CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213478Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Medical Officer's Review of NDA 213478
Resubmission after Complete Response

Document ID Number: SDN 30
Document Type: Resubmission of NDA after Complete Response
Correspondence date: December 23, 2020
CDER Stamp date: December 23, 2020
Applicant: Nobelpharma Co. Ltd.
Drug: Hyftor
Route of Administration: topical
Dosage Form: topical gel
Active Ingredient(s): Sirolimus

Pharmacologic Category: Mammalian target of rapamycin (mTOR) inhibitor
Proposed Indication: treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older
Project Manager: Strother Dixon
Medical Officer: Kevin Clark, MD
Team Leader: Gordana Diglisic, MD
Review completion date: March 19, 2022

Reviews by Consultants and other Review Disciplines

- Division of Medication Error Prevention and Analysis (DMEPA), Madhuri R. Patel, PharmD, reviews dated February 24, 2021 and March 11, 2021
- Division of New Drug Products 2, Office of New Drug Products, Hamid Shafiei, Ph.D., memoranda dated March 17, 2021, June 23, 2021, and March 16, 2022
- Office of Prescription Drug Promotion (OPDP), Laurie Buonaccorsi, PharmD, review dated June 4, 2021
- Division of Medical Policy Programs (DMPP), Jessica Chung, PharmD, MS and OPDP, Laurie Buonaccorsi, PharmD, review dated June 14, 2021

Current Documents

The NDA resubmission included the following:

- Module 1: Reviewer's Guide, Draft Prescribing Information (PI) and Patient Package Insert (PPI), and Proprietary Name Request
- Module 2: Clinical Overview, Summary of Clinical Safety
- Module 3: Chemistry, Manufacturing, and Controls (CMC) information

Recommendation for Action: Approval

Executive Summary

Based on deficiencies identified by the Office of Pharmaceutical Quality (OPQ), the original submission of NDA 213478 for Hyftor (sirolimus topical gel), 0.2% for the treatment of facial angiofibroma (FA) associated with tuberous sclerosis (TS) in adults and (b) (4) received a Complete Response (CR Letter dated August 13, 2020). In this

response to the CR, the Applicant (Nobelpharma Co. Ltd.) resubmitted additional information (SDN 30, dated December 23, 2020) which addressed the deficiencies identified in the CR letter. The FDA completed the required pre-approval inspection with satisfactory results. Therefore, the recommended regulatory action is **approval** of NDA 213478 for Hyftor (sirolimus topical gel), 0.2% for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older.

Regulatory History

On February 18, 2020, the Applicant (Nobelpharma Co. Ltd.) submitted NDA 213478 for Hyftor (sirolimus topical gel), 0.2% for the treatment of facial angiofibroma (FA) associated with tuberous sclerosis (TS) in adults and (b) (4). The Agency granted the Applicant's request for Orphan Drug designation for sirolimus for the treatment of facial angiofibroma (FA) associated with tuberous sclerosis (TS; letter dated 05/17/2017) as well as Fast Track designation (letter dated 11/27/2018).

The application received a Complete Response on August 13, 2020, because of deficiencies noted by the Office of Pharmaceutical Quality (OPQ). Deficiencies included active pharmaceutical ingredient (API) assay result specifications, as well as multiple issues regarding the manufacturing process (e.g., procedures for mixing excipients; data required regarding equipment used in the manufacturing process, evaluation of extractable/leachable data, along with other aspects of the manufacturing process). In addition, an inspection of the TOYO PHARMACEUTICAL CO. LTD. facility (FEI 3016419927) located in Tsurumi-Ku, Osaka, Japan was required before the application could be approved. This inspection was delayed because of travel restrictions related to the COVID-19 public health emergency.

The Applicant resubmitted NDA 213478 on December 23, 2020 (SDN 30). The submission contained product quality information, updated labeling, and updated safety information from the ongoing postmarketing safety study (Study RPG01S). The User Fee goal date for the resubmission was June 23, 2021. However, due to ongoing travel restrictions because of the COVID-19 pandemic, the required facility inspection could not be completed prior to the User Fee goal date. The Division deferred action on the resubmission until the inspection could be completed.

Because the ongoing travel restrictions had not yet been lifted, in lieu of a pre-approval inspection the Office of Regulatory Affairs (ORA) conducted a joint 704(a)(4) based record request and assessment to review firm's adequacy to manufacture the drug product. On March 10, 2022, the review team was notified that ORA completed the inspection review and found that the available information is adequate to confirm that the firm is acceptable to manufacture HYFTOR topical gel. In addition, in a memorandum dated March 16, 2022, Dr. Hamid Shafiei of the Division of New Drug Products 2, Office of New Drug Products notified the review team that the CMC and labeling issues had been satisfactorily resolved, and recommended approval of NDA 213478 from an Office of Pharmaceutical Quality (OPQ) perspective.

Review of Resubmission

The Applicant resubmitted the NDA on December 23, 2020 (SDN 30). The submission contained product quality information, updated labeling, and updated safety information from the ongoing postmarketing safety study (Study RPG01S). The initial Unireview contained analyses of safety information from the postmarketing study through April 30, 2020. Refer to the Multidisciplinary Review and Evaluation (Unireview), dated August 13, 2020, for a discussion of the safety, efficacy, and benefit-risk assessment. The NDA resubmission contained safety information through July 31, 2020 and included 158 new patients in the safety analysis.

The Applicant also resubmitted a request for review of their proposed proprietary name, Hyftor, on December 23, 2020. Refer to the Proprietary name Review by Madhuri R. Patel, PharmD, dated March 17, 2021. In a letter dated March 18, 2021, the Agency informed the Applicant that their proposed proprietary name was conditionally acceptable.

Updated Safety Information

The review team identified no new safety signals based on the additional safety data presented in the resubmission. There were no new deaths, but two additional subjects reported serious AEs (SAEs) of aggravated epilepsy. Neither SAE was considered related to treatment with sirolimus. There were no new SAE preferred terms (PTs) reported in the resubmission.

The adverse reactions (ARs) reported for the post-marketing study in the resubmission were similar to those previously documented in the original Unireview. In the initial Unireview, a total of 44/273 subjects (16.1%) in the postmarketing study reported ARs. The most commonly reported ARs were from the System-Organ Class (SOC) of Skin and Subcutaneous Tissue Disorders (28/273, 10.3%); the most common PTs reported in this SOC were acne (10/273, 3.7%) and dermatitis acneiform (3/273, 1.1%). In addition, 16/273 (5.9%) subjects reported ARs from the SOC of General Disorders and Administration Site Conditions. The most commonly reported PT from this SOC was application site erythema (13/273, 4.8%).

In the resubmission, a total of 103/431 (23.9%) subjects in the postmarketing study reported ARs. As noted in the initial Unireview, the most commonly reported ARs were from the SOC of Skin and Subcutaneous Tissue Disorders (61/431, 14.2%). The most commonly reported PTs from this SOC were acne (19/431, 4.4%), and dry skin and bullous dermatitis (each with 9/431, 2.1%). In addition, 24/431 (5.6%) subjects reported ARs from the SOC of General Disorders and Administration Site Conditions. The most commonly reported PTs from this SOC were application site irritation (10/431, 2.3%) and application site erythema (7/431, 1.6%). No changes are recommended for the proposed labeling based on the updated postmarket safety information.

Labeling

There were no significant disagreements between the FDA and Applicant regarding the content of labeling. Draft labeling, including Patient Labeling, was initially communicated to Applicant on June 25, 2021. The Applicant resubmitted labeling in response to FDA comments at multiple timepoints (July 2, 2021, July 27, 2021, and August 9, 2021.) On February 25, 2022, the Applicant resubmitted labeling (Prescribing Information and Patient Labeling) and agreed with all changes recommended by the Agency and recommended one minor change to Section 7.2 (Effects of HYFTOR on other drugs). The Clinical Pharmacology team agreed with the proposed edit. Refer to the Unireview dated August 13, 2020, for more detailed information regarding the content of the labeling.

Current agreed labeling reflects one minor change in Section 6 (Adverse Reactions) compared with the labeling discussion presented in the Unireview. The text was modified as follows (change is in **bold**):

> "In a 104-week, open-label safety trial, the most common adverse reactions associated with HYFTOR application were application site irritation (31%), dry skin (28%), acne (20%), pruritus (9%), eye irritation (9%), erythema (7%), acneiform dermatitis (6%), contact dermatitis (5%), **solar dermatitis** (b) (4) **1%**), and photosensitivity reaction (1%). Adverse reactions occurred with similar frequency in adult and pediatric subjects 6 years of age and older."

The Applicant stated that only 1% of subjects experienced solar dermatitis that was treatment-related, and this represented an adverse reaction. The submission contained sufficient information to support the Applicant's position and the edit was accepted.

Refer also to the review of the PI by Laurie Buonaccorsi, PharmD, dated June 4, 2021 and review of the PPI by Jessica Chung, PharmD, MS and Laurie Buonaccorsi, PharmD, dated June 14, 2021.

<u>Office of Pharmaceutical Quality</u>

In an email dated April 22, 2021, Dr. Hamid Shafiei of the Division of New Drug Products 2, Office of New Drug Products stated the following:

> "All OPQ discipline reviewers have recommended the approval of this application from the CMC perspective. However, the actual approval of this application is pending on the successful outcome of the required pre-approval inspection of the drug product manufacturing site. As you are aware, due to travel restrictions associated with COVID-19 pandemic we cannot complete the inspection of this site before the PDUFA action date."

This information was conveyed to the Applicant by the OPQ project manager. The Division elected to defer action on the resubmission until the required inspection could be completed.

On March 10, 2022, the review team was notified by OPQ that in lieu of a pre-approval inspection, the Office of Regulatory Affairs (ORA) conducted a joint 704(a)(4) based record request and assessment to review firm's adequacy to manufacture the drug product. ORA completed the review and found that the available information is adequate to confirm that the firm is acceptable to manufacture HYFTOR topical gel.

In a memorandum dated March 16, 2022, Dr. Hamid Shafiei of the Division of New Drug Products 2, Office of New Drug Products stated the following (refer to the memorandum for further details):

> "The Office of Pharmaceutical Quality Assessment (OPMA) has completed the assessment of the drug product manufacturing facility, TOYO Pharmaceutical Co., using the 704(a)(4) process in lieu of the ability to perform preapproval inspection (see Appendix 1).
>
> The CMC labels/labeling issues have been satisfactorily resolved (see Appendix 2).
>
> Therefore, from the OPQ perspective this application is now recommended for **approval**."

For further information, refer to the memorandum by Dr. Shafiei dated March 16, 2022.

Summary and Conclusion

The deficiencies noted in the CR letter by OPQ have been resolved and the drug product manufacturing facility inspection has been satisfactorily completed. Therefore, I recommend **approval** of NDA 213478 for Hyftor (sirolimus topical gel), 0.2% for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older.

Kevin Clark, MD
Medical Officer/Dermatology
Office of Immunology and Inflammation

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEVIN L CLARK
03/21/2022 08:40:31 AM

GORDANA DIGLISIC
03/21/2022 09:15:42 AM

NDA/BLA Multidisciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	213478
Priority or Standard	Priority
Submit Date(s)	02/17/2020
Received Date(s)	02/18/2020
PDUFA Goal Date	08/18/2020
Division/Office	Division of Dermatology and Dentistry (DDD)
Review Completion Date	08/12/2020
Established/Proper Name	sirolimus topical gel, 0.2%
(Proposed) Trade Name	Hyftor
Pharmacologic Class	Mammalian target of rapamycin (mTOR) inhibitor
Code name	NPC-12G and OSD-001
Applicant	Nobelpharma Co, Ltd.
Dosage form	Gel
Applicant proposed Dosing Regimen	Apply Hyftor to the skin of the face affected with angiofibroma twice daily in the morning and at bedtime.
Applicant Proposed Indication(s)/Population(s)	Indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	36025004 - Fibrous skin tumor of tuberous sclerosis
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	36025004 - Fibrous skin tumor of tuberous sclerosis
Recommended Dosing Regimen	Apply Hyftor to the skin of the face affected with angiofibroma twice daily in the morning and at bedtime.

