concentrations of 0.05%-0.2%) was used in a Japanese phase I/II study and Formulation B (its vehicle contains triethanolamine) (sirolimus concentration of 0.2%) was used in Japanese phase III and long-term treatment studies. Formulation B is the proposed commercial formulation.

In clinical studies, whole blood concentrations of unchanged sirolimus were determined by LC/MS/MS, and the LLOQ was 0.1 ng/mL. In an *in vitro* study using human skin, the amount of unchanged sirolimus in the stratum corneum[4)] and the concentrations of unchanged sirolimus in the deeper skin layers and in the receptor fluid were determined by LC/MS/MS, and the LLOQs were 5 ng, 0.01 ng/mg tissue, and 0.05 ng/mL, respectively.

Since the level of a formulation change (Formulation A → Formulation B) fell under Level C according to the "Guideline for Bioequivalence Studies for Formulation Changes of Topical Dermatological Formulations (Semi-solid and Patch Formulations)" (PFSB/ELD Notification No. 1101-1 dated November 1, 2010), an *in vitro* study using human skin and an *in vitro* drug release study were conducted, which demonstrated the bioequivalence of the 2 formulations.

6.2 Clinical pharmacology

6.2.1 *In vitro* study using human biomaterials

6.2.1.1 Skin permeation test (CTD 4.2.2.2-1, Study [redacted])

Following application of 4.4 mg/1.77 cm^2 of 0.2% sirolimus gel (i.e., Formulation A or Formulation B) to the human skin, the skin permeation of sirolimus was investigated for up to 24 hours. The amounts of unchanged sirolimus in the stratum corneum and in the deeper skin layers after a 24-hour application were 2.3% and 0.34%, respectively, of the applied dose, for Formulation A and 2.8% and 0.42%, respectively, of the applied dose, for Formulation B. Unchanged sirolimus that permeated across the skin and reached the receptor fluid was below the LLOQ up to 24 hours after application of either Formulation.

6.2.2 Japanese phase I/II study (CTD 5.3.5.1-1, Study OSD-001-001 [December 2013 to July 2014])

For the summary of the study, see Section 7.1.

4) Since the weight of stratum corneum recovered was very small, unchanged sirolimus was not quantified. Following extraction with methanol for measurement, the total amount of sirolimus contained in the total extract (total amounts of stratum corneum recovered) was determined based on its concentration in methanol extract.

The pharmacokinetics of sirolimus gel were determined in Japanese patients with TSC-associated facial skin lesions (angiofibromas and plaques, erythema or hypomelanotic macules) aged ≥3 and <65 years (target sample size, 36 subjects [n = 12 in the placebo group and n = 8 per sirolimus group).

Placebo or 0.05%, 0.1%, or 0.2% sirolimus gel was applied to the skin lesions twice daily for 12 weeks. The recommended dose was approximately 125 mg of gel per 50 cm^2 of skin lesion, and the maximum daily dose was approximately 375 mg of gel.

As to pharmacokinetics, whole blood concentrations of unchanged sirolimus in patients treated with sirolimus gel are shown in Table 8.

Table 8. Whole blood concentrations of unchanged sirolimus (ng/mL)

Sirolimus concentration (%)	n	Day 1 (1 hour post-dose)	Week 2 (Trough value)	Week 4 (Trough value)	Week 8 (Trough value)	Week 12 (Trough value)	Week 12 (1 hour post-dose)
0.05	8	NC	NC	NC	NC	0.1 [a)]	NC
0.1	8	NC	0.1 [a)]	NC	0.1 [a)]	0.1 [d)]	0.2 [c)]
0.2	8	NC	0.2 [b)]	0.2 [c)]	0.2 [e)]	0.2 [e)]	0.2 [e)]

Mean
NC: not calculated because of concentrations below the LLOQ for all samples.
a) Value for 1 subject, b) Mean of 2 subjects, c) Mean of 4 subjects, d) Mean of 3 subjects, e) Mean of 6 subjects

6.2.3 Japanese phase III study (CTD 5.3.5.1-2, Study NPC-12G-1 [December 2015 to October 2016])

For the summary of the study, see Section 7.2.

The pharmacokinetics of sirolimus gel were determined in Japanese patients with TSC-associated angiofibromas aged ≥3 years (Table 18) (target sample size, 60 subjects [30 per group]).

An appropriate amount of placebo or 0.2% sirolimus gel was applied to the skin lesions twice daily for 12 weeks. The recommended dose was 125 mg of gel per 50 cm^2 of skin lesion, and the maximum daily dose depended on age (≤5 years, 400 mg; 6-11 years, 600 mg; ≥12 years, 800 mg).

As to pharmacokinetics, whole blood concentrations of unchanged sirolimus are shown in Table 9.

Table 9. Whole blood concentrations of unchanged sirolimus (ng/mL)

		Baseline	Week 4	Week 12
Overall	No. of subjects with detectable levels/No. of subjects with measurements	0/30	27/30	21/30
	Median [Min., Max.]	—	0.2 [0.1, 0.4]	0.2 [0.1, 0.5]
Adults	No. of subjects with detectable levels/No. of subjects with measurements	0/17	15/17	11/17
	Median [Min., Max.]	—	0.2 [0.1, 0.4]	0.3 [0.1, 0.5]
Children	No. of subjects with detectable levels/No. of subjects with measurements	0/13	12/13	10/13
	Median [Min., Max.]	—	0.2 [0.1, 0.3]	0.2 [0.1, 0.4]

6.2.4 Japanese long-term treatment study (CTD 5.3.5.2-1, Study NPC-12G-2 [February 2016 to November 2017 (planned to be continued until the date of approval)])

For the summary of the study, see Section 7.3.

The pharmacokinetics of sirolimus gel were determined in patients who completed the Japanese phase III study and patients with TSC-associated skin lesions (angiofibromas, cephalic plaques, or facial hypomelanotic macules) aged ≥3 years (Table 23) (target sample size, ≥80 subjects).

An appropriate amount of 0.2% sirolimus gel was applied to the skin lesions twice daily for 52 weeks. The recommended dose was 125 mg of gel per 50 cm^2 of skin lesion, and the maximum daily dose depended on age (≤5 years, 400 mg; 6-11 years, 600 mg; ≥12 years, 800 mg).

As to pharmacokinetics, whole blood concentrations of unchanged sirolimus are shown in Table 10. All of 8 patients with detectable unchanged sirolimus levels at baseline were new patients treated with sirolimus gel.

Table 10. Whole blood concentrations of unchanged sirolimus (ng/mL)

		Baseline[a)]	Week 12	Week 26	Week 39	Week 52
Overall	No. of subjects with detectable levels/No. of subjects with measurements	8/93	68/88	63/87	60/88	46/87
	Median [Min., Max.]	0.5 [0.2, 1.2]	0.2 [0.1, 3.3]	0.2 [0.1, 1.8]	0.2 [0.1, 1.8]	0.2 [0.1, 0.7]
Adults	No. of subjects with detectable levels/No. of subjects with measurements	2/43	31/40	28/38	25/39	17/38
	Median [Min., Max.]	0.6 [0.3, 1.0]	0.2 [0.1, 3.3]	0.2 [0.1, 1.2]	0.2 [0.1, 0.9]	0.2 [0.1, 0.7]
Children	No. of subjects with detectable levels/No. of subjects with measurements	6/50	37/48	35/49	35/49	29/49
	Median [Min., Max.]	0.5 [0.2, 1.2]	0.2 [0.1, 1.3]	0.2 [0.1, 1.8]	0.2 [0.1, 1.8]	0.2 [0.1, 0.6]

a) Patients who completed the Japanese phase III study and new patients treated with sirolimus gel all had their unchanged sirolimus levels measured at baseline of the Japanese long-term treatment study.

6.R Outline of the review conducted by PMDA

The applicant's explanation about the pharmacokinetics of dermally applied sirolimus gel:

In the Japanese phase I/II study in Japanese patients with TSC-associated skin lesions, there was no trend toward increasing whole blood concentration of unchanged sirolimus over time after Week 2 in any of the 0.05%, 0.1%, and 0.2% sirolimus groups. In the Japanese phase III study, whole blood concentrations of unchanged sirolimus at Weeks 4 were similar to those at Week 12 in the 0.2% sirolimus group. Also in the Japanese long-term treatment study, there was no trend toward increasing whole blood concentration of unchanged sirolimus with prolonged treatment. There was no trend toward differences in whole blood concentrations of unchanged sirolimus after topical application of sirolimus gel between adult and pediatric patients.

When "Rapalimus Tablets 1 mg" which contains the same active ingredient as that of sirolimus gel is orally administered to patients with lymphangioleiomyomatosis, their sirolimus trough concentrations in whole blood are to be measured as needed and the dose is to be adjusted to achieve a blood sirolimus level between 5 and 15 ng/mL (see the Rapalimus Tablets 1 mg Review Report [May 15, 2014]). Whole blood concentrations of unchanged sirolimus after dermal application of sirolimus gel in Japanese patients with TSC-associated skin lesions are very low compared with the therapeutic concentration range of "Rapalimus Tablets 1 mg." At

present, therefore, there is no need to mandate the monitoring of blood sirolimus concentrations for the use of sirolimus gel.

The data from the Japanese long-term treatment study were used to assess potential drug interactions between sirolimus gel and other dermal drug products, which may affect the percutaneous absorption of sirolimus gel. In the Japanese long-term treatment study, 73% (69 of 94) of patients used concomitant topical drugs on their face or head, and the concomitant topical drugs used were corticosteroids (35% [33 patients]), white petrolatum (34% [32 patients]), heparinoid (29% [27 patients]), antibiotics and similar drugs (27% [25 patients]), and other medications (28% [26 patients]). Whole blood concentrations of unchanged sirolimus in patients receiving sirolimus gel with or without these drugs were assessed. Results showed that concomitant use of these drugs had no effects on whole blood concentrations of unchanged sirolimus. Thus, these topical drugs are unlikely to affect the percutaneous absorption of sirolimus gel.

An assessment was made on drug interactions with sirolimus absorbed into the circulation after topical application of sirolimus gel. Whole blood concentrations of unchanged sirolimus after topical application of sirolimus gel were well below the levels at which drug interactions may occur. At present, there is no need for the sirolimus gel package insert to provide precautions about concomitant use with drugs that are listed in the "Precautions for Concomitant Use" section of the "Rapalimus Tablets 1 mg" package insert.