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Reviewers of Multidisciplinary Review and Evaluation

Regulatory Project Manager	Strother D. Dixon
Nonclinical Reviewer	Jill Merrill, PhD
Nonclinical Supervisor	Barbara Hill, PhD
Office of Clinical Pharmacology Reviewer(s)	Da Zhang, PhD
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla, PhD
Clinical Reviewer	Patricia Brown, MD and Kevin Clark, MD
Clinical Team Leader	Gordana Diglisic, MD
Statistical Reviewer	Marilena Flouri, PhD
Statistical Team Leader	Mohamed Alosh, MD
Cross-Disciplinary Team Leader	Gordana Diglisic, MD
Division Director	Kendall A. Marcus, MD

Additional Reviewers of Application

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DPMH	Kristie Baisden, DO, Medical Officer, Maternal Health Tamara Johnson, MD, MS, Team Leader, Maternal Health
OPDP	Laurie Buonaccorsi, PharmD
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OSI	Cheryl Grandinetti, PharmD
OSE/DMEPA	Madhuri Patel, PharmD

CDRH, Center for Devices and Radiological Health
COA, Clinical Outcomes Assessment
DMEPA, Division of Medication Error Prevention and Analysis
DPMH, Division of Pediatric and Maternal Health
OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
OSI, Office of Scientific Investigations
OSE, Office of Surveillance and Epidemiology
PLT, Patient Labeling Team

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Product Quality Team Leader	Hamid Shafei, PhD	OPQ/Office of New Drug Products/ Division of New Drug Products II	Sections: 4.2	Select one: _X_ Authored _X__ Approved
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Nonclinical Reviewer	Jill Merrill, PhD	Office of Immunology and Inflammation (OII)/ Division of Pharm-Tox for Immunology and Inflammation (DPTII)	Sections: 5, 15.3	Select one: _X_ Authored ___ Approved
	Signature in DARRTS			
Nonclinical Supervisor	Barbara Hill, PhD	OII/DPT-II	Sections: 5, 15.3	Select one: ___ Authored _X_ Approved
	Signature in DARRTS			
Clinical Pharmacology Reviewer	Da Zhang, PhD	Office of Clinical Pharmacology (OCP)/ Division Of Inflammation & Immune Pharmacology (DIIP)	Sections 6, 15.5	Select one: _X_ Authored ___ Approved
	Signature in DARRTS			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP/DIIP	Section: 6, 15.5	Select one: ___ Authored _X__ Approved
	Signature in DARRTS			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Patricia Brown, MD	Office of Immunology and Inflammation (OII)/DDD	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 15.2	Select one: _X_ Authored ___ Approved
	Signature in DARRTS			
Clinical Reviewer	Kevin Clark, MD	OII/DDD	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 15.2	Select one: _X_ Authored ___ Approved
	Signature in DARRTS			
Clinical Team Leader	Gordana Diglisic, MD	OII/DDD	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 15.2	Select one: ___ Authored _X_ Approved
	Signature in DARRTS			
Division Director (Clinical)	Kendall A. Marcus, MD	OII/DDD	Sections: Authored: 14; Approved: All	Select one: _X__ Authored _X__ Approved
	Signature in DARRTS			
Statistical Reviewer	Marilena Flouri, PhD	Office of Translational Sciences (OTS)/Division of Biometrics (DB) III	Sections: 8.1, 8.3, 8.4, 15.4	Select one: _X_ Authored ___ Approved
	Signature in DARRTS			
Statistical Team Leader	Mohammed Alosh, PhD	OTS/DB III	Sections: 8.1, 8.3, 8.4, 15.4	Select one: ___ Authored _X_ Approved
	Signature in DARRTS			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Division Director (OB)	Laura Lee Johnson, PhD	OTS/DB III	Sections: 8.1, 8.3, 8.4, 15.4	Select one: ___ Authored _X_ Approved
	Signature in DARRTS			

Glossary

AE	adverse event
AF	angiofibroma
API	active pharmaceutical ingredient
AR	adverse reaction
BA	bioavailability
BL	baseline
BSA	body surface area
CDLQI	Children Dermatology Life Quality Index
CDRH	Center for Devices and Radiological Health
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease-2019
CYP	cytochrome P450
DCOA	Division of Clinical Outcome Assessment
DLQI	Dermatology Life Quality Index
DMF	drug master file
DPMH	Division of Pediatric and Maternal Health
ECG	electrocardiogram
FA	facial angiofibroma
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practices
ICH	International Council for Harmonisation
IND	investigational new drug
IR	information request
IRC	Independent Review Committee
LAM	lymphangioleiomyomatosis
LD	listed drug
LTS	long-term safety
mTOR	mammalian target of rapamycin
NDA	new drug application
NF-1	neurofibromatosis type 1
NOAEL	no observable adverse effect level
OPDP	Office of Prescription Drug Promotion
OSI	Office of Scientific Investigation
p-gp	p-glycoprotein
PI	prescribing information
PK	pharmacokinetics
PPI	patient package insert (also known as patient information)
PPK	population pharmacokinetics

PRO	patient-reported outcome
PT	preferred term
RGB	red, green, blue
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SDTM	Study Data Tabulation Model
SOC	system organ class
TEAE	treatment-emergent adverse event
TS	tuberous sclerosis
UV	ultraviolet

1. Executive Summary

1.1. Product Introduction

The Applicant is seeking approval for Hyftor (sirolimus) Topical Gel, 0.2% (hereafter referred to as sirolimus gel, 0.2%) under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The listed drug is Rapamune (sirolimus) Tablets (new drug application [NDA] 021110), which is indicated for prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants, and for the treatment of patients with lymphangioleiomyomatosis (LAM). The Applicant established a clinical bridge between sirolimus gel, 0.2% and Rapamune Tablets, and proposed to rely upon the Agency's findings of safety for nonclinical toxicology data (reproductive toxicity, carcinogenesis, mutagenesis, and impairment of fertility) for the listed drug (LD).

The Applicant's request for Orphan Drug designation for sirolimus, for the treatment of facial angiofibroma (FA) associated with tuberous sclerosis (TS), was granted (letter dated 05/17/2017). Also, the Applicant's request for Fast Track designation was granted (letter dated 11/27/2018).

The active ingredient is sirolimus, which is an inhibitor of the mammalian target of rapamycin (mTOR). Sirolimus is marketed in the United States in dosage forms including tablets and oral solution. There are no topical formulations of sirolimus currently marketed in the United States. The indication proposed by the Applicant is treatment of FA associated with TS in adults and pediatric patients (b) (4) or older. The proposed dosing regimen is application to the skin of the face affected by AF twice daily—in the morning and at bedtime.

The Agency concluded that the proposed proprietary name, Hyftor™, was acceptable from both promotional and safety perspectives under NDA 212379 (Proprietary Name Review by Dr. Madhuri Patel, Division of Medication Error Prevention and Analysis, dated 04/29/2020).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from a Phase 3 trial (NPC-12G-1), which provided evidence of the effectiveness of sirolimus gel, 0.2% for the treatment of FA associated with TS in adults and pediatric patients 6 years of age or older. The trial assessed the primary endpoint of "composite improvement in angiofibroma assessed using photographs by an Independent Review Committee (IRC) at Week 12." The composite improvement in angiofibroma (AF) was assessed in terms of the size and color (redness) of tumors.

However, several problems with the assessment of photographs were identified during review of this application. The photographic technique was not standardized in terms of lighting, background, distance from the camera to the subject, or subject position. Investigators, as well as personnel who performed the editing of photographs, were blinded only to the treatment

arm, and not to whether photographs were taken before or after treatment. In addition, the Applicant did not provide validation testing to demonstrate that their use of the camera in Auto Mode, the image correction procedure, and the Casmatch system do not alter the color or size of skin lesions for assessment of the primary endpoint. Because of these issues, the designated primary endpoint, based on the IRC assessment, is not considered acceptable for assessing efficacy for the indication of treatment of FA associated with TS. The secondary endpoint, based on the investigator live assessment, is considered more appropriate than the designated primary endpoint for assessing efficacy.

Despite the several issues regarding the efficacy assessment summarized in this review, and given the proportion of subjects assessed as "Improved" or "Markedly Improved" by the investigator based on composite improvement, some subjects with FA associated with TS appear to benefit from treatment with sirolimus gel in terms of improvement of the size and redness of FA in comparison to the vehicle gel. The proportion of subjects assessed in person by the investigator as "Improved" or "Markedly Improved" at Week 12 was 23% for subjects treated with sirolimus gel, 0.2%, and 6% for subjects treated with vehicle. Although this result did not reach statistical significance, the review team concluded that the result was clinically meaningful.

The Applicant has demonstrated that sirolimus gel, 0.2% is effective for its intended use in the target population, and has met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval. However, because of deficiencies noted by the Office of Product Quality, the review team recommends a Complete Response for NDA 213478. Refer to Section 4.2 for further information regarding deficiencies noted by the Office of Pharmaceutical Quality.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant, Nobelpharma Co., Ltd., submitted NDA 213478 for Hyftor (sirolimus) Topical Gel, 0.2% (hereafter referred to as sirolimus gel, 0.2%) under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The indication proposed by the Applicant is treatment of facial angiofibroma (FA) associated with tuberous sclerosis (TS) in adults and pediatric patients (b) (4) of age or older. Sirolimus is an inhibitor of the mammalian target of rapamycin (mTOR). The listed drug (LD) is Rapamune (sirolimus) Tablets (New Drug Application [NDA] 021110), which is currently indicated for prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants, and for the treatment of patients with lymphangioleiomyomatosis (LAM). The Applicant established a clinical bridge between sirolimus gel, 0.2% and Rapamune Tablets, and proposed to rely upon the Agency's findings of safety in the nonclinical toxicology data (reproductive toxicity, carcinogenesis, mutagenesis, and impairment of fertility) for the LD.

In a Phase 3, multicenter, randomized, double-blind, vehicle-controlled trial conducted in 62 subjects aged 6 years and older with TS and three or more FA lesions ≥2 mm in diameter with redness in each, the proportion of subjects assessed in person by the investigator as 'Improved' or 'Markedly Improved' at Week 12 was 23% for subjects treated with sirolimus gel, 0.2%, and 6% for subjects treated with vehicle. This was a protocol-specified secondary efficacy endpoint. Although this result did not reach statistical significance, the review team concluded that the result was clinically meaningful. Despite the several issues regarding the efficacy assessment summarized in the review, given the proportion of subjects assessed as "Improved" or "Markedly Improved" by the investigator based on composite improvement, some subjects with FA associated with TSC appear to benefit from the treatment of sirolimus gel in terms of improvement of the size and redness of angiofibroma in comparison to the vehicle gel.

The safety profile for sirolimus gel, 0.2% was adequately characterized during the development program. No deaths occurred during the development program. However, a total of four deaths has been reported to date in the postmarketing safety study in Japan; none was considered related to treatment with sirolimus gel, 0.2%. During the Phase 3 trial, one subject (1/30; 3.3%) treated with sirolimus gel, 0.2% experienced two serious adverse events (SAEs) of acute pancreatitis and gastric hemorrhage. Neither was related to treatment with sirolimus gel, 0.2%. No SAEs were reported in subjects treated with vehicle. The most common adverse reactions (ARs) were dry skin, application site irritation, pruritus, acne, acneiform dermatitis, ocular hyperemia, skin hemorrhage, and skin irritation. Dry skin was reported by 40% of subjects treated with sirolimus gel, 0.2%, and by 13% of subjects treated with vehicle. Application site irritation was reported by 37% of subjects treated with sirolimus gel, 0.2% and 28% of subjects treated with vehicle. Pruritus was reported by 17% of subjects treated with sirolimus gel, 0.2%, and by 13% of subjects treated with vehicle. Acne was reported by 7% of subjects treated with sirolimus gel, 0.2%, and by no subject treated with vehicle. Acneiform dermatitis, ocular hyperemia, skin hemorrhage, and skin irritation were each reported by 3% of subjects treated with sirolimus gel, 0.2%, and by no subject treated with vehicle. ARs were mild or moderate in severity. The Applicant also submitted long-term safety data from a 104-week, open-label, long-term safety trial and a postmarketing study conducted in Japan.

In summary, FA associated with TS may cause hemorrhage, obstruction of facial orifices, and disfigurement, which may result in functional impairment and/or emotional distress. Surgical intervention may be indicated for lesions causing impaired function, irritation, bleeding, pain, or disfigurement. However, the benefits of invasive treatments must be weighed against the risk of scarring and the need for general anesthesia, especially in medically complex patients such as those with TS. There are no drug products currently approved in the United States for the treatment of AF associated with TS. The available evidence of safety and efficacy supports the approval of NDA 213478, Hyftor (sirolimus) Topical Gel, 0.2% for the treatment of AF associated with TS in adults and pediatric patients 6 years of age and older. However, because of the deficiencies noted by the Office of Pharmaceutical Quality, the review team recommends a Complete Response for NDA 213478.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• TS in an inherited neurocutaneous disorder involving many organ systems. TS is caused by a mutation in either the TSC1 or TSC2 gene, and is inherited in an autosomal dominant pattern. TS affects 1 in 6000 newborns in the United States. Approximately 40,000 to 80,000 people in the United States, and as many as 2 million people worldwide, have TS. FA associated with TS begins to appear as early as during the first 2 years of life, and by adolescence angiofibromas are present in approximately 80% of patients with TS.	• FA associated with TS may cause hemorrhage, obstruction of facial orifices, and disfigurement, which may lead to emotional distress.
Current Treatment Options	• There are no drug products currently approved in the United States for the treatment of FA associated with TS. Surgical intervention may be indicated for lesions causing impaired function, irritation, bleeding, pain, or disfigurement. However, the benefits of invasive treatments must be weighed against the risk of scarring and the need for general anesthesia, especially in medically complex patients such as those with TS. • Afinitor (everolimus; NDA 22334) is an orally administered inhibitor of mTOR approved in the United States for the treatment of TS-associated renal angiomyolipoma, subependymal giant cell astrocytoma, and partial-onset seizures. In clinical trials for these indications, improvement in skin manifestations was also noted. However, Section 5 (Warnings and Precautions) of the labeling for everolimus includes predisposition to infections (including opportunistic infections), severe hypersensitivity, stomatitis, renal failure, risk of impaired wound healing, metabolic disorders (hyperglycemia, hypercholesterolemia, and hypertriglyceridemia), and myelosuppression.	• An mTOR inhibitor formulated for topical application that demonstrates a treatment effect for FA associated with TS, with less systemic toxicity than orally administered mTOR inhibitors, would be an important addition to the therapeutic armamentarium for this condition.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Data from a Phase 3 clinical trial provide substantial evidence of the effectiveness of sirolimus gel, 0.2% for the treatment of FA associated with TS. The trial was conducted in 62 subjects aged 6 years and older with TS and three or more FA lesions ≥2 mm in diameter with redness in each. The proportion of subjects assessed, in person by the investigator, as 'Improved' or 'Markedly Improved' at Week 12 was 23% for subjects treated with sirolimus gel, 0.2%, and 6% for subjects treated with vehicle; this assessment being a protocol-specified secondary efficacy endpoint. Although this result did not reach statistical significance, the review team concluded that the result was clinically meaningful. • Despite the several issues regarding the efficacy assessment summarized in this review, given the proportion of subjects assessed as "Improved" or "Markedly Improved" by the investigator based on composite improvement, some subjects with FA associated with TS appear to benefit from the treatment of sirolimus gel in improving the size and redness of angiofibroma in comparison to the vehicle gel. • Review of the safety data from the clinical trials revealed that sirolimus gel, 0.2% was well tolerated by all subgroups.	• Sirolimus gel, 0.2% provides an effective and safe treatment option for AF associated with TS in patients 6 years of age and older.
Risk and Risk Management	• The primary safety database (Phase 3 Trial NPC-12G-1) included 30 subjects who were treated with sirolimus gel, 0.2%. No deaths occurred during the development program. However, a total of four deaths has been reported to date in the postmarketing safety study in Japan; none was considered related to treatment with sirolimus gel, 0.2%. There were no SAEs related to treatment with sirolimus gel, 0.2%. The most common ARs were dry skin, application site irritation, pruritus, acne, acneiform dermatitis, ocular hyperemia, skin hemorrhage, and skin irritation. Dry skin was reported by 40% of subjects treated with sirolimus gel, 0.2% and 13% of subjects treated with vehicle. Application site irritation was reported by 37% of subjects treated with sirolimus gel, 0.2% and 28% of subjects treated with vehicle. Pruritus was reported by 17% of subjects treated with sirolimus gel, 0.2% and 13% of subjects treated with vehicle. Acne was reported by 7% of subjects treated with sirolimus gel, 0.2% and no subjects treated with vehicle. Acneiform	• The risks associated with the use of sirolimus gel, 0.2% appear to be favorable. ARs were mostly related to skin and application site, and were mild or moderate in intensity. • Prescription labeling, patient labeling, and routine pharmacovigilance are adequate to manage the risks of the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	dermatitis, ocular hyperemia, skin hemorrhage, and skin irritation were each reported by 3% of subjects treated with sirolimus gel, 0.2% and no subjects treated with vehicle. ARs were mild or moderate in severity. The Applicant also submitted long-term safety data from a 104-week, open-label, long-term safety trial and a postmarketing study conducted in Japan. • Labeling: Prescription labeling adequately addresses the known risks associated with the moiety and those identified during product development. • No issues require further assessment with a postmarketing requirement or postmarketing commitment. • A risk evaluation and mitigation strategy is not recommended.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient-reported outcome (PRO)	8.1.1.6
		□	Observer-reported outcome (ObsRO)	
		X	Clinician-reported outcome (ClinRO)	8.1.1, 8.2.6
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

TS is an inherited neurocutaneous disorder involving many organ systems. TS is caused by a mutation in either the *TSC1* or *TSC2* gene, and is inherited in an autosomal dominant pattern. De novo mutations account for approximately 80% of TS cases (Randle 2020).

TS affects 1 in 6000 newborns in the United States. Approximately 40,000 to 80,000 people in the United States, and as many as 2 million people worldwide, have TS. Males and females are affected in equal numbers, and the disorder occurs in all races and ethnic groups (NORD 2019).

A diagnosis of TS is based upon the identification of characteristic symptoms, a detailed patient and family history, a thorough clinical evaluation, and a variety of specialized tests. Generally, a diagnosis is considered definitive in individuals with two or more major features, or one major feature and two or more minor features of the disorder. A possible diagnosis is sought when one major feature, or two or more minor features, is present (NORD 2019). The diagnostic criteria for TS are presented in Table 1.

Table 1. Diagnostic Criteria According to the International Tuberous Sclerosis Consensus Conference

Definite diagnosis: Two major features or one major feature with ≥ two minor features **Possible diagnosis: Either one major feature or ≥ two minor features**		
Dermatology / dental medicine	Major feature: ▸ Hypomelanotic macules (n ≥ 3, ≥ 5 mm in diameter) ▸ Angiofibromas (n ≥ 3) or fibrous cephalic plaque ▸ Ungual fibromas (n ≥ 2) ▸ Shagreen patch	Minor feature: ▸ "Confetti" skin lesions ▸ Dental enamel pits (n > 3) ▸ Intraoral fibromas (n ≥ 2)
Neurology	Major feature: ▸ Cortical dysplasias (includes tubers and cerebral white matter radial migration lines) ▸ Subependymal nodules (SEN) ▸ Subependymal giant cell astrocytoma (SEGA)	
Ophthalmology	Major feature: ▸ Multiple retinal hamartomas	Minor feature: ▸ Retinal achromic patch
Cardiology	Major feature: ▸ Cardiac rhabdomyoma	
Pulmonology	Major feature: ▸ Lymphangioleiomyomatosis (LAM)[1]	
Nephrology	Major feature: ▸ Angiomyolipomas (n ≥ 2)[1,2]	Minor feature: ▸ Multiple renal cysts
Other organs		Minor feature: ▸ Nonrenal hamartomas
Genetics	Identification of a pathogenic mutation of either *TSC1* or *TSC2*[3] in DNA from normal tissue is sufficient to make a definite diagnosis	

[1]A combination of the two major clinical features (lymphangioleiomyomatosis and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.
[2]Anatomic location may include the liver or other organ systems.
[3]A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins, prevents protein synthesis or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd.nl/TSC2).

Source: Ebrahimi-Fakhari et al. (2017); Table 1, p. 696

The severity of TS can vary substantially among affected individuals within the same family, and from one family to another. Systemic manifestations may include lesions in the brain, heart, kidney, lungs, and eyes. Brain involvement may be associated with seizures, cognitive deficits, and neurodevelopmental disorders including autism. Cardiovascular manifestations include cardiac rhabdomyoma, which may be multifocal. Renal lesions also commonly occur with TS; angiomyolipomas being the most common manifestation. Patients with TS and renal lesions may have renin-dependent hypertension, and are at risk of developing chronic kidney disease because of replacement and compression of the renal parenchyma. Some adults with TS develop a pulmonary disease that is indistinguishable from the diffuse interstitial fibrosis known as LAM. Both children and adults with TS are at risk of malignancy, primarily in the kidneys, brain, and soft tissues (Randle 2020).

The dermatologic features of TS include hypopigmented macules, AFs, Shagreen patches, and fibrous forehead plaque. AFs begin to appear as early as within the first 2 years of life, and by adolescence AFs are present in approximately 80% of patients with TS (their number remains

stable thereafter). The lesions may begin as erythematous macules and then mature into pink to red, or red to brown, papules or papulonodules, which may coalesce into plaques. AFs typically develop on the malar regions of the face and may cause hemorrhage, obstruction of facial orifices, and disfigurement, which can lead to emotional distress (Randle 2020).

2.2. Analysis of Current Treatment Options

There are no drug products currently approved in the United States for the treatment of FA associated with TS. Surgical intervention may be indicated for lesions causing impaired function, irritation, bleeding, pain, or disfigurement. However, the benefits of invasive treatments must be weighed against the risk of scarring and the need for general anesthesia, especially in medically complex patients such as those with TS (Ebrahimi-Fakhari et al. 2017).

Afinitor (everolimus; NDA 22334) is an orally administered inhibitor of mTOR that is approved in the United States for the treatment of TS-associated renal angiomyolipoma, subependymal giant cell astrocytoma, and partial-onset seizures. In clinical trials conducted with everolimus for these indications, improvement in skin manifestations was noted as well (Ebrahimi-Fakhari et al. 2017). However, Section 5 (Warnings and Precautions) of the labeling for everolimus includes predisposition to infections (including opportunistic infections), severe hypersensitivity, stomatitis, renal failure, risk of impaired wound healing, metabolic disorders (hyperglycemia, hypercholesterolemia, and hypertriglyceridemia), and myelosuppression.

An mTOR inhibitor formulated for topical application that demonstrates a treatment effect for FA associated with TS, with less systemic toxicity than orally administered mTOR inhibitors, would be an important addition to the therapeutic armamentarium for this condition.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Because sirolimus topical gel, 0.2% is not currently marketed in the United States, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed sirolimus gel, 0.2% under investigational new drug (IND) application 137467 using the 505(b)(2) regulatory pathway. The Applicant selected Rapamune (sirolimus) Tablets (NDA 021110) as the LD, and proposed to establish a clinical bridge to the LD to rely upon the Agency's findings of safety for nonclinical toxicology data (reproductive toxicity, carcinogenesis, mutagenesis, and impairment of fertility) for the LD. The Applicant's request for Orphan Drug designation for sirolimus for the treatment of AF associated with TS was granted

(letter dated 05/17/2017). The product was approved in Japan in March 2018 for the treatment of "skin lesions including angiofibromas associated with tuberous sclerosis."