PMDA's view:
At present, there is no need to mandate the monitoring of blood sirolimus concentrations for the use of sirolimus gel, and there is no need for the sirolimus gel package insert to provide precautions about concomitant use with drugs that are listed in the "Precautions for Concomitant Use" section of the "Rapalimus Tablets 1 mg" package insert [for the safety and efficacy of sirolimus gel in combination with other mTOR inhibitors, see Section 7.R.6].

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

The applicant submitted evaluation data, in the form of the results from Japanese phase I/II, phase III, and long-term treatment studies in patients with TSC (Table 11).

Table 11. Overview of efficacy and safety evaluation data

Phase	Study Identifier	Study population	Study design	Duration of treatment	Group (No. of subjects treated)	Primary efficacy endpoint
I/II	OSD-001-001 (Investigator-initiated clinical study)	Patients with TSC-associated facial skin lesions (angiofibromas and plaques, erythema or hypomelanotic macules)	Double-blind, parallel group	12 weeks	Placebo: 12 (6 adults and 6 children) 0.05% sirolimus: 8 (4 adults and 4 children) 0.1% sirolimus: 8 (4 adults and 4 children) 0.2% sirolimus: 8 (4 adults and 4 children)	Composite variable (the sum of improvement scores for tumor volume and redness of 3 target tumors) at Week 12
III	NPC-12G-1	Patients with TSC-associated angiofibromas	Double-blind, parallel group	12 weeks	Placebo: 32 (18 adults, 14 children) 0.2% sirolimus: 30 (17 adults, 13 children)	Improvement in angiofibromas at Week 12 based on centralized photographic assessment
III	NPC-12G-2	Patients with TSC-associated angiofibromas, cephalic plaques, or facial hypomelanotic macules	Open-label, uncontrolled	52 weeks	0.2% sirolimus: 94 (44 adults, 50 children) 62 patients who completed phase III study 32 new patients treated with sirolimus gel	Improvement in angiofibromas at different time points based on centralized photographic assessment

7.1 Japanese phase I/II study (CTD 5.3.5.1-1, Study OSD-001-001 [December 2013 to July 2014])

A single-center, randomized, double-blind, parallel-group study was conducted at 1 site in Japan to evaluate the efficacy and safety of sirolimus gel in patients with TSC-associated facial skin lesions (angiofibromas and plaques, erythema or hypomelanotic macules) aged ≥3 and <65 years (Table 12) (target sample size, 36 subjects [n = 12 [6 adults and 6 children] in the placebo group, n = 8 [4 adults and 4 children] per sirolimus group]).

Table 12. Key inclusion criteria

· Patients with a definite diagnosis of TSC according to the diagnostic criteria specified in the TSC treatment guideline 2008 · Patients with ≥3 solitary angiofibroma papules (that were ≥2 mm in their longest diameters and had a redness score of ≥2[a]) on the face

a) A score of 2 indicates PANTONE COLOR BRIDGE Coated 486C or a lighter color.

An appropriate amount of placebo or 0.05%, 0.1%, or 0.2% sirolimus gel was applied to the skin lesions twice daily for 12 weeks. The recommended dose was 125 mg of gel per 50 cm^2 of skin lesion, and the maximum daily dose was 375 mg of gel.

The distribution of "a composite variable (the sum of the improvement scores for volume and redness of the 3 target tumors) at Week 12 (Table 13)" as the primary efficacy endpoint is shown in Table 14. Compared with the placebo group, all sirolimus groups showed statistically significant improvement ([Table 15] 0.05% sirolimus group, $P = 0.011$; 0.1% sirolimus group, $P = 0.028$; 0.2% sirolimus group, $P < 0.001$; Shirley-Williams test for multiplicity adjustment, one-sided significance level of 5%).

Table 13. Definition of composite variable (the sum of improvement scores for volume and redness of 3 targeted tumors)

Targeted tumors	**Among solitary red papules that were ≥2 mm in their longest diameters, the 3 largest separate papules were selected.**
Improvement score for volume of 3 target tumors	**Change in the summed volumes of 3 target tumors after application was scored on a 5-point scale.** **Tumor volume = long diameter × short diameter × short diameter/2** **Percent change in summed tumor volumes (%) = (1 − summed volumes of 3 target tumors at Week 12/summed volumes of 3 target tumors at baseline) × 100** **−1.0: Worsening (a ≥20% increase)** **0: No change (a <20% reduction or increase)** **0.5: Slight improvement (a 20%-50% reduction)** **1.0: Moderate improvement (a 50%-80% reduction)** **2.0: Marked improvement (a ≥80% reduction)**
Improvement score for redness of 3 target tumors	**Redness of each tumor was scored from 1 to 6 points (redness score), and change in the summed scores for redness of 3 target tumors (lessening of the redness of 3 target tumors) after application was scored on a 5-point scale.** **−1.0: Worsening (a change of −12 to −3)** **0: No change (a change of −2 to 2)** **0.5: Slight improvement (a change of 3 to 5)** **1.0: Moderate improvement (a change of 6 to 8)** **2.0: Marked improvement (a change of ≥9)**
Composite variable	**Improvement score for volume of 3 target tumors + Improvement score for redness of 3 target tumors**

Table 14. Distribution of composite variable at Week 12 (FAS)

Treatment group	Composite variable value												
	−2	−1.5	−1	−0.5	0	0.5	1	1.5	2	2.5	3	3.5	4
Placebo (N = 12)	1	0	3	0	2	2	1	2	0	1	0	0	0
0.05% sirolimus (N = 8)	0	0	0	0	0	1	3	1	1	0	2	0	0
0.1% sirolimus (N = 8)	0	0	0	0	1	1	3	2	1	0	0	0	0
0.2% sirolimus (N = 8)	0	0	0	0	0	0	0	5	1	0	2	0	0

Table 15. Composite variable at Week 12 (FAS)

	Critical value	Z	*P*-value[a)]
Placebo (N = 12)	—	—	—
0.05% sirolimus (N = 8)	1.645	2.297	0.011
0.1% sirolimus (N = 8)	1.716	1.968	0.028
0.2% sirolimus (N = 8)	1.739	3.343	< 0.001

a) Shirley-Williams test (stepping down sequentially from a comparison between the highest dose and control groups), one-sided significance level of 5%

Safety analysis showed that the incidences of adverse events were 58.3% (7 of 12 subjects) in the placebo group, 75.0% (6 of 8 subjects) in the 0.05% sirolimus group, 87.5% (7 of 8 subjects) in the 0.1% sirolimus group, and 87.5% (7 of 8 subjects) in the 0.2% sirolimus group, and that the incidences of adverse drug reactions were 25.0% (3 of 12 subjects) in the placebo group, 37.5% (3 of 8 subjects) in the 0.05% sirolimus group, 50.0% (4 of 8 subjects) in the 0.1% sirolimus group, and 87.5% (7 of 8 subjects) in the 0.2% sirolimus group. Adverse events and adverse drug reactions reported by ≥2 subjects in any group are shown in Table 16 and Table 17, respectively.

Table 16. Adverse events reported by ≥2 subjects in any group

	Placebo (N = 12)	0.05% sirolimus (N = 8)	0.1% sirolimus (N = 8)	0.2% sirolimus (N = 8)
Any adverse event	58.3 (7)	75.0 (6)	87.5 (7)	87.5 (7)
Dry skin	8.3 (1)	37.5 (3)	37.5 (3)	50.0 (4)
Dermatitis acneiform	0 (0)	0 (0)	0 (0)	37.5 (3)
Nasopharyngitis	16.7 (2)	37.5 (3)	25.0 (2)	12.5 (1)
Application site irritation	16.7 (2)	12.5 (1)	12.5 (1)	0 (0)

MedDRA/J ver.19.0, Incidence % (n)

Table 17. Adverse drug reactions reported by ≥2 subjects in any group

	Placebo (N = 12)	0.05% sirolimus (N = 8)	0.1% sirolimus (N = 8)	0.2% sirolimus (N = 8)
Any adverse drug reaction	**25.0 (3)**	**37.5 (3)**	**50.0 (4)**	**87.5 (7)**
Dry skin	**8.3 (1)**	**37.5 (3)**	**37.5 (3)**	**50.0 (4)**
Dermatitis acneiform	**0 (0)**	**0 (0)**	**0 (0)**	**25.0 (2)**
Application site irritation	**16.7 (2)**	**12.5 (1)**	**12.5 (1)**	**0 (0)**

MedDRA/J ver.19.0, Incidence % (n)

There were no deaths or adverse events leading to treatment discontinuation in any group. Epilepsy in 1 subject in the placebo group and pneumothorax in 1 subject in the 0.2% sirolimus group were reported as serious adverse events, but their causal relationship to study drug was ruled out and both events resolved.

7.2 Japanese phase III study (CTD 5.3.5.1-2, Study NPC-12G-1 [December 2015 to October 2016])

A multicenter, randomized, double-blind, parallel-group study was conducted at 9 sites in Japan to evaluate the efficacy and safety of sirolimus gel in patients with TSC-associated angiofibromas aged ≥3 years (Table 18) (target sample size, 60 subjects [30 per group]).

Table 18. Key inclusion criteria

- **Patients with a definite diagnosis of TSC according to the diagnostic criteria for TSC (updated in the 2012 International Tuberous Sclerosis Complex Consensus Conference)**
- **Patients with ≥3 angiofibroma papules (which were ≥2 mm in their longest diameters and red) on the face**

An appropriate amount of 0.2% sirolimus gel or placebo was applied to the skin lesions twice daily for 12 weeks. The recommended dose was 125 mg of gel per 50 cm^2 of skin lesion, and the maximum daily dose depended on age (≤5 years, 400 mg; 6-11 years, 600 mg; ≥12 years, 800 mg). For patients who deviated substantially from the normal body size (body surface area) for their age group, the maximum daily dose depended on body surface area (<0.8 m^2 of body surface area, 400 mg; ≥0.8 m^2 and <1.3 m^2 of body surface area, 600 mg; ≥1.3 m^2 of body surface area, 800 mg).