The Agency held a pre-IND meeting with the Applicant on 02/21/2018. It was noted at this meeting that the principal efficacy and safety trials had already been conducted. The protocols had not yet been submitted to the Agency for review, and the Agency did not provide input regarding trial design, population, or endpoints. During the pre-IND meeting, the Agency provided advice regarding the establishment of a clinical bridge to the LD. Information regarding application for Fast Track and Breakthrough Therapy designations was also provided. At the time of the pre-IND meeting, the Agency did not agree that the clinical data package consisting of the Phase 1/2 dose-finding trial, the pivotal Phase 3 trial, and the open-label long-term safety trial was sufficient to support approval. The Agency also asked the Applicant to clarify the baseline (BL) disease severity studied in the clinical trials. The Applicant was also asked to clarify whether or how the components of the primary endpoint ("change from BL in tumor volume" and "change from BL in redness") were determined to be clinically meaningful. The Agency further advised that the primary endpoint should be evaluated in person by the clinician.

The Applicant opened their IND on 07/10/2018 (b) (4) and submitted the request for Fast Track and Breakthrough Therapy designations. (b) (4)

The Agency denied the Applicant's request for Breakthrough Therapy designation, (b) (4) However, the Agency granted the Applicant's request for Fast Track Designation (letter dated 11/27/2018).

The Agency held a pre-NDA meeting with the Applicant on 12/03/2018, during which it provided general guidance regarding the data requirements to support filing, as well as the content and format of the submission. The Agency again advised the Applicant to establish a clinical bridge to the LD, for which the Applicant proposed to conduct a relative bioavailability (BA) study to establish the clinical bridge. The Agency recommended that the Applicant submit a protocol for review prior to initiating the study. The Applicant was also advised that if the systemic exposure of the topical product, under maximal use conditions, is lower than the oral LD, then a thorough QT study would not be required per International Council for Harmonisation (ICH) E14. In addition, advice was provided regarding the content of the 120-day safety update.

During the pre-NDA meeting, the Agency also emphasized the importance of evidence to support the claim that the treatment effect was clinically meaningful. The Applicant was also asked to clarify why change in lesion color and size were selected as the key factors for evaluating improvement from baseline, and are hence relevant for the assessment of treatment effect, the interpretation of study findings, and for addressing the disagreement in treatment effect between investigator (live) assessment and assessment by panel review of photographs. The Agency also requested the Applicant to provide information about the standardized methods used in taking the photographs (e.g., distance, lighting, camera type), and to provide photographs for all subjects. The Agency also expressed concerns about assessing improvement in the absence of a BL score. In addition, the Agency requested the Applicant to provide a scientific discussion of the applicability of data collected in the Japanese population relative to the U.S. population. The Agency also advised that because their studies were initiated prior to December 2016, the Applicant would not be required to submit Clinical Data Interchange Standards Consortium-compliant datasets (i.e., Study Data Tabulation Model [SDTM] and Analysis Data Model datasets). The Applicant was advised that the datasets should be submitted in Statistical Analysis System (SAS) transport format (.xpt).

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Following discussions between the Office of Scientific Investigations (OSI) and the Division of Dermatology and Dentistry, a decision was made that assessment of the application could proceed without good clinical practices (GCP) inspections. Refer to the Memo to File by Cheryl Grandinetti, Ph.D. dated 06/02/2020.

4.2. Product Quality

The Applicant, Nobelpharma Co., Ltd. has submitted this 505(b)(2) NDA for Hyftor® (sirolimus) Topical Gel, 0.2% for the treatment of AF associated with TS in adult and pediatric patients (b) (4) of age or older. However, based on the clinical information provided in the application, this drug product will only be considered for use in patients 6 years of age or older. Hyftor is intended for topical administration (b) (4) to the affected skin area twice daily with a maximum daily dose of 0.8 g (800 mg) of gel, equivalent to 1.6 mg of sirolimus. This application was granted Orphan Drug and Fast-Track designations.

Conclusions:

- Drug substance:
  - The Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, sirolimus.

- Drug product:
  - The Applicant has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, Hyftor (sirolimus) Topical Gel, 0.2%.
- Facilities:
  - Facilities have not been cleared because of pending required preapproval inspections of TOYO Pharmaceutical Co., Ltd. manufacturing facility, FEI 3016419927 because of the current travel restrictions imposed by the coronavirus disease-2019 (COVID-19) pandemic.
- Label/labeling:
  - The CMC issues on labels/labeling have not been satisfactorily resolved.
- Categorical exclusion from the environmental assessment:
  - The Applicant's request for categorical exclusion from the environmental assessment has been granted.

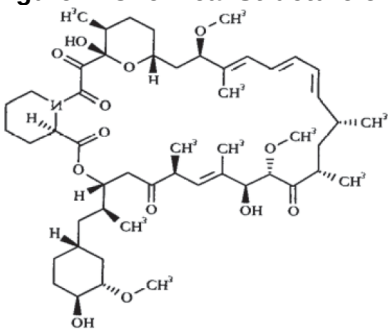
From the OPQ perspective, this NDA is recommended for a Complete Response per 21 CFR 314.125(b)(1)(6),(13) until the above issues are satisfactorily resolved (see the list of deficiencies).

Drug Substance

The drug substance sirolimus, also known as rapamycin, is an antifungal antibiotic which is also an mTOR inhibitor immunosuppressive agent. It is a naturally occurring macrolide that is isolated from *Streptomyces hygroscopicus*. Sirolimus was first approved on 08/25/1999 as the active ingredient in Rapamune oral solution. Since its original approval, multiple generic products containing this active ingredient have been approved for the U.S. market. Sirolimus is a white to off-white powder that is practically insoluble in water, but freely soluble in acetone, methanol, and dimethyl sulfoxide.

Sirolimus has the chemical name (3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34AS)-9,10,12,13, 14,21,22,23,24,25,26,27,32,33,34,34A-hexadecahydro-9,27-dihydroxy-3-((1R)-2-((1S,3R, 4R)-4-hydroxy-3-methoxycyclohexyl)-1-methylethyl)-10,21-dimethoxy-6,8,12,14,20,26- hexamethyl-23,27-epoxy-3H-pyrido(2,1-C)-(1,4)oxaazacyclohentriacontine-1,5,11,28,29- (4H,6H,31H)-pentone, a molecular formula of $C_{51}H_{79}NO_{13}$, and a molecular weight of 914.17. The chemical structure of sirolimus is shown in Figure 1.

Figure 1. Chemical Structure of Sirolimus



Sirolimus drug substance for this application is manufactured in accordance with current good manufacturing practices by [redacted] (b) (4) It is tested and released against an adequate drug substance specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest period of [redacted] (b) (4) when stored at the long-term storage condition of [redacted] (b) (4) °C. The information regarding the manufacture of sirolimus supplied by this manufacturer is provided in Drug Master File (DMF) [redacted] (b) (4). This DMF has been reviewed and was found to be adequate.

Drug Product

Hyftor (sirolimus) Topical Gel, 0.2% has been developed for the treatment of FA associated with TS in adults and children 6 years of age or older. This drug is intended to be topically administered [redacted] (b) (4) to the affected skin area twice daily at a maximum daily dose of 600 mg of gel (equivalent to 1.2 mg of sirolimus) for 6 to 11 years old, and at a maximum daily dose of 800 mg of gel (equivalent to 1.6 mg of sirolimus) for 12 years of age or older. [redacted] (b) (4)

Hyftor is a transparent, colorless, aqueous gel packaged as 10 g in aluminum tubes with [redacted] (b) (4) caps. Each gram of Hyftor Gel contains 2 mg of sirolimus as the active ingredient, and [redacted] (b) (4) alcohol [redacted] (b) (4), Carbomer 940 [redacted] (b) (4) purified water [redacted] (b) (4), and trolamine (pH modifier) as inactive ingredients. The inactive ingredients used in the composition of the drug product are compendial materials.

The drug product is manufactured by TOYO Pharmaceutical Co., Ltd., Osaka, Japan for Nobelpharma Co., Ltd. It is tested and released against a specification that includes testing and acceptance criteria for all physical and chemical attributes essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout its currently proposed expiration dating period of 15 months. The Applicant has provided sufficient stability data to support the proposed expiration dating period of 15 months when stored under the long-term storage condition of 2 to 8°C.

Multiple manufacturing process deficiencies regarding the manufacture of Hyftor have been identified. Furthermore, because of the travel restrictions imposed by the COVID-19 pandemic, the required preapproval inspection of TOYO Pharmaceutical's drug product manufacturing site cannot be performed at this time. Therefore, the application cannot be approved until the deficiencies noted below are appropriately addressed. The following are recommended to be included in the Action Letter/Complete Response:

1. The Agency acknowledges that if the active pharmaceutical ingredient (API) assay result is outside the range of (b) (4) We remind you that if the API assay for a batch of sirolimus falls outside the range of (b) (4) %, it fails to meet the drug substance specification and cannot be used in the manufacture of the commercial drug product.
2. You acknowledged in your response to Information Request 5 (b) (4)
   a) Revise all manufacturing process parameters for commercial production to conform to either a set point, or a range with lower and upper limits. Those parameters should be supported by data collected from the manufacturing process used for development and/or registration batches, and by adequate discussion of potential scalability issues for scale-dependent parameters.
   b) Revise the pertinent section of P.3 and the master batch record accordingly.
3. (b) (4)
4.

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Facilities

An inspection of the TOYO Pharmaceutical Co. Ltd. facility (FEI 3016419927) located in Tsurumi-Ku, Osaka, Japan; is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with current good manufacturing practices. Due to restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. You may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted, and any findings are assessed with regard to your application. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections once safe travel resumes, and according to public health need and other factors.

For more information, please see the FDA guidances related to COVID-19. These can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

4.3. Clinical Microbiology

This section is not applicable.

4.4. Devices and Companion Diagnostic Issues

In the Phase 3 clinical trial, the Applicant used photographs to assess primary and secondary endpoints by an IRC. According to the NPC-12G-1 clinical protocol (Ver. 1.06), the photographs were used to evaluate:

- Improvement in the size of AF based on shrinkage, flattening, or disappearance of tumors.
- Improvement in the color (reddishness) of AF based on overall change in reddishness relative to that of the normal region as indicated by the Pantone® color sample (Figure 2). Reddishness was judged by applying the Applicant-specified sample for assessing reddishness to the lesions of AF, to compare the sample with the tumor, as well as with photographs of lesions taken before the prescribed visit.

Figure 2. Reddishness Scale

[Status of reddishness in terms of the Pantone® color sample]

Level	Status of Reddishness	Pantone® Color Sample Remark
1	As dark as or paler than Pantone® 489C	
2	As dark as or paler than Pantone® 486C	
3	As dark as or paler than Pantone® 7416C	
4	As dark as or paler than Pantone® 485C	
5	As dark as or paler than Pantone® 704C	
6	Darker than Pantone® 704C	-

Remarks The colors shown in the Pantone® color sample column in the above table are not accurate reproduction of the color tones indicated by the numbers. In the assessment of reddishness, always use a sample for assessing reddishness.

- Improvement of hypomelanotic macule on the head (above the neck) assessed by the change in color tone from BL, and by the area of the lesion based on comparison in color tone between the lesion and a normal region near the lesion.
- Improvement in plaque on the head (above the neck),assessed by shrinkage or enlargement of eminence when compared to photographs of the lesions taken before the prescribed visit.

According to the NPC-12G-1 clinical protocol (Ver. 1.06), the photographs of each lesion; i.e., AF and hypomelanotic macule and plaque on the head, together with a color sample (Casmatch®) and scale bar were taken at each efficacy assessment time point. The photographic equipment (camera) specified and distributed by the Applicant were used. The Applicant states that the photographs were taken by photographers with adequate education in the procedure, and the number of photographers at each study institution was kept to the minimum required. With respect to hypomelanotic macules and plaques observed on subjects' heads, to which the investigational product was applied, no photographs were taken, and no assessment of improvement was performed.

(b) (4)

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(b) (4)

Historically, CDRH has accepted beforeand after treatment photographs for the assessment of endpoints when standardized photographs are provided (using the same camera model in manual mode with fixed settings, the same camera distance from the imaging target, and the same lighting and facial positioning for all patients, before, during, and after the treatment) and images have not been intentionally altered. This would separate the noise introduced by changes in the environment from clinical changes in the patient caused by the treatment. In addition, the general procedures in clinical trials were as follows: photographs are reviewed in a blinded manner (e.g., "before" and "after" treatments are not indicated to the reviewer), blinded reviewers correctly identify a predefined percentage of "after" images, and/or achieve a responder rate of at least X% (predefined endpoint) where "Responder" is selected by at least two of three blinded reviewers scoring a change of at least N points (predefined) on a validated severity scale for that subject's before and after photographs.