All of 62 randomized subjects (32 in the placebo group [18 adults and 14 children], 30 in the sirolimus group [17 adults and 13 children]) received study drug. All the subjects were included in the FAS and in the Safety Set. The FAS was used for the primary efficacy analysis. There were no withdrawals in either group.

The primary efficacy endpoint for the study was the improvement in angiofibromas at Week 12 based on centralized photographic assessment (Table 19). The results of the primary efficacy endpoint are shown in Table 20. The sirolimus group showed statistically significant improvement, compared with the placebo group ($P < 0.001$, Wilcoxon rank sum test, two-sided significance level of 5%).

Table 19. Assessment criteria for improvement in angiofibromas

Improvement is assessed based on tumor size and redness using a 6-point scale.	
Marked improvement	**Tumor size reduction, tumor flattening, or tumor disappearance in approximately ≥75% of baseline lesion area. A substantial reduction in redness[a)] or a return to almost normal skin color in approximately 50% to 75% of baseline lesion area.**
Improvement	**Tumor size reduction or tumor flattening, and a reduction in redness[b)] in approximately 50% to 75% of baseline lesion area. Or, tumor disappearance and a substantial reduction in redness[a)] in approximately 25% to 50% of baseline lesion area.**
Slight improvement	**Tumor size reduction or tumor flattening, and a reduction in redness[b)] in approximately 25% to 50% of baseline lesion area. Or, a slight reduction in redness[c)] in approximately 50% to 75% of baseline lesion area.**
No change	**No apparent changes in tumor status or redness.**
Slight worsening	**Tumor growth or new tumor, and an increase in redness[b)] in approximately 25% to 50% of baseline lesion area. Or, a slight increase in redness[c)] in approximately 50% to 75% of baseline lesion area.**
Worsening	**Tumor growth or new tumor in approximately 50% to 75% of baseline lesion area, or substantial tumor growth and an increase in redness[b)] in approximately 25% to 50% of baseline lesion area. Or, further worsening.**

a) A substantial reduction in redness: a ≥3-stage change in redness based on PANTONE color cards.
b) A reduction/increase in redness: a 2-stage change in redness based on PANTONE color cards.
c) A slight reduction/increase in redness: a 1-stage change in redness based on PANTONE color cards.

Table 20. Improvement in angiofibromas at Week 12 based on centralized photographic assessment (FAS)

Treatment group	Marked improvement	Improvement	Slight improvement	No change	Slight worsening	Worsening	Unassessable	*P*-value[a)]
Placebo (N = 32)	**0 (0)**	**0 (0)**	**15.6 (5)**	**81.3 (26)**	**0 (0)**	**0 (0)**	**3.1 (1)**	**< 0.001**
0.2% sirolimus (N = 30)	**16.7 (5)**	**43.3 (13)**	**36.7 (11)**	**3.3 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	

Proportion % (n)
a) Wilcoxon rank sum test, two-sided significance level of 5%

Safety analysis showed that the incidences of adverse events were 68.8% (22 of 32 subjects) in the placebo group and 90.0% (27 of 30 subjects) in the sirolimus group, and that the incidences of adverse drug reactions were 46.9% (15 of 32 subjects) in the placebo group and 73.3% (22 of 30 subjects) in the sirolimus group. Adverse events and adverse drug reactions reported by ≥2 subjects in either group are shown in Table 21 and Table 22, respectively.

Table 21. Adverse events reported by ≥2 subjects in either group

	Placebo (N = 32)	0.2% sirolimus (N = 30)
Any adverse event	**68.8 (22)**	**90.0 (27)**
Application site irritation	**28.1 (9)**	**36.7 (11)**
Dry skin	**12.5 (4)**	**36.7 (11)**
Pruritus	**12.5 (4)**	**23.3 (7)**
Influenza	**0 (0)**	**10.0 (3)**
Acne	**0 (0)**	**6.7 (2)**
Nasopharyngitis	**9.4 (3)**	**3.3 (1)**
Eye irritation	**6.3 (2)**	**3.3 (1)**
Stomatitis	**6.3 (2)**	**3.3 (1)**
Upper respiratory tract inflammation	**6.3 (2)**	**0 (0)**
Skin abrasion	**6.3 (2)**	**0 (0)**

MedDRA/J ver.19.0, Incidence % (n)

Table 22. Adverse drug reactions reported by ≥2 subjects in either group

	Placebo (N = 32)	0.2% sirolimus (N = 30)
Any adverse drug reaction	46.9 (15)	73.3 (22)
Application site irritation	28.1 (9)	36.7 (11)
Dry skin	12.5 (4)	36.7 (11)
Pruritus	12.5 (4)	16.7 (5)
Acne	0 (0)	6.7 (2)
Eye irritation	6.3 (2)	3.3 (1)

MedDRA/J ver.19.0, Incidence % (n)

There were no deaths or adverse events leading to treatment discontinuation in either group. No serious adverse events occurred in the placebo group. Acute pancreatitis and gastric haemorrhage were reported by 1 subject in the sirolimus group as serious adverse events. A causal relationship to sirolimus was ruled out for gastric haemorrhage, but acute pancreatitis was classified as an adverse drug reaction. Both events resolved.

7.3 Japanese long-term treatment study (CTD 5.3.5.2-1, Study NPC-12G-2 [February 2016 to November 2017 (planned to be continued until the date of approval)])

A multicenter, open-label, uncontrolled study was conducted at 10 sites in Japan to evaluate the efficacy and safety of sirolimus gel in patients who completed the Japanese phase III study and patients with TSC-associated skin lesions (angiofibromas, cephalic plaques, or facial hypomelanotic macules) aged ≥3 years (Table 23) (target sample size, ≥80 subjects).

Table 23. Key inclusion/exclusion criteria

Key inclusion criteria
· Patients with a definite diagnosis of TSC according to the diagnostic criteria for TSC (updated in the 2012 International Tuberous Sclerosis Complex Consensus Conference)
· Patients with TSC-associated angiofibromas, hypomelanotic macules, or plaques on the face
· Patients deemed eligible for use or continued use of sirolimus gel by the investigator etc.
Key exclusion criteria
· Patients who were withdrawn from the Japanese phase III study due to their request (consent withdrawal)

An appropriate amount of 0.2% sirolimus gel was applied to the skin lesions twice daily for 52 weeks. The recommended dose was 125 mg of gel per 50 cm^2 of skin lesion, and the maximum daily dose depended on age (≤5 years, 400 mg; 6-11 years, 600 mg; ≥12 years, 800 mg). For patients who deviated substantially from the normal body size (body surface area) for their age group, the maximum daily dose depended on body surface area (<0.8 m^2 of body surface area, 400 mg; ≥0.8 m^2 and <1.3 m^2 of body surface area, 600 mg; ≥1.3 m^2 of body surface area, 800 mg). If dosage adjustment was considered necessary by the investigator etc. because of the occurrence of an adverse event, the frequency of application was allowed to be reduced to once daily (at bedtime). After that, dosage adjustment (e.g., increasing the frequency of application to twice daily) was permitted at the discretion of the investigator etc.

All of 94 subjects enrolled in the study (62 patients who completed the phase III study [32 patients receiving placebo and 30 patients receiving sirolimus in the previous study], 32 new patients to be treated with sirolimus gel) received study drug. All the subjects were included in the Safety Set. A total of 92 patients were included in the FAS because 2 patients with no efficacy data after the start of treatment were excluded from the analysis. The FAS was used for the primary efficacy analysis. There were 5 withdrawals, and the reasons

for withdrawals were patient's (or his/her legally acceptable representative's) request for withdrawal from the study (4 patients) and adverse event (1 patient).

Efficacy analysis was performed. Table 24 shows the results of "improvement in angiofibromas at Week 52 based on centralized photographic assessment (Table 19)." The size and redness of angiofibromas at baseline were measured before the start of treatment with sirolimus gel in the long-term treatment study for both patients who completed the phase III study and new patients to be treated with sirolimus gel.

Table 24. Improvement in angiofibromas at Week 52 based on centralized photographic assessment (FAS)

Treatment group		Marked improvement	Improvement	Slight improvement	No change	Slight worsening	Worsening	Unassessable
Overall (N = 65)		20.0 (13)	55.4 (36)	23.1 (15)	1.5 (1)	0 (0)	0 (0)	0 (0)
New patients treated with sirolimus gel (N = 24)		20.8 (5)	54.2 (13)	25.0 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Patients who completed Japanese phase III study (N = 41)[a)]	Those on placebo in phase III study (N = 21)	33.3 (7)	52.4 (11)	14.3 (3)	0 (0)	0 (0)	0 (0)	0 (0)
	Those on 0.2% sirolimus in phase III study (N = 20)	5.0 (1)	60.0 (12)	30.0 (6)	5.0 (1)	0 (0)	0 (0)	0 (0)

Proportion % (n)

Safety analysis showed that the incidence of adverse events was 96.8% (91 of 94 subjects), and that the incidence of adverse drug reactions was 72.3% (68 of 94 subjects). Adverse events and adverse drug reactions reported by ≥5.0% of all subjects are shown in Table 25 and Table 26, respectively.