The Applicant was asked on 05/01/2020, and again on 06/01/2020, to provide validation that the image correction and Casmatch system do not alter the color or size of skin lesions, to demonstrate how differences in the location or tilt (x,y,z) of the marker, artifacts, noise, curvature, angle, distance, nonuniform spatial illumination, or any other environmental parameters affect the processed image, and to demonstrate whether changes in the color (or other image parameters) are a result of processing artifacts or are actual change(s), because some of their processed images show significant changes in the subject's full-face skin color before and after treatment.

In response to an FDA IR dated 05/01/2020, the Applicant provided high-level information (not details) on the image correction method, without any validation data. The Applicant also included images of subjects' before and after correction, and a list of inquiry contacts from the

imaging center when "*color correction was considered impossible*" (29 inquiries), "*photograph angles were mismatched with the baseline*" (11 inquiries), "*unclear tumor lesion*" (8 inquiries), and "*blurring in the focus*" (15 inquiries). For some of the inquiries, the Applicant noted that they provided other patient images to the image center for image correction.

(b) (4)

Validation testing is necessary to adequately demonstrate that the camera's Auto Mode, the image correction, and the Casmatch system do not alter the color or size of skin lesions (which are the components of the primary efficacy endpoint). Therefore, in the absence of validation testing, use of altered photographs to establish the efficacy of the product is not acceptable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted a 505(b)(2) application for Hyftor (sirolimus) Topical Gel, 0.2% for the treatment of AF associated with TS in adults and (b) (4), using Rapamune®(sirolimus) Tablets as the LD. Rapamune® has, since 2000, been approved as an original NDA for the prophylaxis of organ rejection in patients undergoing renal transplantation under NDA 21110.

The Applicant has established an adequate clinical bridge to the LD, Rapamune®(sirolimus) Tablets. Refer to Section 6 (Clinical Pharmacology) of this review for details. The Applicant is relying on the Agency's finding of safety for the LD. The nonclinical information from the approved labeling for the LD, that the Applicant intends to rely on, includes fertility and reproduction, embryofetal development, genetic toxicity, and carcinogenicity. The toxicity profile of sirolimus is well-characterized and typical for the mTOR inhibitor immunosuppressant pharmacologic class.

The Applicant submitted a pivotal 39-week repeat-dose dermal toxicity study of sirolimus gel in cynomolgus monkeys (4/sex/group) with twice daily dosing to a treatment area approximately equal to 5% of the body surface area (BSA) (0, 0.05%, 0.2%, 0.8% sirolimus gel; 0, 0.125, 0.5, 2.0 mg/kg/dose sirolimus; 0, 0.25, 1.0, 4.0 mg/kg/day sirolimus). Based on deaths after at least 37 weeks of dosing (1/4 males at 4.0 mg/kg/day and 1/4 females at 1.0 mg/kg/day), decreased body weights and immunosuppressant effects, a no observable adverse effect level (NOAEL) could not be determined in this study. No preneoplastic or hyperplastic changes were reported in the treated skin or in any other tissues. Based on the lack of preneoplastic/hyperplastic changes at the treatment site and the immunosuppressant effects noted during 39 weeks of treatment, a waiver request for conducting a 2-year dermal carcinogenicity study with sirolimus gel, 0.2% was granted.

Hyftor (sirolimus) Topical Gel, 0.2% does not contain any novel excipients. Several degradants have been identified in the drug substance/product. The Applicant's justifications for the levels of these degradants have been reviewed, and the specifications are acceptable from a pharmacology/toxicology perspective.

The NDA for Hyftor (sirolimus) Topical Gel, 0.2% is approvable for the treatment of AF associated with TS in adults and pediatric patients 6 years of age or older from a pharmacology/toxicology perspective. There are no recommended nonclinical postmarketing commitments/postmarketing requirements for this NDA.

5.2. Referenced NDAs, Biologics License Applications, DMFs

The Applicant intends to rely on the Agency's findings of safety for Rapamune® (sirolimus) Tablets (NDA 21110, approved 08-25-2000 for prophylaxis of organ rejection in patients receiving renal transplants, Wyeth Pharmaceuticals) as the LD.

The Applicant provided a letter of authorization from (b) (4) authorizing FDA to review Rapamycin (sirolimus) (D)MF (b) (4) n support of any application filed by Nobelpharma Co., Ltd.

5.3. Pharmacology

5.3.1. Primary and Secondary Pharmacology

Sirolimus binds to and inhibits the activity of mTOR, a serine/threonine protein kinase with a central role in the pathogenesis of TS. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting progression from the G_1 to the S phase of the cell cycle.

5.3.2. Safety Pharmacology

Safety pharmacology studies for topically applied drugs, for which systemic exposure is demonstrated to be low, are not required.

5.4. Absorption, Distribution, Metabolism, and Excretion/Pharmacokinetics

Absorption, distribution, metabolism, and excretion studies have not been conducted with sirolimus topical gel, 0.2%. The sirolimus content in plasma was determined in a 13- and 39-week repeat-dose dermal toxicity study in cynomolgus monkeys conducted with sirolimus topical gel, 0.2%. Toxicokinetic analysis was difficult because of the small number of animals and difficulties associated with blood sampling in studies where dosing is percutaneous and remains on the skin, potentially contaminating the blood sample. However, systemic exposure increased with dose in both male and female monkeys.

The Applicant conducted a human maximal-use pharmacokinetic study to determine biocomparability between Hyftor and the LD to establish a clinical bridge to the LD. It was determined that the Applicant established an adequate clinical bridge to the LD, Rapamune® Tablets. Refer to Section 6.2.1 of this review for the details.

5.5. Toxicology

5.5.1. General Toxicology

The following nonclinical toxicology study was previously reviewed and is summarized below.

Study 1: A 39-week repeated percutaneous dose-toxicity study of sirolimus (for external use) in cynomolgus monkeys (Study #SBL324-001)

Cynomolgus monkeys (4/sex/group) were treated for 39 weeks with twice daily dermal administration of sirolimus gel (0 [(b) (4), water], 0.05%, 0.2%, 0.8% sirolimus gel; 0, 0.125, 0.5, 2.0 mg/kg/dose sirolimus; 0, 0.25, 1.0, 4.0 mg/kg/day sirolimus). The 0.8% formulation was the maximum soluble concentration of sirolimus achievable in the formulation. The drug product was applied (0.25 g/kg) to a clipped

dorsal area representing ~5% of BSA. One male monkey at 4.0 mg/kg/day and one female monkey at 1.0 mg/kg/day were terminated in moribund condition on Day 264 and Day 260 (Week 38 of dosing), respectively. All other animals survived to scheduled termination. Small thymus and enlarged adrenals were observed in the male monkey that received 4.0 mg/kg/day, and the subject was terminated prematurely. In both of these monkeys, high absolute and relative adrenal weights, and low absolute and relative thymus weights were observed. Treatment-related thymic involution was observed at ≥0.25 mg/kg/day. No preneoplastic, hyperplastic, or other histological changes were reported in the treated skin or other tissues. Based on deaths (1/4 male monkeys at 4.0 mg/kg/day, 1/4 female monkeys at 1.0 mg/kg/day), decreased body weights, and immunosuppressant effects, a NOAEL could not be determined.

5.5.2. Genetic Toxicology

The following genetic toxicology information is included in the Rapamune® labeling, and the same information will be conveyed in Section 13.1 of the Hyftor labeling.

Sirolimus was not genotoxic in the in vitro bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the in vivo mouse micronucleus assay.

5.5.3. Carcinogenicity

A waiver request for conducting a dermal carcinogenicity study of Hyftor was granted based on the results from a 39-week dermal toxicity study of sirolimus topical gel, 0.2% in monkeys. No preneoplastic or hyperplastic changes were reported in the treated skin following 39 weeks of twice daily dermal dosing to an area ~5% of BSA.

The following carcinogenicity information is included in the Rapamune® labeling, and the same information will be conveyed in Section 13.1 of the Hyftor labeling.

Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study, at sirolimus doses 30- to 120-fold higher than the 2 mg daily clinical dose (adjusted for BSA), there was a statistically significant increase in malignant lymphoma at all dose levels compared with controls. In a second mouse study at dosages approximately 3- to 16-fold the clinical dose (adjusted for BSA), hepatocellular adenoma and carcinoma in males were considered sirolimus-related. In the 104-week rat study, at dosages equal to or lower than the clinical dose of 2 mg daily (adjusted for BSA), there were no significant findings.

The multiples of exposure referenced in the above Rapamune® labeling are for the maximum recommended human dose for the oral sirolimus indication; i.e., 2 mg/day. However, the current application is for a 1.6 mg/day topical sirolimus dose. Based on the Clinical Pharmacology review, systemic exposure after topical administration of sirolimus is considerably less than after oral administration. The available data do not allow comparison of the systemic exposure of sirolimus observed in animal studies to the systemic exposure that would be expected in humans after topical use of Hyftor.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The following fertility and embryofetal development information is included in the Rapamune labeling, (b) (4)

When female rats were treated by oral gavage with sirolimus and mated to untreated males, female fertility was decreased at 0.5 mg/kg (2.5-fold the clinical dose of 2 mg, on a BSA basis) due to decreased implantation. In addition, reduced ovary and uterus weights were observed. The NOAEL for female rat fertility was 0.1 mg/kg (0.5-fold the clinical dose of 2 mg).

When male rats were treated by oral gavage with sirolimus and mated to untreated females, male fertility was decreased at 2 mg/kg (9.7-fold the clinical dose of 2 mg, on a BSA basis). Atrophy of the testes, epididymides, prostate, and seminiferous tubules, and reduced sperm counts were observed. The NOAEL for male rat fertility was 0.5 mg/kg (2.5-fold the clinical dose of 2 mg).

Testicular tubular degeneration was also seen in a 4-week intravenous study of sirolimus in monkeys at 0.1 mg/kg (1-fold the clinical dose of 2 mg, on a BSA basis).

Embryo-Fetal Development

The following embryo-fetal development information is included in the Rapamune® labeling, (b) (4)

Sirolimus crossed the placenta and was toxic to the conceptus.

In rat embryo-fetal development studies, pregnant rats were administered sirolimus orally during the period of organogenesis (Gestational Day 6 to 15). Sirolimus produced embryo-fetal lethality at 0.5 mg/kg (2.5-fold the clinical dose of 2 mg, on a BSA basis) and reduced fetal weight at 1 mg/kg (5-fold the clinical dose of 2 mg). The NOAEL for fetal toxicity in rats was 0.1 mg/kg (0.5-fold the clinical dose of 2 mg). Maternal toxicity (weight loss) was observed at 2 mg/kg (10-fold the clinical dose of 2 mg). The NOAEL for maternal toxicity was 1 mg/kg. In combination with cyclosporine, rats had increased embryo-fetal mortality compared with sirolimus alone.

In rabbit embryo-fetal development studies, pregnant rabbits were administered sirolimus orally during the period of organogenesis (Gestation Day 6 to 18). There were no effects on embryo-fetal development at doses up to 0.05 mg/kg (0.5-fold the clinical dose of 2 mg, on a BSA basis); however, at doses of 0.05 mg/kg and above, the ability to sustain a successful pregnancy was impaired (i.e., embryo-fetal abortion or early resorption). Maternal toxicity (decreased body weight) was observed at 0.05 mg/kg. The NOAEL for maternal toxicity was 0.025 mg/kg (0.25-fold the clinical dose of 2 mg).

Prenatal and Postnatal Development

The following prenatal and postnatal development information is included in the Rapamune labeling (b) (4)

In a pre- and post-natal development study in rats, pregnant females were dosed during gestation and lactation (Gestational Day 6 through Lactation Day 20). An increased incidence of dead pups, resulting in reduced live litter size, occurred at 0.5 mg/kg (2.5-fold the clinical dose of 2 mg/kg on a BSA basis). At 0.1 mg/kg (0.5-fold the clinical dose of 2 mg), there were no adverse effects on offspring. Sirolimus did not cause maternal toxicity or affect developmental parameters in the surviving offspring (morphological development, motor activity, learning, or fertility assessment) at 0.5 mg/kg, the highest dose tested.