Table 25. Adverse events reported by ≥5.0% of all subjects

	New patients treated with sirolimus gel (N = 32)	Patients who completed phase III study (N = 62)		Overall (N = 94)
		Those on placebo in phase III study (N = 32)	Those on 0.2% sirolimus in phase III study (N = 30)	
Any adverse event	100 (32)	96.9 (31)	93.3 (28)	96.8 (91)
Nasopharyngitis	43.8 (14)	40.6 (13)	43.3 (13)	42.6 (40)
Dry skin	28.1 (9)	37.5 (12)	26.7 (8)	30.9 (29)
Application site irritation	31.3 (10)	34.4 (11)	20.0 (6)	28.7 (27)
Acne	15.6 (5)	21.9 (7)	33.3 (10)	23.4 (22)
Influenza	15.6 (5)	3.1 (1)	16.7 (5)	11.7 (11)
Dermatitis contact	12.5 (4)	18.8 (6)	3.3 (1)	11.7 (11)
Eczema	12.5 (4)	15.6 (5)	6.7 (2)	11.7 (11)
Stomatitis	9.4 (3)	0 (0)	23.3 (7)	10.6 (10)
Pruritus	3.1 (1)	15.6 (5)	10.0 (3)	9.6 (9)
Erythema	3.1 (1)	15.6 (5)	10.0 (3)	9.6 (9)
Folliculitis	6.3 (2)	12.5 (4)	6.7 (2)	8.5 (8)
Dermatitis acneiform	9.4 (3)	9.4 (3)	6.7 (2)	8.5 (8)
Skin abrasion	3.1 (1)	9.4 (3)	10.0 (3)	7.4 (7)
Eye irritation	9.4 (3)	6.3 (2)	6.7 (2)	7.4 (7)
Urticaria	12.5 (4)	6.3 (2)	0 (0)	6.4 (6)
Angular cheilitis	6.3 (2)	12.5 (4)	0 (0)	6.4 (6)
Gastroenteritis	9.4 (3)	6.3 (2)	3.3 (1)	6.4 (6)
Arthropod sting	9.4 (3)	3.1 (1)	3.3 (1)	5.3 (5)
Pyrexia	9.4 (3)	3.1 (1)	3.3 (1)	5.3 (5)
Epilepsy	3.1 (1)	9.4 (3)	3.3 (1)	5.3 (5)
Upper respiratory tract inflammation	3.1 (1)	6.3 (2)	6.7 (2)	5.3 (5)

MedDRA/J ver.20.1, Incidence % (n)

Table 26. Adverse drug reactions reported by ≥5.0% of all subjects

	New patients treated with sirolimus gel (N = 32)	Patients who completed phase III study (N = 62)		Overall (N = 94)
		Those on placebo in phase III study (N = 32)	Those on 0.2% sirolimus in phase III study (N = 30)	
Any adverse drug reaction	71.9 (23)	75.0 (24)	70.0 (21)	72.3 (68)
Application site irritation	31.3 (10)	34.4 (11)	20.0 (6)	28.7 (27)
Dry skin	25.0 (8)	25.0 (8)	26.7 (8)	25.5 (24)
Acne	6.3 (2)	12.5 (4)	20.0 (6)	12.8 (12)
Pruritus	3.1 (1)	12.5 (4)	10.0 (3)	8.5 (8)
Eye irritation	9.4 (3)	6.3 (2)	6.7 (2)	7.4 (7)
Dermatitis acneiform	9.4 (3)	6.3 (2)	3.3 (1)	6.4 (6)
Erythema	3.1 (1)	12.5 (4)	3.3 (1)	6.4 (6)
Dermatitis contact	9.4 (3)	3.1 (1)	3.3 (1)	5.3 (5)

MedDRA/J ver.20.1, Incidence % (n)

There were no deaths. The incidence of serious adverse events was 7.4% (7 of 94 subjects) (corpus callosotomy and incorrect route of drug administration, corpus callosotomy, pneumothorax, therapeutic embolisation, pneumonia mycoplasmal, seizure, and brain oedema [1 subject each]). A causal relationship to sirolimus gel was ruled out for all those events. The incidence of adverse events leading to treatment discontinuation was 2.1% (2 of 94 subjects) (eye irritation and erythema, and dermatitis contact [1 subject each]). All of those events were classified as adverse drug reactions and resolved.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA's view:

The following considerations and confirmations presented in Section 7.R.1.1 to 7.R.1.5 support the efficacy of sirolimus gel in the treatment of TSC-associated skin lesions.

A final decision on the efficacy of sirolimus gel will be made, taking account of comments from the Expert Discussion.

7.R.1.1 Primary endpoint

The applicant's explanation about the rationale for the selection of the primary endpoint for the Japanese phase III study:

In addition to a reduction in the size of angiofibroma, a lessening of the redness of tumors was assessed in the Japanese phase I/II study because the degree of redness is an indicator of the degree of vasodilation or angiogenesis, and intense redness decreases the patient's QOL. Thus, a composite variable that includes tumor volume and redness was considered appropriate. The sum of the improvement scores for volume and redness of the 3 target tumors was chosen as the primary endpoint. Prior to the Japanese phase I/II study, clinical research studies were conducted in which topical 0.2% sirolimus[5)] was applied to TSC patients twice daily for 12 weeks. As a result, changes in the redness of angiofibromas, reductions in papule size, and others were observed after 12 weeks of treatment (*Br J Dermatol*. 2011;165: 912-916, *Br J Dermatol*. 2013;169: 1314-1318). Therefore, Week 12 was selected as the timing of the primary endpoint. The primary endpoint for the Japanese phase I/II study was a composite variable (the sum of the improvement scores for volume and redness of the 3 target tumors) at Week 12. Its results are shown in Table 14. All sirolimus groups showed statistically significant improvement, compared with the placebo group (0.05% sirolimus group, $P = 0.011$; 0.1% sirolimus group, $P = 0.028$; 0.2% sirolimus group, $P < 0.001$; Shirley-Williams test, one-sided significance level of 5%).

Since tumor size reduction and a lessening of the redness of tumors were considered clinically important for the evaluation of angiofibromas also in the Japanese phase III study, the evaluation method was reviewed, taking also account of the results of the Japanese phase I/II study. Because angiofibromas present as a variety of symptoms, there are no established criteria for its severity or clinical evaluation. In order to prevent inter-rater variability and objectively evaluate a variety of symptoms wherever possible in a multicenter clinical study, certain assessment criteria based on tumor size and redness should be developed and then the images (photographs) of tumors should be assessed centrally. Thus, the improvement in angiofibromas at Week 12 based on centralized photographic assessment (Table 19) was chosen as the primary endpoint for the Japanese phase III study. The results of the primary endpoint are shown in Table 20. The sirolimus group showed statistically significant improvement, compared with the placebo group ($P < 0.001$, Wilcoxon rank sum test, two-sided significance level of 5%).

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5) A gel or ointment formulation was prepared from crushed sirolimus tablets (Rapamune, not marketed in Japan). The maximum possible concentration of sirolimus in the formulation was 0.2% because of the effect of excipients or other reasons.

PMDA's view:

There is no particular problem with the applicant's explanation about the selection of the patient population and the primary endpoint for the Japanese phase III study. The Japanese phase III study showed a significant difference between sirolimus and placebo in the primary endpoint (improvement in angiofibromas at Week 12 based on centralized photographic assessment [Table 20]), demonstrating the efficacy of sirolimus gel.

7.R.1.2 Secondary endpoints

A secondary endpoint for the Japanese phase III study was "the improvement rate for angiofibromas (the proportion of patients with improvement or marked improvement) at Week 12 based on centralized photographic assessment (FAS)." The results of the secondary endpoint were 0% (0 of 32 subjects) in the placebo group and 60.0% (18 of 30 subjects) in the sirolimus group, showing a higher improvement rate in the sirolimus group than in the placebo group.

Table 27 shows "investigator-assessed improvement in angiofibromas at Week 12" in the Japanese phase III study. Also when assessed by the investigator etc., there was a trend toward improvement with sirolimus gel compared with placebo.

Table 27. Investigator-assessed improvement in angiofibromas at Week 12 (FAS)

Treatment group	Marked improvement	Improvement	Slight improvement	No change	Slight worsening	Worsening	
Placebo (N = 32)	3.1 (1)	3.1 (1)	25.0 (8)	68.8 (22)	0 (0)	0 (0)	
0.2% sirolimus (N = 30)	10.0 (3)	13.3 (4)	46.7 (14)	30.0 (9)	0 (0)	0 (0)	

Proportion % (n)

Table 28 shows improvements in the size and redness of angiofibromas at Week 12, based on centralized photographic assessment, in the Japanese phase III study. There was a trend toward improvements in the size and redness of angiofibromas with sirolimus gel compared with placebo.

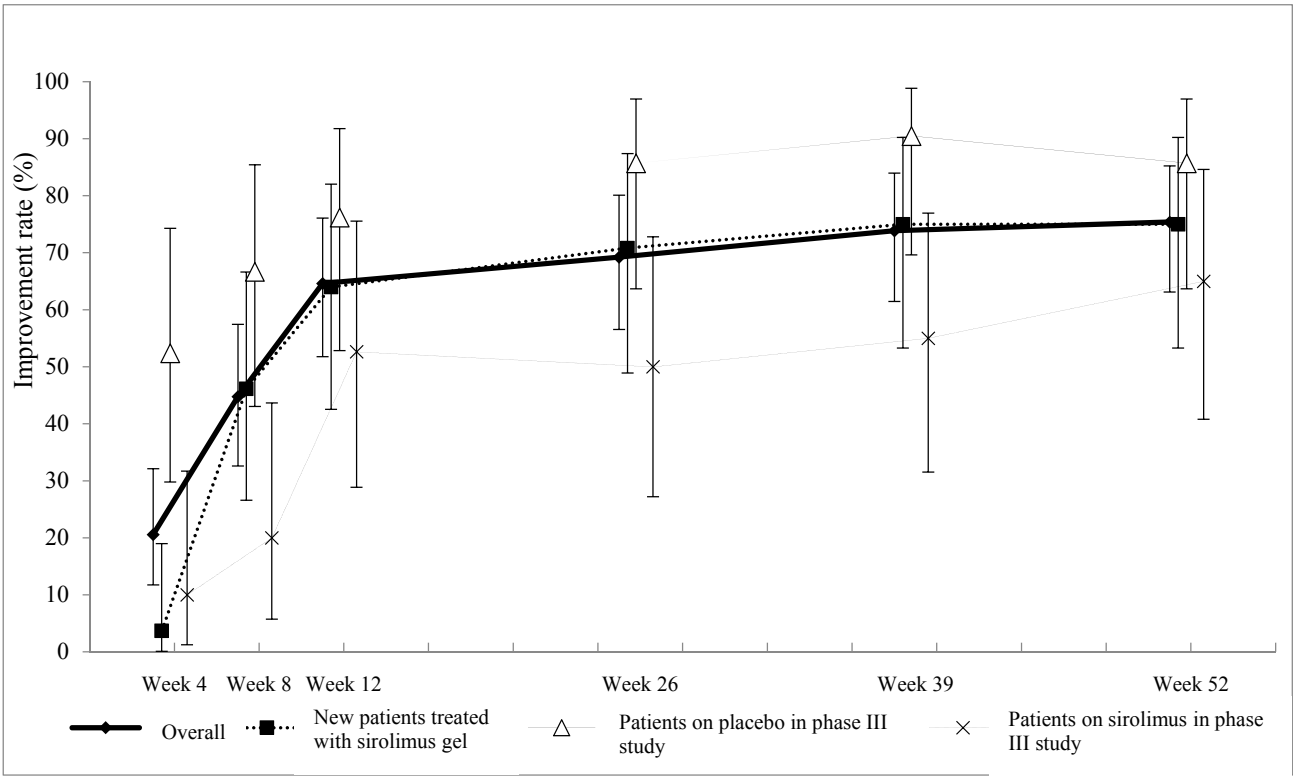
Table 28. Improvements in size and redness of angiofibromas at Week 12 based on centralized photographic assessment (FAS)