Lactation

The following animal lactation information is included in the Rapamune® labeling, and the same information will be conveyed in Section 8.2 of the Hyftor labeling.

Sirolimus (b) (4) present in the milk of lactating rats.

5.5.5. Other Toxicology Studies

The following nonclinical toxicology studies were previously reviewed and are summarized below.

Juvenile Toxicity

The Applicant conducted a juvenile toxicology study in rats with twice daily dermal administration of sirolimus topical gel (0, 0, 0.01%, 0.05%, 0.2%, 0.8% sirolimus topical gel; 0, 0, 0.05, 0.25, 1.0, 4.0 mg/kg/dose sirolimus; 0, 0, 0.1, 0.5, 2.0, or 8.0 mg/kg/day sirolimus). The age at initiation of dosing (postnatal day 22), duration of dosing (until postnatal day 49), and route of exposure were chosen to correspond with the proposed clinical use of topical administration from 2 years of age to sexual maturity. Standard toxicological endpoints, in addition to measures of sexual maturation, and a functional observational battery, were evaluated. No treatment-related effects were observed, but bone development, toxicokinetics, and reproductive capacity were not assessed.

Skin Sensitization

The Applicant measured the skin sensitizing potential of sirolimus topical gels (0.05%, 0.2%, and 0.8%) in male Hartley guinea pigs using the adjuvant and patch test method. No skin reactions were observed at either 24 or 48 hours after application to the challenge site in either the vehicle control group of animals or those previously induced with sirolimus. In the positive control group, erythema and edema were observed after challenge with 1-chloro-2,4-dinitrobenzene. Under the conditions of this assay, sirolimus gels were not considered to be skin sensitizers.

Phototoxicity

Sirolimus was tested for its photocytotoxicity potential in Balb/c 3T3 fibroblast cells by neutral red uptake assay. Duplicate cultures of fibroblast cells seeded into 96-well plates were treated with eight concentrations of sirolimus (from 7.81 to 1000 µg/mL) for about 1 hour. One set of plates was subsequently exposed to ultraviolet (UV) A light (315 to 400 nm), and one set was maintained in the dark. Cell viability was measured 24 hours after irradiation by neutral red uptake assay. The results of the test showed dose-dependent cytotoxicity independent of UV irradiation, indicating that sirolimus did not exert a phototoxic effect in Balb/c 3T3 cells.

Acute Ocular Irritation

An acute eye irritation study was conducted with sirolimus topical gels (0%, 0.1%, 0.05% and 0.2%) administered into the conjunctival sac of rabbits. Based on the maximum values and mean total scores, sirolimus topical gels were classified as moderately irritating, with the effect caused by an ingredient in the vehicle base.

The submitted nonclinical studies were conducted to meet foreign regulatory requirements. They would have more closely satisfied U.S. regulatory recommendations if the 39-week nonrodent dermal toxicity study had been conducted in minipigs, in which once daily dosing to 10% of BSA is readily achieved. Additionally, juvenile animal testing is best conducted with oral exposure, including tests capable of detecting juvenile-specific toxicities. Also, the ocular irritation potential of a topical drug product is readily tested in an in vitro model, such as the bovine corneal opacity and permeability assay. However, the submitted studies indicate the drug product is an immunosuppressant with a toxicity profile characteristic of sirolimus, fulfilling the nonclinical testing requirements.

Impurities

As detailed in ICH M7(R1), *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (2018)*, the threshold of toxicologic concern for a mutagenic impurity in a drug product is conservatively estimated to be (b) (4) µg/day. This corresponds to a theoretical (b) (4) excess lifetime risk of cancer, justified by the drug product's clinical benefit. (b) (4) systemic exposure of topical drug products, conservatively estimated to be (b) (4)%, supports use of a safety concern threshold for sirolimus topical gel, 0.2% of (b) (4) µg/day.

Drug Product Excipients

All of the inactive ingredients used in the final formulation are listed in the FDA's Inactive Ingredient Database, and at amounts less than the maximum potency in approved products with the exception (b) (4)

(b) (4)

Qualification of (b) (4) was achieved during the 39-week repeat-dose dermal toxicity study conducted in monkeys.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted the current NDA pursuing approval for Hyftor (sirolimus) Topical Gel, 0.2% through a 505(b)(2) regulatory pathway using Rapamune® (sirolimus) Tablets as a listed drug to support the treatment of subjects with AF associated with TS. Rapamune was approved for the prophylaxis of organ rejection in patients receiving renal transplants under NDA 21110 in 2000.

In this NDA, the Applicant has proposed the dose regimen of Hyftor (sirolimus) Topical Gel, 0.2% as:

- Apply Hyftor to the skin of the face affected with AF twice daily
- For patients 6 to 11 years old, the maximum daily dose should not exceed 600 mg (2 cm)
- For patients 12 years of age or older, the maximum daily dose should not exceed 800 mg (2.5 cm)

To support this indication, the Applicant has conducted a Phase 1 pharmacokinetic (PK) study (NPC-12G-4/US), a pivotal Phase 3 study (NPC-12G-1), a long-term safety (LTS) study (NPC-12G-2), as well as a population PK (PPK) analysis.

6.1.1. Recommendations

From a clinical pharmacology standpoint, Hyftor (sirolimus) Topical Gel, 0.2% for the treatment of AF associated with TS is approvable with the proposed dosing regimens in the target population.

6.1.2. Postmarketing Requirements and Commitments

None.

6.2. Summary of Clinical Pharmacology Assessment

The Clinical Pharmacology review focused on the data that supported establishment of a clinical bridge and the BA assessment of sirolimus gel in the NPC-12G 0.2% formulation from the following trials:

- NPC-12G-4/US (Phase 1 PK trial)
- NPC-12G-1 (Phase 3 trial)

- NPC-12G-2 (LTS study)
- Special Study: PPK study (Report NOBE-PMX-NPC12G-1635)

Data supporting establishment of a clinical bridge: The highest topical dose across all clinical trials was 1.6 mg, applied at one time. The highest oral daily dose in the Rapamune labeling is 40 mg. The oral BA of the tablet is approximately 17.8%. Hence, the maximum oral bioavailable dose will be approximately 7.12 mg. Based on this information, even if the topical dose of 1.6 mg was 100% absorbed, it is highly unlikely that it would yield a systemic exposure that is higher than that produced following the highest labeled oral dose of 40 mg. Even with twice daily administration of the topical dose, this conclusion will not change. Based on this information, a relative BA study between the topical and oral listed drug was deemed unnecessary, because the difference in dosing between oral and topical routes supported establishment of a clinical bridge. Furthermore, because treatment is to be restricted to the face, the use of higher doses on a larger BSA is highly unlikely.

PK assessment under maximal-use conditions was recommended. The Applicant did not obtain a full PK profile; but rather assessed PK using sparse blood sampling in the Phase 3 trial. Although obtaining a full PK profile is highly desirable, the limited PK information would not be an approvability issue because of availability of oral product at higher doses.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Based on the PK data across the submitted clinical trials, sirolimus gel, 0.2% produced low systemic exposure of sirolimus after topical application for the treatment of patients with AF associated with TS compared to oral sirolimus tablets. The same drug product formulation, NPC-12G sirolimus gel, 0.2%, was used in all Phase 1 (NPC-12G-4/US) and pivotal Phase 3 clinical trials (NPC-12G-1 and NPC-12G-2).

Although a dedicated maximal-use PK study was not conducted, a clinical bridge to Rapamune tablets is considered established based on the fact that the highest topical dose was lower than the highest oral bioavailable dose. Hence, even if there was 100% absorption following topical administration, the systemic exposure would not be higher than that produced following the highest labeled oral daily dose of 40 mg. The limited PK data suggest that there are no differences in sirolimus systemic exposure between males and females or between adults and pediatrics following topical administration, although concrete conclusions could not be reached because of the lack of PK data from a dedicated maximal-use study.

The PPK analysis is deemed exploratory and will not be discussed in detail in this review. The bioanalytical analysis and validation assessment are considered adequate to support the clinical development of sirolimus gel, 0.2%.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The efficacy and safety results in the pivotal Phase 3 trial (NPC-12G-1) and the LTS study (NPC-12G-2) support the acceptability of the proposed dosing regimens for subjects with AF associated with TS:

- Apply Hyftor to the skin of the face affected by AF twice daily
- For patients 6 to 11 years old, the maximum daily dose should not exceed 600 mg (2 cm)
- For patients 12 years of age or older, the maximum daily dose should not exceed 800 mg (2.5 cm)

Therapeutic Individualization

As with the age-tiered dosing regimen, therapeutic individualization based on intrinsic and extrinsic factors is not considered necessary. The limited PK data suggest that there are no differences in sirolimus systemic exposure between males and females, or between adults and pediatrics following sirolimus topical administration.

Outstanding Issues

There are no outstanding issues that would preclude the approval of Hyftor (sirolimus) Topical Gel, 0.2% for the treatment of subjects with AF associated with TS from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The PK of sirolimus after Hyftor Topical Gel, 0.2% topical application could not be fully estimated because of the lack of PK data from a dedicated maximal-use study. This would not be an approvability issue for the reasons listed in Section 6.2.

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Evidence Supportive of Effectiveness?

The overall efficacy data from the Phase 3 trial NPC-12G-1 and LTS trial NPC-12G-2 provide evidence that Hyftor (sirolimus) Topical Gel, 0.2% is effective for the treatment of subjects with AF associated with TS. See Section 7 of this multidisciplinary review for details of the study design and efficacy results. The PK of sirolimus after Hyftor topical application could not be evaluated due to lack of PK data from a dedicated maximal use study. Exposure-response relationships therefore could not be determined to provide evidence supportive of effectiveness.

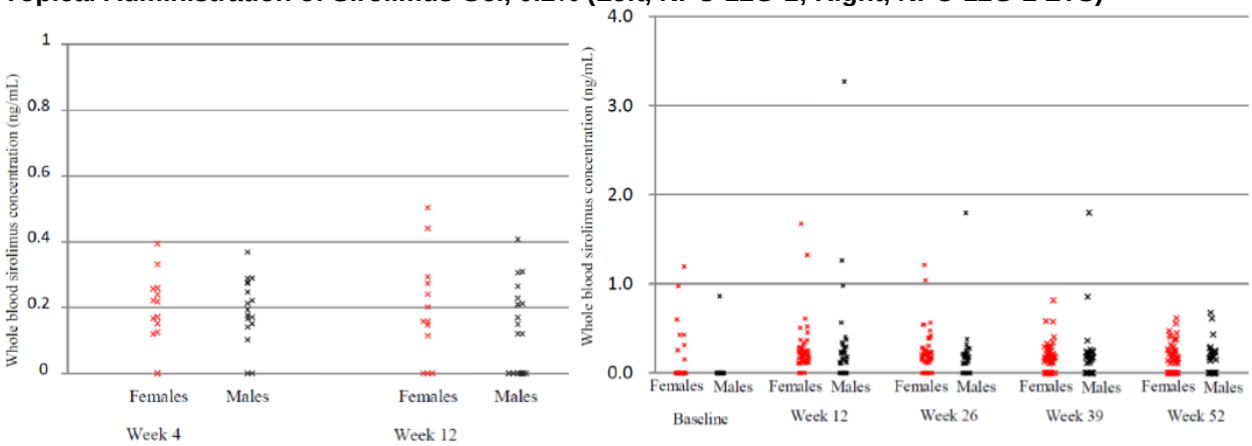
Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

Yes. The efficacy and safety data from the Phase 3 trial NPC-12G-1 and LTS trial NPC-12G-2 overall support the proposed age-tiered dosing regimens. See Section 7 of this multidisciplinary review for details of the efficacy and safety results of the Phase 3 trials. The PK and exposure-response analysis could not be conducted because of the lack of PK data from a dedicated maximal-use study.

Is an Alternative Dosing Regimen or Management Strategy Required For Subpopulations Based on Intrinsic Patient Factors?

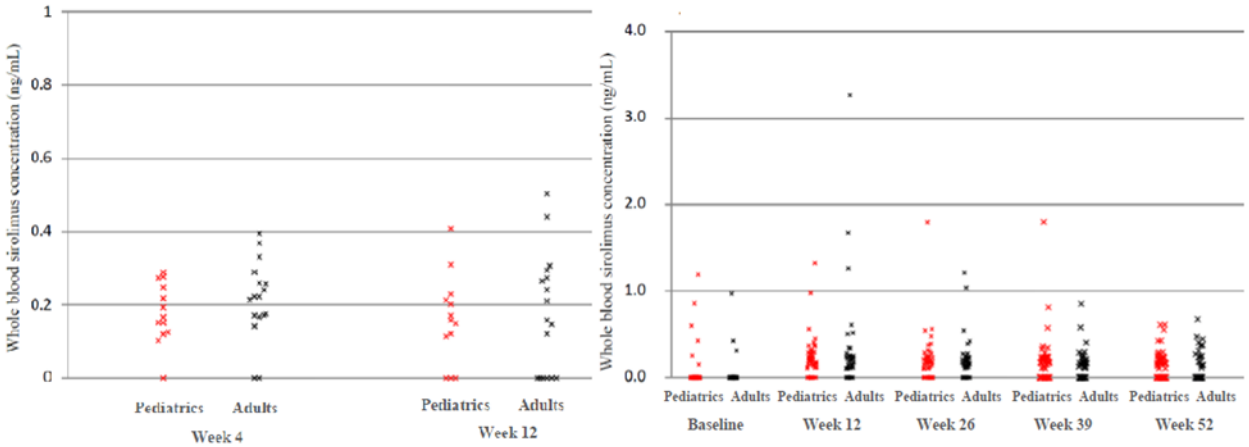
No. The age-tiered Hyftor (sirolimus) Topical Gel, 0.2% was investigated in the clinical trial included with this submission. An alternative dosing regimen or management strategy is not necessary for subpopulations based on intrinsic patient factors. The limited PK data suggest no differences in sirolimus systemic exposure between males and females, nor between adults and pediatrics, following topical administration (Figure 8 and Figure 9). Definitive conclusions cannot be reached because of the lack of PK data under maximal-use conditions.

Figure 8. Comparison of Whole Blood Sirolimus Concentrations in Males and Females After Topical Administration of Sirolimus Gel, 0.2% (Left, NPC-12G-1; Right, NPC-12G-2 LTS)



Source: Figure 10, Figure 11, 2.7.2 Summary of Clinical Pharmacology Studies

Figure 9. Comparison of Whole Blood Sirolimus Concentrations in Adults and Pediatrics After Topical Administration of Sirolimus Gel, 0.2% (Left, NPC-12G-1; Right, NPC-12G-2 LTS)



Source: Figure 10, Figure 11, 2.7.2 Summary of Clinical Pharmacology Studies

Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

Food-drug interactions are not applicable because Hyftor (sirolimus) Topical Gel, 0.2% is administered topically.

Drug interaction studies with Hyftor have not been conducted. The drug-drug interaction recommendations were made based on the Rapamune labeling and are detailed below.

Sirolimus is a substrate for both cytochrome P-450 3A4 (CYP3A4) and p-glycoprotein (p-gp). Inducers of CYP3A4 and p-gp may decrease sirolimus concentration, whereas inhibitors of CYP3A4 and p-gp may increase sirolimus concentration.

Strong Inducers and Strong Inhibitors of CYP3A4 and p-gp

Exercise caution with concomitant use of sirolimus with strong inducers (e.g., rifampin, rifabutin) and strong inhibitors (e.g., erythromycin, telithromycin, clarithromycin) of CYP3A4 and p-gp.

Weak and Moderate Inducers or Inhibitors of CYP3A4 and p-gp

Exercise caution with concomitant use of sirolimus with drugs or agents that are modulators of CYP3A4 and p-gp.

- Drugs that could increase sirolimus blood concentrations: Bromocriptine, cimetidine, cisapride, clotrimazole, danazol, diltiazem, fluconazole, protease inhibitors (e.g., HIV and hepatitis C, including drugs such as ritonavir, indinavir, boceprevir, and telaprevir), metoclopramide, nicardipine, troleandomycin, and verapamil
- Drugs and other agents that could decrease sirolimus concentrations: Carbamazepine, phenobarbital, phenytoin, rifapentine, St. John's Wort (*Hypericum perforatum*)
- Drugs whose concentrations could increase when administered with sirolimus: Verapamil

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The clinical studies relevant to this multidisciplinary review are summarized in Table 3.

Table 3. List of Clinical Trials Relevant to NDA 213478

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers/ Countries
Controlled Studies to Support Efficacy and Safety							
NPC-12G-1	Phase 3, multicenter, stratified, randomized, double-blind, placebo-controlled, comparative study	Sirolimus topical gel 0.2% or vehicle applied topically twice daily to facial angiofibroma (FA), hypomelanotic macule, and cephalic plaque	Primary: The composite improvement in angiofibromas as assessed using photographs by the Independent Review Committee at 12 weeks Key secondary: Composite improvement in angiofibromas assessed by the investigator	Treatment duration: 12 weeks Follow-up: 4 weeks	N=62 Active: N=30 (17 adults; 13 peds) Vehicle: N=32 (20 adults; 12 peds)	Subjects 3 years of age or older with tuberous sclerosis (TS) with ≥3 FA, each ≥2 mm	9; all in Japan
Studies to Support Safety							
NPC-12G-2	Open-label, multicenter long-term safety study	Sirolimus topical gel 0.2% or vehicle applied topically twice daily to FA	Primary: Rates of discontinuation due to adverse events (AEs) and AEs leading to discontinuation	52 weeks	N=92 (44 adults; 48 peds)	Subjects 3 years of age and older with FA, hypo-melanotic macules, or plaques of TS	10; all in Japan

Trial Identity	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers/ Countries
Other Studies Pertinent to the Review of Efficacy or Safety (e.g., Clinical Pharmacological Studies)							
OSD-001-001	Phase 1/2, randomized, double-blind, placebo-controlled, parallel-group, pharmacokinetic (PK) and dose-finding study	Sirolimus topical gel 0.05%, 0.1%, or 0.2% or vehicle applied topically to target site twice daily; 1 pump (≈125 mg) per tumor 50 cm^2; 1.5 pumps per application, 3 pumps per day as upper limits	Primary: Composite variable consisting of degree of shrinkage of tumors of target site and improvements in redness of tumors at 12 weeks. Composite variable defined as total score of improvements in volume and redness of the 3 small target site tumors.	Treatment duration: 12 weeks Follow-up: 4 weeks	N=36 Active: N=24 (12 adults;12 peds. 8 per dose) Vehicle: N=12 (6 adults; 6 pediatrics; 4 per dose)	Subjects 3 years of age or older with TS with ≥3 sites of solitary AF, each ≥2 mm	1 in Japan
NPC-12-4/US	Phase 1, open-label, fixed-sequence, two-period comparative bioavailability study	Sirolimus topical gel 0.2%, single dose applied topically containing 1.6 mg sirolimus or single dose 2 mg Rapamune ® Tablet administered orally	Primary objective: To compare the systemic exposure to sirolimus following topical application of sirolimus gel to the central face to that observed from a single oral dose of Rapamune® 2 mg, under fasting conditions.	Single dose	N=12	Healthy volunteers under fasting conditions ≥ 18 and ≤65 years of age, nonsmokers	1 in the US
RPG1S1A01 (ongoing)	Postmarketing safety study	Sirolimus topical gel 0.2% or vehicle applied topically twice daily	Objectives: Evaluation of safety and efficacy	1 year	As of 10/31/2019: 674	Patients with AF of TS	Approx 100 in Japan

Source: Applicant's Summary of Clinical Safety, Table 2, pp.12-13; also, individual clinical study reports

7.2. Review Strategy

Data Sources

The data sources used to evaluate the efficacy and safety of sirolimus gel, 0.2% included the Applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in electronic common technical document format and was entirely electronic. The analysis datasets used in this review are archived at:

- Phase 3 Trial NPC-12G-1:
  Application 213478 - Sequence 0001 - Analysis Dataset Legacy
- Open-Label LTS Trial NPC-12G-2:
  Application 213478 - Sequence 0001 - Analysis Dataset Legacy

Data and Analysis Quality

The statistical and clinical teams evaluated the fitness of the data. In general, the data submitted by the Applicant were sufficient to support the review of safety and efficacy of sirolimus gel, 0.2% for the proposed indication.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial NPC-12G-1

8.1.1.1. Trial Design and Endpoints

The Applicant conducted a multicenter, randomized, double-blind, vehicle-controlled Phase 3 trial, NPC-12G-1, in Japan to verify the efficacy of sirolimus gel, 0.2% for the treatment of AF associated with TS.

Eligibility to enroll in the trial was determined by the following key inclusion criteria:

- Male or female subjects aged 3 years or older
- Subjects with a "definite diagnosis" of TS (International Tuberous Sclerosis Complex Consensus Conference 2012)
- Subjects with three or more papules of AF (≥2 mm in diameter with redness in each) on the face at screening tests
- Subjects who are not suitable for therapy with laser or surgery (including liquid nitrogen therapy and phototherapy) for AF, or who are unwilling to receive such interventions

According to the protocol, approximately 60 subjects were planned to be randomized in a 1:1 ratio to sirolimus gel, 0.2% (N=30) or vehicle gel (N=30). The trial was planned to include at least 20 subjects aged 18 years or younger, and 25 subjects aged 19 years or older. The minimum number of subjects required in each age group is shown in Table 4. Randomization

was performed for both age groups by the allocation manager using the permuted block method.

Table 4. Minimum Number of Subjects in Each Age Group

Age Category	Standard Body Surface Area	Minimum Number of Subjects planned	Upper Limit of the Amount of Daily Application
3 to 5 years	<0.8 m^2	3	400 mg
6 to 11 years	≥0.8 m^2 and <1.3 m^2	6	600 mg
12 to 18 years		6	
19 years or older	≥1.3 m^2	25	800 mg

Source: NPC-12G-1 protocol, page 53
Abbreviation: BSA, body surface area

The trial consisted of a screening period, a 12-week double-blind treatment period, and a 4-week follow-up posttreatment observation period. Subjects were instructed to apply study medication evenly to AF lesions twice daily (in the morning and at bedtime). The amount of application was 125 mg per lesion of 50 cm^2, and should not exceed the upper limit of the amount of daily application prescribed for the age category. The study medication was to be applied to the lesions of AF first, then to both hypomelanotic macules and plaques on the head (above the neck). Subjects were scheduled to attend visits at Screening, BL, and Weeks 4, 8, 12 and 16 (follow-up visit).

Primary Endpoint

The protocol and the Statistical Analysis Plan (SAP) specified the primary endpoint of composite improvement in AF assessed using photographs by an IRC at Week 12. According to the clinical study report, the IRC consisted of three dermatologists (referred to as IRC raters in this review) who were independent from persons involved in the sponsorship or the conduct of the trial, and had no direct conflict of interest with the Applicant. The IRC assessments were based on photographs of skin lesions of individual subjects collected from the trial institutions.

Composite improvement in AF was assessed in terms of the size and color (redness) of tumors in accordance with the scales in Table 5 and Table 6. Table 35 in Appendix 15.4 contains a guide for assessing the composite score provided in the Applicant's "*Instructions for Completing Assessments of Efficacy Outcomes in Accordance with the Protocol-Specified Assessment Criteria.*"

Table 5. Criteria for Composite Improvement in Angiofibroma–Trial NPC-12G-1

Score	Degree of improvement	Criteria
3	Markedly Improved	Shrinkage, flattening, or disappearance of tumors is observed overall. A large decrease in the intensity of redness or a change in redness to the level equal to that of the normal region is observed nearly overall.
2	Improved	Shrinkage or flattening of tumors and a decrease in the intensity of redness are observed nearly overall. Or, disappearance of tumors and a large decrease in the intensity of redness is partially observed.
1	Slightly improved	Shrinkage or flattening of tumors and a partial decrease in the intensity of redness are partially observed. Or, a slight decrease in the intensity of redness is observed nearly overall.
0	Unchanged	There is no definite change in the size or the redness of tumors.
-1	Slightly exacerbated	Enlargement or new formation of tumors and a partial increase in the intensity of redness are partially observed. Or, a slight increase in the intensity of redness is observed nearly overall.
-2	Exacerbated	An enlargement or new formation of tumors is observed nearly overall, or a huge enlargement of tumors and an increase in the intensity of redness are partially observed. Or, more severe exacerbation is observed.