	Treatment group	Marked improvement	Improvement	Slight improvement	No change	Slight worsening	Worsening	Unassessable
Tumor size	Placebo (N = 32)	0 (0)	3.1 (1)	6.3 (2)	87.5 (28)	0 (0)	0 (0)	3.1 (1)
	0.2% sirolimus (N = 30)	16.7 (5)	43.3 (13)	33.3 (10)	6.7 (2)	0 (0)	0 (0)	0 (0)
Tumor redness	Placebo (N = 32)	0 (0)	0 (0)	9.4 (3)	87.5 (28)	0 (0)	0 (0)	3.1 (1)
	0.2% sirolimus (N = 30)	6.7 (2)	33.3 (10)	40.0 (12)	20.0 (6)	0 (0)	0 (0)	0 (0)

Proportion % (n)

7.R.1.3 Long-term efficacy

Figure 1 shows the improvement rate for angiofibromas (the proportion of patients with "improvement" or "marked improvement") over time, based on centralized photographic assessment, in the long-term treatment study. The results demonstrated that a treatment effect is maintained after Week 12.



Time point (Week)	4	8	12	26	39	52
Overall (N)	68	67	65	65	65	65
New patients treated with sirolimus gel (N)	27	26	25	24	24	24
Patients on placebo in phase III study (N)	21	21	21	21	21	21
Patients on sirolimus in phase III study (N)	20	20	19	20	20	20

Figure 1. Improvement rate for angiofibromas (95% CI) over time up to Week 52 based on centralized photographic assessment (long-term treatment study, FAS)

7.R.1.4 Efficacy by age

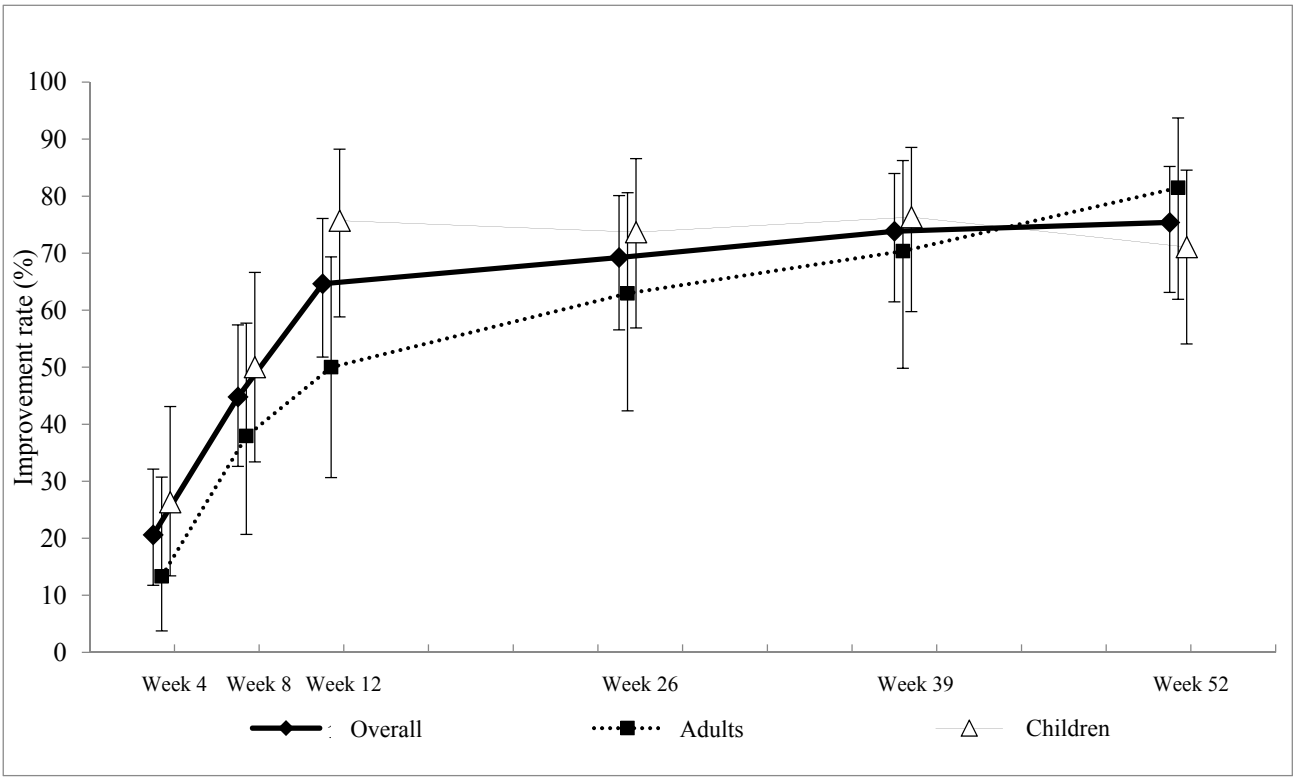
Table 29 shows "improvement in angiofibromas at Week 12 based on centralized photographic assessment" in adult and pediatric patients in the Japanese phase III study. There was a trend toward improvement with sirolimus gel compared with placebo in both adult and pediatric patients.

Table 29. Improvement in angiofibromas at Week 12 based on centralized photographic assessment (FAS)

	Treatment group	Marked improvement	Improvement	Slight improvement	No change	Slight worsening	Worsening	Unassessable
Adults	Placebo (N = 18)	0 (0)	0 (0)	11.1 (2)	83.3 (15)	0 (0)	0 (0)	5.6 (1)
	0.2% sirolimus (N = 17)	17.6 (3)	23.5 (4)	58.8 (10)	0 (0)	0 (0)	0 (0)	0 (0)
Children	Placebo (N = 14)	0 (0)	0 (0)	21.4 (3)	78.6 (11)	0 (0)	0 (0)	0 (0)
	0.2% sirolimus (N = 13)	15.4 (2)	69.2 (9)	7.7 (1)	7.7 (1)	0 (0)	0 (0)	0 (0)
Overall	Placebo (N = 32)	0 (0)	0 (0)	15.6 (5)	81.3 (26)	0 (0)	0 (0)	3.1 (1)
	0.2% sirolimus (N = 30)	16.7 (5)	43.3 (13)	36.7 (11)	3.3 (1)	0 (0)	0 (0)	0 (0)

Proportion % (n)

Figure 2 shows the improvement rate for angiofibromas over time based on centralized photographic assessment in adult and pediatric patients in the long-term treatment study. The results demonstrated that a treatment effect is maintained after Week 12 in both adult and pediatric patients.



Time point (Week)	4	8	12	26	39	52
Overall (N)	68	67	65	65	65	65
Adults (N)	30	29	28	27	27	27
Children (N)	38	38	37	38	38	38

Figure 2. Improvement rate for angiofibromas (95% CI) over time up to Week 52 based on centralized photographic assessment (long-term treatment study, FAS)

PMDA confirmed that the efficacy of sirolimus gel was demonstrated in both adult and pediatric patients.

7.R.1.5 Efficacy in the treatment of fibrous cephalic plaques and hypomelanotic macules

The applicant's explanation about the efficacy of sirolimus gel in the treatment of fibrous cephalic plaques and hypomelanotic macules in the Japanese phase III study:

The Japanese phase III study also evaluated the efficacy of sirolimus gel in the treatment of fibrous cephalic plaques and hypomelanotic macules, which are TSC-associated skin lesions on the face and often seen with angiofibromas.

Improvement in cephalic plaques (Table 30) in the Japanese phase III study is shown in Table 31. There was a trend toward improvement with sirolimus gel compared with placebo.

Table 30. Assessment criteria for improvement in fibrous cephalic plaques

Plaque elevation is assessed on a 6-point scale.	
Marked improvement	An approximately ≥75% reduction in height
Improvement	An approximately 50%-75% reduction in height
Slight improvement	An approximately 25%-50% reduction in height
No change	No apparent changes in height
Slight worsening	An approximately 25%-50% increase in height
Worsening	An approximately ≥50% increase in height

Table 31. Improvement in fibrous cephalic plaques at Week 12 based on centralized photographic assessment (Japanese phase III study, FAS)

Treatment group	Marked improvement	Improvement	Slight improvement	No change	Slight worsening	Worsening	Unassessable
Placebo (N = 16)	0 (0)	6.3 (1)	37.5 (6)	56.3 (9)	0 (0)	0 (0)	0 (0)
0.2% sirolimus (N = 13)	0 (0)	46.2 (6)	46.2 (6)	7.7 (1)	0 (0)	0 (0)	0 (0)

Proportion % (n)

Improvement in hypomelanotic macules (Table 32) in the Japanese phase III study is shown in Table 33. Only 9 patients had facial hypomelanotic macules (5 in the placebo group and 4 in the sirolimus group). Although the number of patients assessed was limited, there was no apparent trend toward improvement with sirolimus gel compared with placebo.

Table 32. Assessment criteria for improvement in hypomelanotic macules

The size and color of hypomelanotic macules are assessed on a 6-point scale.	
Marked improvement	A return to almost normal skin color (cannot be distinguished from normal skin). An approximately ≥75% reduction in size.
Improvement	A return towards normal skin color (can be distinguished from normal skin). An approximately 50%-75% reduction in size.
Slight improvement	A slight return toward normal skin color. An approximately 25%-50% reduction in size.
No change	No apparent changes in color or size.
Slight worsening	Become slightly distinct from normal skin color. An approximately 25%-50% increase in size.
Worsening	Become distinct from normal skin color. An approximately ≥50% increase in size.

Table 33. Improvement in hypomelanotic macules at Week 12 based on centralized photographic assessment (Japanese phase III study, FAS)

Treatment group	Marked improvement	Improvement	Slight improvement	No change	Slight worsening	Worsening	Unassessable
Placebo (N = 5)	0 (0)	40.0 (2)	40.0 (2)	20.0 (1)	0 (0)	0 (0)	0 (0)
0.2% sirolimus (N = 4)	0 (0)	25.0 (1)	75.0 (3)	0 (0)	0 (0)	0 (0)	0 (0)

Proportion % (n)

PMDA's view:

While the Japanese phase III study suggested the efficacy of sirolimus gel in the treatment of fibrous cephalic plaques, its efficacy in the treatment of hypomelanotic macules is unclear. Appropriate lesions that should be treated with sirolimus gel will continue to be discussed in Section 7.R.4.

7.R.2 Safety

PMDA's view:

Based on the following considerations and confirmations in Sections 7.R.2.1 to 7.R.2.4, the safety of sirolimus gel in patients with TSC is acceptable. However, because the number of patients included in Japanese clinical studies is limited, information on the safety of sirolimus gel should continue to be collected via post-marketing surveillance etc.

A final decision on the safety of sirolimus gel will be made, taking account of comments from the Expert Discussion.

7.R.2.1 Comparison with placebo

The applicant's explanation about the safety of sirolimus gel compared with placebo based on a pooled analysis of the Japanese phase I/II and III studies:

Table 34 shows the incidence of adverse events, which is based on a pooled analysis of the Japanese phase I/II and III studies. The incidences of adverse events and adverse drug reactions were high with sirolimus gel compared with placebo. Especially, dry skin, pruritus, and dermatitis acneiform occurred more frequently in the sirolimus group, but there were no clinically relevant differences in the incidences of other events. There were no deaths or adverse events leading to treatment discontinuation. The serious adverse events reported were epilepsy (1 subject) in the placebo group, and pneumothorax (1 subject) and acute pancreatitis and gastric haemorrhage (1 subject) in the sirolimus group, and a causal relationship to study drug was ruled out for all those events except for acute pancreatitis reported in the sirolimus group. Acute pancreatitis reported by 1 subject in the sirolimus group was classified as an adverse drug reaction, but resolved.

Table 34. Summary of adverse events reported by ≥2 subjects in either group (Pooled analysis of Japanese phase I/II and III studies)

	Placebo (N = 44)	0.2% sirolimus (N = 38)
Adverse events	65.9 (29)	89.5 (34)
Adverse drug reactions	40.9 (18)	76.3 (29)
Serious adverse events	2.3 (1)	5.3 (2)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)
Dry skin	11.4 (5)	39.5 (15)
Application site irritation	25.0 (11)	28.9 (11)
Pruritus	9.1 (4)	18.4 (7)
Dermatitis acneiform	0 (0)	10.5 (4)
Influenza	2.3 (1)	7.9 (3)
Nasopharyngitis	11.4 (5)	5.3 (2)
Stomatitis	4.5 (2)	5.3 (2)
Acne	0 (0)	5.3 (2)
Eye irritation	4.5 (2)	2.6 (1)
Epilepsy	4.5 (2)	0 (0)
Upper respiratory tract inflammation	4.5 (2)	0 (0)
Skin abrasion	4.5 (2)	0 (0)
Sinusitis	4.5 (2)	0 (0)

MedDRA/J ver.19.0 Incidence % (n)

PMDA's view:

The pooled analysis of the Japanese phase I/II and III studies showed no major differences in the trend of occurrence of adverse events except for dry skin, pruritus, and dermatitis acneiform, between the sirolimus and placebo groups. Skin-related events including dry skin, pruritus, and dermatitis acneiform that tended to occur at a higher incidence with sirolimus gel are assessed in Section 7.R.2.2.

7.R.2.2 Skin-related events

The applicant's explanation about the occurrence of skin-related events:

Skin-related events assessed in the Japanese phase I/II and III studies were defined as events coded to the MedDRA SOC "skin and subcutaneous tissue disorders," events affecting skin (excluding oral cavity), or events of skin irritation.

Table 35 shows the incidence of skin-related events, which is based on a pooled analysis of the Japanese phase I/II and III studies. The incidences of dry skin, pruritus, and dermatitis acneiform were high with sirolimus gel compared with placebo. Most of those events were classified as adverse drug reactions but were mild or moderate in severity. The events resolved without treatment discontinuation.

Table 35. Summary of skin-related events reported by ≥2 subjects in either group (Pooled analysis of Japanese phase I/II and III studies)

Event term	Placebo (N = 44)	0.2% sirolimus (N = 38)
Any skin-related adverse event	50.0 (22)	84.2 (32)
Dry skin	11.4 (5)	39.5 (15)
Application site irritation	25.0 (11)	28.9 (11)
Pruritus	9.1 (4)	18.4 (7)
Dermatitis acneiform	0 (0)	10.5 (4)
Acne	0 (0)	5.3 (2)
Eye irritation	4.5 (2)	2.6 (1)
Skin abrasion	4.5 (2)	0 (0)

MedDRA/J ver.19.0, Incidence % (n)

PMDA's view:

The pooled analysis of the Japanese phase I/II and III studies showed no adverse events occurring more frequently in the sirolimus group than in the placebo group, except for dry skin, pruritus, and dermatitis acneiform. Dry skin, pruritus, and dermatitis acneiform were mild or moderate in severity and resolved without treatment discontinuation. For these reasons, skin-related events associated with sirolimus gel are clinically tolerable.

7.R.2.3 Adverse events during long-term treatment

The applicant's explanation about the long-term safety of sirolimus gel:

Table 36 shows the incidence of adverse events by time from the onset of therapy in the Japanese long-term treatment study. The incidence of adverse events did not increase with increasing duration of treatment. The incidence of skin-related events was high through Week 12 and did not tend to increase thereafter.

Table 36. Incidence of adverse events by time from onset of therapy (Japanese long-term treatment study)

	Weeks 1-12 (N = 94)	Weeks 13-26 (N = 91)	Weeks 27-39 (N = 89)	Week ≥40 (N = 63)	Entire period (N = 94)
Any adverse event	**78.7 (74)**	**72.5 (66)**	**44.9 (40)**	**38.1 (24)**	**96.8 (91)**
Any skin-related event	**74.5 (70)**	**45.1 (41)**	**23.6 (21)**	**20.6 (13)**	**86.2 (81)**
Dry skin	**21.3 (20)**	**5.5 (5)**	**6.7 (6)**	**1.6 (1)**	**29.8 (28)**
Pruritus	**6.4 (6)**	**1.1 (1)**	**0 (0)**	**3.2 (2)**	**9.6 (9)**
Dermatitis acneiform	**3.2 (3)**	**5.5 (5)**	**1.1 (1)**	**1.6 (1)**	**9.6 (9)**

MedDRA/J ver.20.1, Incidence % (n)

7.R.2.4 Adverse events in adults and children

The applicant's explanation about safety in children:

Pediatric patients aged ≥3 years were enrolled in the Japanese phase I/II, phase III, and long-term treatment studies to evaluate safety in pediatric patients. Table 37 shows the incidences of adverse events in adult and pediatric patients, which are based on a pooled analysis of the Japanese phase I/II and III studies. Although the incidences of influenza and nasopharyngitis were higher in pediatric patients than in adult patients, their causal relationship to sirolimus gel was ruled out. There was no trend toward increased severity of adverse events in pediatric patients compared with adult patients.

Table 37. Adverse events reported by ≥2 subjects in either group in adult or pediatric patients (Pooled analysis of Japanese phase I/II and III studies)

	Children (N = 37)		Adults (N = 45)	
	Placebo (N = 20)	0.2% sirolimus (N = 17)	Placebo (N = 24)	0.2% sirolimus (N = 21)
Adverse events	65.0 (13)	82.4 (14)	66.7 (16)	95.2 (20)
Adverse drug reactions	35.0 (7)	64.7 (11)	45.8 (11)	85.7 (18)
Serious adverse events	0 (0)	0 (0)	4.2 (1)	9.5 (2)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)
Dry skin	10.0 (2)	41.2 (7)	12.5 (3)	38.1 (8)
Application site irritation	20.0 (4)	23.5 (4)	29.2 (7)	33.3 (7)
Pruritus	10.0 (2)	5.9 (1)	8.3 (2)	28.6 (6)
Dermatitis acneiform	0 (0)	5.9 (1)	0 (0)	14.3 (3)
Acne	0 (0)	0 (0)	0 (0)	9.5 (2)
Stomatitis	0 (0)	5.9 (1)	8.3 (2)	4.8 (1)
Influenza	0 (0)	17.6 (3)	4.2 (1)	0 (0)
Nasopharyngitis	20.0 (4)	11.8 (2)	4.2 (1)	0 (0)

MedDRA/J ver.19.0, Incidence % (n)

Table 38 shows the incidence of adverse events by time from the onset of therapy in adult or pediatric patients in the Japanese long-term treatment study. The incidence of adverse events did not increase with increasing duration of treatment in pediatric patients, either.

Table 38. Incidence of adverse events by time from onset of therapy in adult or pediatric patients (Japanese long-term treatment study)

	Adverse event term	Weeks 1-12 (N = 50)	Weeks 13-26 (N = 49)	Weeks 27-39 (N = 49)	Week ≥40 (N = 35)	Entire period (N = 50)
Children	Any adverse event	78.0 (39)	73.5 (36)	53.1 (26)	45.7 (16)	98.0 (49)
	Any skin-related event	74.0 (37)	42.9 (21)	24.5 (12)	22.9 (8)	86.0 (43)
	Dry skin	20.0 (10)	10.2 (5)	6.1 (3)	0 (0)	30.0 (15)
	Pruritus	4.0 (2)	0 (0)	0 (0)	2.9 (1)	6.0 (3)
	Dermatitis acneiform	2.0 (1)	6.1 (3)	2.0 (1)	2.9 (1)	10.0 (5)
	Adverse event term	Weeks 1-12 (N = 44)	Weeks 13-26 (N = 42)	Weeks 27-39 (N = 40)	Week 40 onward (N = 28)	Entire period (N = 44)
Adults	Any adverse event	79.5 (35)	71.4 (30)	35.0 (14)	28.6 (8)	95.5 (42)
	Any skin-related event	75.0 (33)	47.6 (20)	22.5 (9)	17.9 (5)	86.4 (38)
	Dry skin	22.7 (10)	0 (0)	7.5 (3)	3.6 (1)	29.5 (13)
	Pruritus	9.1 (4)	2.4 (1)	0 (0)	3.6 (1)	13.6 (6)
	Dermatitis acneiform	4.5 (2)	4.8 (2)	0 (0)	0 (0)	9.1 (4)

MedDRA/J ver.20.1, Incidence % (n)

PMDA's view:

Pediatric patients aged ≥3 years were enrolled in the Japanese clinical studies. There was no trend toward occurrence of specific adverse events or increased severity of adverse events in pediatric patients compared with adult patients. The package insert should advise that there is no clinical experience in children aged <3 years.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of sirolimus gel:

Patients with TSC develop skin lesions such as angiofibromas in childhood. Once developed, the symptoms persist or progress. There are no drugs approved for the treatment of TSC-associated skin lesions in or outside of Japan, and only highly invasive therapies, mainly surgical resection and laser treatment, are available (TSC treatment guideline 2008).

Sirolimus gel is the world's first topical agent for the treatment of TSC-associated skin lesions, and should be highly clinically meaningful.

PMDA's view:

Sirolimus gel will offer a new therapeutic option for patients with TSC-associated skin lesions, on the following grounds: (1) The Japanese phase III study demonstrated the efficacy and safety of sirolimus gel [see Sections 7.R.1 and 7.R.2], and (2) there are currently no drugs indicated for TSC-associated skin lesions such as angiofibromas.

7.R.4 Indication

The applicant's explanation about the indication for sirolimus gel:

Since facial angiofibromas are typical cutaneous manifestations of TSC, patients with TSC-associated facial angiofibromas were included in the Japanese phase III study. Other cutaneous manifestations of TSC are hypomelanotic macules, fibrous cephalic plaques (or forehead fibrous plaques), shagreen patches (shagreen skin), and ungual fibromas (TSC treatment guideline 2008).

The Japanese phase III study showed statistically significant improvement in TSC-associated angiofibromas with sirolimus gel compared with placebo. There was a trend toward improvement in fibrous cephalic plaques with sirolimus gel compared with placebo in the study [see Section 7.R.1]. TSC-associated shagreen patches and ungual fibromas are classified as hamartomas (tumor-like skin lesions) like angiofibromas and fibrous cephalic plaques, and the symptoms are considered attributable to the constitutive activation of the mTOR associated with the dysfunction of the hamartin/tuberin complex (Frontiers of Diagnosis and Treatment of Tuberous Sclerosis Complex. The Japanese Society of Tuberous Sclerosis Complex ed. SHINDAN TO CHIRYO SHA Inc. 2016). Oral sirolimus markedly improved TSC-associated shagreen patches and ungual fibromas (*Transplant Proc*. 2009;41: 3677-3682, *J Am Acad Dermatol*. 2015;73: 802-808, and other articles). On the basis of the above findings, sirolimus gel is expected to be effective also in the treatment of TSC-associated shagreen patches and ungual fibromas.

On the other hand, TSC-associated hypomelanotic macules are non-tumorous skin lesions caused by impaired melanin synthesis. Although the mechanism of development of TSC-associated hypomelanotic macules is unclear, impairment of the autophagy-lysosome system associated with the dysfunction of the hamartin/tuberin complex is considered to be involved (*Arch Dermatol*. 2012;148: 138-139). Because of the limited number of patients included in the Japanese phase I/II and III studies, the efficacy of

sirolimus gel in the treatment of TSC-associated hypomelanotic macules could not been evaluated adequately [see Section 7.R.1.5]. However, the improvement rate for facial hypomelanotic macules increased over time in the Japanese long-term treatment study (31.3% [5 of 16 subjects] at Week 12, 52.9% [9 of 17 subjects] at Week 26, 76.5% [13 of 17 subjects] at Week 52), and the inhibition of mTOR by sirolimus increased the activities of various enzymes involved in melanogenesis (*J Cell Physiol.* 2005;205: 444-451). Based on the above findings, sirolimus gel is considered to improve impaired melanin synthesis in patients with TSC and as a result, the color of hypomelanotic macules may return towards the normal skin color. In addition, topical sirolimus treatment was reported to improve TSC-related hypomelanotic macules (*JAMA Dermatol.* 2015;151: 722-730, *Arch Dermatol*. 2012;148: 138-139, and other articles). Thus, there is no information that denies the use of sirolimus gel for the treatment of TSC-associated hypomelanotic macules. The applicant therefore considered that TSC-associated hypomelanotic macules can also be treated with sirolimus gel.

PMDA's view:
The Japanese clinical studies demonstrated the efficacy of sirolimus gel in the treatment of angiofibromas and suggested its efficacy in the treatment of fibrous cephalic plaques. Given its mechanism of action, sirolimus gel is expected to be effective also in the treatment of hamartomas such as shagreen patches and ungual fibromas. However, information on the efficacy and safety of sirolimus gel should continue to be collected via post-marketing surveillance etc., as its efficacy in the treatment of those lesions was not evaluated in the Japanese clinical studies. For the treatment of TSC-associated hypomelanotic macules, there are no non-clinical data clearly demonstrating that sirolimus gel exerts its effects by inhibiting the mTOR. Although the applicant discussed the efficacy of sirolimus gel from the viewpoint of the mechanism of development of the symptom, such discussion is pure inference. The Japanese phase III study did not clearly demonstrate the efficacy and safety of sirolimus gel in the treatment of hypomelanotic macules. Thus, there is currently no evidence to recommend the use of sirolimus gel to treat TSC-associated hypomelanotic macules.

A final decision on the indication for sirolimus gel will be made, taking account of comments from the Expert Discussion.

7.R.5 Dosage and administration

The applicant's explanation about the dosage and administration of sirolimus gel:
Prior to the Japanese phase I/II study, clinical research studies were conducted in which topical 0.2% sirolimus[5)] was applied to TSC patients twice daily for 12 weeks. In the studies, changes in the redness of angiofibromas, reductions of papule size, and other changes were observed after 12 weeks of treatment (*Br J Dermatol*. 2011;165: 912-916, *Br J Dermatol*. 2013;169: 1314-1318). Based on the results, the applicant decided to topically apply sirolimus gel in concentrations of 0.05%, 0.1%, and 0.2% twice daily for 12 weeks in the Japanese phase I/II study. Since a preliminary study showed that the proper amount of sirolimus gel to be applied to an area of 50 cm^2 (the area of both cheeks) is 125 mg, a dose of 125 mg of gel per 50 cm^2 was selected as the recommended dose. In the phase I/II study using the regimen, all sirolimus groups showed significant improvement in angiofibromas compared with the placebo group. Although the incidence of adverse events increased in a sirolimus concentration-dependent manner, adverse events occurring in the 0.2%

sirolimus group were all mild or moderate in severity, except for 1 case of pneumothorax. The safety of sirolimus gel was considered clinically tolerable. Because there were no major differences in efficacy or safety between adult and pediatric patients, the applicant decided to apply 0.2% sirolimus gel at a recommended dose of 125 mg of gel per 50 cm^2 of skin lesion twice daily for 12 weeks in both adult and pediatric patients in the Japanese phase III study, based on the dosage regimen used in the Japanese phase I/II study. As there was a possibility that the blood concentration of sirolimus may increase with increasing amount applied, for safety considerations, study drug was to be applied to the skin lesions on the face and head only. The maximum daily dose was determined based on age and body surface area (BSA): ≤5 years (BSA <0.8 m^2), 400 mg; 6 to 11 years (BSA ≥ 0.8 m^2 and < 1.3 m^2), 600 mg; and ≥12 years (BSA ≥1.3 m^2), 800 mg.

The Japanese phase III study demonstrated the superiority of sirolimus gel over placebo and its clinically tolerable safety profile and showed no major differences in efficacy or safety between adult and pediatric patients. These results justify selecting the dosage regimen for both adult and pediatric patients based on the dosage regimen used in the Japanese phase III study.

Since TSC-associated skin lesions progress or increase over time, the area of skin to which sirolimus gel is applied may change according to the presence or absence and severity of symptoms. If the applied dose is increased according to the symptoms, an increased amount of sirolimus will be absorbed into circulation, resulting in increased blood sirolimus concentrations, though drug concentrations in the skin is unlikely to be affected. However, given the relationship between the mean dose of sirolimus gel applied and its blood concentrations in the Japanese phase III and long-term treatment studies, it is estimated that even a 1-g increase in the maximum daily dose results in only approximately a 0.1- to 0.4-ng/mL increase in blood sirolimus levels. Hence, even if the amount of sirolimus gel used exceeds the maximum daily dose as recommended in the Japanese phase III and long-term treatment studies, the increase in blood sirolimus concentrations will be limited. Although the mean daily dose of sirolimus gel applied was higher than the recommended maximum daily dose in 16 patients in the Japanese phase III and long-term treatment studies, there was no trend toward increasing blood sirolimus concentration or increasing incidence of adverse events in these patients. It is recommended, therefore, that the dosage of sirolimus gel is adjusted according to the symptoms and severity of skin lesions.

PMDA's view:
There is no particular problem with selecting the dosage regimen of sirolimus gel based on the dosage regimen used in the Japanese phase III study. Since the recommended maximum daily dose was exceeded in a limited number of patients in the Japanese phase III study, the safety and efficacy of sirolimus gel applied at a dose higher than the recommended maximum daily dose are undefined. Thus, as in the cases of the Japanese phase III and long-term treatment studies, the package insert should advise the maximum daily dose based on age and body surface area. Moreover, in order to prevent unnecessary exposure to sirolimus gel, the package insert should advise that if symptoms do not improve within 12 weeks of treatment, treatment with sirolimus gel should be discontinued to avoid the injudicious use of sirolimus gel over a prolonged period of time.

A final decision on dosage and administration will be made, taking account of comments from the Expert Discussion.

7.R.6 Concomitant use with mTOR inhibitors

The applicant's explanation about the safety and efficacy of sirolimus gel in combination with other mTOR inhibitors:

Concomitant use with other mTOR inhibitors was prohibited in the Japanese phase III study, with consideration of the possibility that it affects efficacy and safety evaluation. The safety and efficacy of sirolimus gel in combination with other mTOR inhibitors (oral sirolimus and oral everolimus) were evaluated based on the data from the Japanese long-term treatment study. In the Japanese long-term treatment study, the incidences of adverse events in patients with and without concomitant mTOR inhibitors were 100% (14 of 14 subjects) and 96.3% (77 of 80 subjects), respectively, and the incidences of adverse drug reactions in patients with and without concomitant mTOR inhibitors were 71.4% (10 of 14 subjects) and 72.5% (58 of 80 subjects), respectively. The improvement rates for angiofibromas at Week 52 based on centralized photographic assessment in patients with and without concomitant mTOR inhibitors were 55.6% (5 of 9 subjects) and 78.6% (44 of 56 subjects), respectively. There was no clinically relevant problem with the safety and efficacy of sirolimus gel in combination with mTOR inhibitors, although it should be noted that the number of patients treated with sirolimus gel in combination with other mTOR inhibitors in the Japanese long-term treatment study was limited. Taking also into account that the blood sirolimus concentrations after dermal application of sirolimus gel are very low compared with those after oral administration of "Rapalimus Tablets 1 mg" [see Section 6.R], a clinically relevant problem is unlikely to arise in patients treated with sirolimus gel in combination with other mTOR inhibitors.

PMDA's view:

At present, there is no particular problem with the safety and efficacy of sirolimus gel in combination with other mTOR inhibitors. However, information on the safety and efficacy of sirolimus gel in combination with other mTOR inhibitors should continue to be collected via post-marketing surveillance etc., for the following reasons: (i) Only a limited number of patients were treated with sirolimus gel in combination with other mTOR inhibitors in the Japanese long-term treatment study, and (ii) it is envisaged that sirolimus gel may be used in combination with other mTOR inhibitors in clinical practice.

7.R.7 Post-marketing investigations

The applicant is planning a post-marketing use-results survey as shown in Table 39. The ongoing Japanese long-term treatment study will be reclassified as a post-marketing clinical study after approval and continued until the launch date of the product.

Table 39. Outline of use-results survey (draft)

Objective	**To evaluate the safety and efficacy of sirolimus gel in patients with TSC-associated skin lesions in clinical practice.**
Survey method	**Central registry system**
Population	**Patients with TSC-associated skin lesions**
Planned number of patients	**300 patients**
Survey period	**4 years (enrollment period, 3 years)**
Observation period	**26 weeks**
Main survey items	**· Patient characteristics (age, gender, disease duration, clinical symptoms of TSC, complications, medical history, etc.)** **· Use of sirolimus gel (duration of treatment, applied dose)** **· Previous and concomitant medications (Yes/No, drug name, route of administration, duration of treatment, etc.)** **· Efficacy** **· Adverse events (onset date, seriousness, outcome, discontinuation of sirolimus gel (Yes/No), a causal relationship to sirolimus gel, etc.)** **· Clinical laboratory tests**

PMDA's view:

The number of patients included in the Japanese clinical studies is very limited, and sirolimus gel is intended for long-term use (including intermittent administration). Therefore, a long-term survey should be conducted. Post-marketing surveillance should also cover the following issues, but the details will be finalized, taking account of comments from the Expert Discussion.

- Safety and efficacy of sirolimus gel in children
- Safety and efficacy of sirolimus gel in combination with other mTOR inhibitors

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

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

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

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

The new drug application data (CTD 5.3.5.1-1, CTD 5.3.5.1-2, CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection verified that the clinical studies as a whole were conducted in compliance with GCP. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted. Although the outcome of the overall assessment of the studies was not affected significantly, the inspection revealed the following finding at some of the study sites used by the applicant. The heads of the relevant medical institutions were notified of the finding(s) requiring corrective action.

[Finding(s) requiring corrective action]

Study sites

- Protocol deviations (non-compliance with the rules for reporting serious adverse events)

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

On the basis of the data submitted, PMDA has concluded that sirolimus gel has efficacy in the treatment of tuberous sclerosis complex-associated skin lesions, and that sirolimus gel has acceptable safety in view of its benefits. Sirolimus gel is clinically meaningful because it is a topical agent containing sirolimus as the active ingredient and offers a new treatment option for patients with tuberous sclerosis complex-associated skin lesions. PMDA considers that the efficacy, safety, indication, dosage and administration, and post-marketing investigations of sirolimus gel need further discussion.

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

Review Report (2)

February 15, 2018

Product Submitted for Approval

Brand Name	Rapalimus Gel 0.2%
Non-proprietary Name	Sirolimus
Applicant	Nobelpharma Co., Ltd.
Date of Application	October 20, 2017

1. Content of the Review

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

1.1 Efficacy, safety, indication, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in Sections "7.R.1 Efficacy," "7.R.2 Safety," "7.R.4 Indication," and "7.R.5 Dosage and administration" in the Review Report (1). The expert advisors made the following comment.

- Japanese clinical studies did not evaluate the efficacy etc. of sirolimus gel in the treatment of shagreen patches and ungual fibromas among tuberous sclerosis complex (TSC)-associated skin lesions. At present, there is the possibility that sirolimus gel may not be absorbed sufficiently in the skin and therefore cannot exert adequate efficacy in patients with shagreen patches (which frequently present on the back etc. having a thicker stratum corneum than the face) or ungual fibromas (which are tumors that present a cartilaginous hardness). On the above grounds, the package insert should advise that the efficacy of sirolimus gel in the treatment of shagreen patches and ungual fibromas as well as hypomelanotic macules has not been demonstrated.

Based on the comment from the Expert Discussion, PMDA accepted the proposed indication as shown below. PMDA requested the applicant to modify the dosage and administration statement and the statements in the "Precautions for Indication" section and the "Precautions for Dosage and Administration" section of the package insert as shown below. The applicant responded appropriately, and PMDA accepted it.

Indication

Tuberous sclerosis complex-associated skin lesions

Precautions for Indication

The efficacy of Rapalimus Gel in the treatment of hypomelanotic macules, shagreen patches, and ungual fibromas has not been demonstrated.

Dosage and Administration

Usual dosage: Apply an appropriate amount of Rapalimus Gel to the affected skin areas twice daily.

Precautions for Dosage and Administration

(1) The recommended maximum daily dose is shown in the table below.

Age (body surface area) category	Maximum daily dose
≤5 years (<0.8 m^2)	400 mg
6-11 years (≥0.8 m^2 and <1.3 m^2)	600 mg
≥12 years (≥1.3 m^2)	800 mg

(2) If symptoms do not improve within 12 weeks of treatment, the need for Rapalimus Gel should be reconsidered to avoid continuing treatment unnecessarily.

1.2 Risk management plan (draft)

The expert advisors supported PMDA's conclusion presented in Section "7.R.7 Post-marketing investigations" in the Review Report (1).

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for sirolimus gel should include the safety and efficacy specifications presented in Table 40, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 41 and a use-results survey presented in Table 42.

Table 40. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
· None	· Photosensitivity	· None
Efficacy specification		
· None		

Table 41. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
· Early post-marketing phase vigilance · Use-results survey · Post-marketing clinical study[a)]	· Disseminate data gathered during early post-marketing phase vigilance

a) The Japanese long-term treatment study will be continued as a post-marketing clinical study after approval.

Table 42. Outline of use-results survey (draft)

Objective	**To evaluate the safety and efficacy of sirolimus gel, etc. in patients with TSC-associated skin lesions in clinical practice.**
Survey method	**All-case surveillance by central registry system**
Population	**Patients with TSC-associated skin lesions**
Planned number of patients	**All patients treated (planned number of patients, 300 patients)**
Observation period	**52 weeks**
Main survey items	**· Patient characteristics (age, gender, disease duration, clinical symptoms of TSC, complications, medical history, etc.)** **· Use of sirolimus gel (duration of treatment, applied dose)** **· Previous and concomitant medications (Yes/No, drug name, route of administration, duration of treatment, etc.)** **· Efficacy** **· Patient satisfaction** **· Adverse events (onset date, seriousness, outcome, discontinuation of sirolimus gel (Yes/No), a causal relationship to sirolimus gel, etc.)** **· Clinical laboratory values**

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Since the product is an orphan drug, the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. The drug product is classified as a powerful drug.

Indication

Tuberous sclerosis complex-associated skin lesions

Dosage and Administration

Usual dosage: Apply an appropriate amount of Rapalimus Gel the affected skin areas twice daily.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients studied in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a specified number of patients will be collected, in order to further understand the characteristics of patients treated with the product and collect data on the safety and efficacy of the product as soon as possible, thereby taking necessary measures to ensure proper use of the product.

List of Abbreviations

Adverse drug reaction	An adverse event for which a causal relationship to study drug cannot be ruled out
A/G ratio	Albumin/globulin ratio
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
BLQ	Below the lower limit of quantification
C_{max}	Maximum concentration
CTD	Common technical document
DMBA	7,12-dimethylbenz[a]anthracene
FAS	Full analysis set
GC	Gas chromatography
GCP	Good clinical practice
HPLC	High performance liquid chromatography
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
IR	Infrared absorption spectrum
J	Joule
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
MCB	Master cell bank
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MF	Master file
mTOR	mammalian Target of rapamycin
NC	Not calculated
NMR	Nuclear magnetic resonance spectrum
PMDA	Pharmaceuticals and Medical Devices Agency
QOL	Quality of life
RH	Relative humidity
SAR	Structure-activity relationship
Sirolimus gel	Rapalimus Gel
SOC	System organ class
TPA	12-*O*-tetradecanoylphorbol-13-acetate
TSC	Tuberous sclerosis complex
TSC1	Tuberous sclerosis complex1
TSC2	Tuberous sclerosis complex2
TSC treatment guideline 2008	Diagnostic Criteria and Treatment Guideline for Tuberous Sclerosis Complex 2008. The Japanese Dermatological Association ed.
UV	Ultraviolet-visible absorption spectrum
UVA	Ultraviolet A
WCB	Working cell bank