[Definition of terms]

Overall	: Not less than about 75% of the extent of the lesion at baseline
Nearly overall	: About 50% to 75% of the extent of the lesion at baseline
Partial	: About 25% to 50% of the extent of the lesion at baseline
Large decrease in intensity of redness	: Changes of 3 levels or more in redness in accordance with the Pantone® color sample
Decrease/increase in intensity of redness	: Changes of 2 levels or more in redness in accordance with of the Pantone® color sample
Slight decrease/increase in intensity of redness	: Changes of 1 level in redness in accordance with the Pantone® color sample

Source: Reviewer's annotation of Applicant's Table 9-4 on page 44 of the NCP-12G-1 Study Report

Table 6. Levels of Redness

Level	Appearance of Redness	Pantone® Color Sample [a)]
1	Same as or paler than Pantone® 489C	
2	Same as or paler than Pantone® 486C	
3	Same as or paler than Pantone® 7416C	
4	Same as or paler than Pantone® 485C	
5	Same as or paler than Pantone® 704C	
6	More intense in color than Pantone® 704C	—

a) The colors shown in the Pantone® color sample column in the above table are not accurate reproduction of the color tones indicated by the numbers. In the assessment of redness, always use a sample for assessing redness.

Source: Applicant's Table 9-5 on page 45 of the NCP-12G-1 Study Report

IRC Meetings

The Applicant, the contract research organization responsible for the control and compensation of image files, and the members of the IRC held three meetings in accordance with the written procedure for holding IRC meetings, which was prepared separately. The IRC meetings were held on 07/29/2016, 09/28/2016, and 12/13/2016. The Applicant participated in IRC meetings as the organizer, and the contract research organization responsible for control and compensation of image files entered the assessment results and projected images of lesions on a screen. The first two meetings assessed 20 subjects each, while the final meeting assessed 22 subjects (total 62 subjects). During the meetings, each member of the IRC undertook a review and assessment of the improvement of AF, as well as hypomelanotic macules and plaques on the head, using the photographs displayed on the monitor. Photographs taken at BL were shown in the upper part of the monitor, and photographs at Week 4, Week 8, and Week 12 after treatment initiation, as well as at 4 weeks after the last dose (Week 16), were shown in

the lower part of the monitor. The final IRC score was based on a consensus with concordance of two out of three IRC raters.

Consensus Discussion 1: If none of the independent assessments by the three IRC raters agreed, a consensus discussion was held to resolve the disagreement. For the cases that were subject to a consensus discussion, the photographs from all photograph time points, including photographs from time points that were not subject to discussion, were again displayed on the monitor, and the three raters discussed the cases while checking the photographs on the same monitor.

Consensus Discussion 2: When the assessment results for a subject at any time point were subject to discussion, or when the assessment results of any of the three assessment parameters (composite improvement in AF, improvement in AF size, or improvement in AF redness) for a subject at any time point were subject to discussion, the raters were asked to examine the necessity for a second review and assessment of images at other photograph time points, or of the remaining assessment parameters, and asked as needed to perform the second review and assessment. In addition, if the decision on the first assessment of images at any photograph time point, or if the assessment parameters that had not been subject to a consensus discussion changed after the second review and assessment (i.e., if a new decision was established following the second consensus discussion), the results of the second consensus discussion were to be adopted based upon the unanimous agreement of all raters.

At the pre-IND meeting (dated 1/23/2018) and the pre-NDA meeting (dated 12/3/2018), the Agency expressed concerns for the efficacy assessments. In particular, the Agency stated that the scale for assessing treatment effect is subjective relative to the BL, and in the absence of an appropriate quantifiable scale for assessing disease severity along with establishing a criterion for enrollment, it is difficult to interpret the study findings.

In their response to the IR letter dated 5/1/2020 (response dated 5/6/2020), the Applicant noted on page 1 that “after obtaining images, the data center performed color correction, scale correction, rotation correction, etc. using Adobe image-editing software Photoshop.” In their response to the IR letter dated 6/2/2020 (response dated 6/5/2020), the Applicant also clarified that the imaging manager and the person responsible for the image editing were blinded to the treatment arm, but were informed of the time at which the photograph was taken. The Applicant stated on pages 1 to 2 that the IRC raters had to know which photographs were taken as BL (before treatment), because they had to confirm whether the locations of the target tumors after treatment were consistent with those at BL, and also whether the photography angles of the target tumors after treatment were consistent with those at BL.

The Center for Devices and Radiological Health (CDRH) review team expressed concerns regarding the color-corrected photographs. In particular, as noted in Section 4.4 of this review, some of the Applicant’s processed images show significant changes in subjects’ full-face skin color before and after treatment. Furthermore, the Applicant did not provide the validation data requested by the Agency to demonstrate that image correction does not alter the color or size of skin lesions. Because color (redness) is a component of the efficacy assessment, in the absence of the validation testing data, the team questioned the appropriateness of IRC

assessment to establish efficacy using this component. See the discussion in Section 4.4 of this review for more details.

Furthermore, the Division of Clinical Outcome Assessment (DCOA) review team expressed the following concerns regarding the scale used for assessing composite improvement and the procedure of the IRC assessments. The reader is referred to the DCOA review signed in DARRTS on 7/11/2020 for more details.

- "A key limitation of the scale for use as a primary endpoint is that it assesses change in AF relative to BL and does not capture absolute severity. The scales used to assess size and redness, respectively, were also ratings of change. Therefore, we do not have information on quantifying AF severity."
- "The NDA submission does not include any qualitative evidence in support of this instrument. It is unclear how the scales composing the instrument were developed, and whether they were cognitively tested in clinicians for their understanding of the different categories, descriptors, thresholds etc."
- "The categories of change appear to have overlapping descriptors (e.g., shrinkage, flattening, or disappearance). It is important that response categories should be distinct (i.e., non-overlapping) and should represent a clinically meaningful gradation of disease."
- "The descriptors for all categories are either double- or triple-barreled. Use of multi-barreled items is generally discouraged as they do not allow assessment and reporting of each component within the multi-barreled item, and could lead to inconsistent reporting by respondents."
- "Based on the evidence submitted, the reliability (inter-rater reliability) of the Composite Improvement in Angiofibroma instrument is questionable. Ideally, reliability of the instrument should be evaluated prior to its use in a confirmatory study. Of note, the intrarater reliability of the instrument was not evaluated in this study."
- "It is possible that some raters may have been influenced by the other raters, or may have felt pressured in offering their true rating."
- "While the IRC raters were blinded to the treatment, they were not blinded to the assessments from other time points (before and after treatment photographs were displayed on their monitors for comparison). The raters may have been influenced (in either direction) by a previous time point rating."
- "The final score could be modified based on the consensus discussions. A rationale for conducting the consensus discussions was not included in the submission. Additionally, changing the scores of several assessments during the trial raises concerns that the instrument may be problematic."
- "We are unable to comment on the other measurement properties (i.e., construct validity and ability to detect change etc.) as the submission did not include any related evidence. It appears that a psychometric study was not conducted."

The DCOA review concluded that the Composite Improvement in Angiofibroma scale is not considered to be "an appropriate instrument to support regulatory decision making based on its design (e.g., overlapping descriptors, multi-barreled items) and lack of sufficient supportive evidence of content validity (e.g., evidence of clinicians' understanding of the categories, descriptors, thresholds etc.) and inter- and intra-rater reliability." Additionally, given that the

scale assesses change in AF relative to baseline, and does not capture absolute severity, this is a key limitation of this scale for use as a primary endpoint.

Secondary Efficacy Endpoints

The protocol/SAP listed the following secondary efficacy endpoints. The first endpoint was evaluated at Weeks 4 and 8, and 4 weeks after the end of administration (Week 16). The other measures were evaluated at Week 12.

- Composite improvement in AF assessed using photographs by the IRC
- Composite improvement in AF assessed by the Investigator
- Improvement in the size of AF assessed by the IRC and the Investigator; the scale is provided in Appendix 15.4
- Improvement in the color of AF assessed by the IRC and the Investigator; the scale is provided in Appendix 15.4
- Improvement in hypomelanotic macules and plaques of the upper neck assessed by the IRC and the Investigator; the scales are provided in Appendix 15.4
- Proportion of subjects assessed as "Improved" or "Markedly Improved" in the primary endpoint and in secondary efficacy endpoints #1 to #5
- Change in the total score from BL for Dermatology Life Quality Index (DLQI) and Children Dermatology Life Quality Index (CDLQI)

The assessments by the Investigator were conducted separately from the IRC assessments, using the same scales. According to the protocol, the Investigator assessments were in-person assessments (i.e., the lesions were closely observed), using the BL photographs as reference. In their response to the IR letter dated 5/14/2020 (response dated 5/15/2020), the Applicant clarified on page 1 that "the baseline photographs used by Investigators for live evaluation/comparison did not have any type of image processing or color adjustment."

8.1.1.2. Statistical Methodologies

According to the Applicant, the SAP was originally finalized on 12/21/2016 and the database was locked on 12/22/2016. The SAP was modified on 02/20/2017 to document methods for additional post hoc analyses. The changes included the calculation of Kendall's coefficient of concordance for verification of the agreement between the IRC and Investigator assessments. There were no changes to the analysis plans for the primary endpoint.

The primary analysis population specified in the protocol/SAP was the full analysis set (FAS), defined as "subjects with definitive registration, except those who have not received the investigational product and those for whom no efficacy information has been obtained after the start of administration."

The protocol/SAP specified analyzing the primary efficacy endpoint (i.e., composite improvement in AF assessed using photographs by the IRC at Week 12) using the Wilcoxon rank-sum test. The protocol/SAP specified analyzing the first five secondary efficacy endpoints listed in Section 8.1.1 similarly to the primary efficacy endpoint; i.e., using the Wilcoxon rank-sum test.

The protocol/SAP specified analyzing improvement rates, defined as the proportion of subjects assessed as "Improved" or "Markedly Improved" (see secondary efficacy endpoint #6 listed in Section 8.1.1), using the Fisher exact test.

The SAP specified verifying the agreement between IRC and Investigator assessments with respect to improvements in AF (composite improvement, improvement in size and improvement in color) and in hypomelanotic macule and plaque of the upper neck, by preparing cross-tabulations and evaluating the Kendall coefficient of concordance and the rank correlation coefficient for each time point (post hoc analyses).

With respect to the analysis of change from BL in the total score of DLQI/CDLQI, and the analysis of change from BL in each subscale score of DLQI, the protocol/SAP specified using the Wilcoxon rank-sum test.

The protocol/SAP listed many secondary endpoints, with some evaluated at different time points, without prioritizing these endpoints based on clinical relevance or specifying any adjustment for multiplicity. The following comment was conveyed to the Applicant at the pre-IND meeting dated 1/23/2018: "Secondary endpoints should be clinically meaningful, limited in number, and adjusted for multiplicity."

8.1.1.3. Subject Disposition, Demographics, and BL Disease Characteristics

A total of 62 subjects (30 subjects in the sirolimus gel arm and 32 subjects in the vehicle arm) was enrolled in the trial. All 62 subjects were included in the FAS, because there were no subjects that did not receive study drugs, or from whom efficacy data were not collected after the start of the study medication. All 62 subjects completed their treatment and no subjects discontinued treatment.

Demographics and BL characteristics are presented in Table 7. All subjects participating in the trial were Japanese. The majority of the subjects (60%) were adults (at least 18 years old). The demographics were generally balanced across treatment arms; however, slightly more male subjects were randomized to sirolimus gel compared to vehicle.

Table 7. Demographics and Baseline Characteristics–Trial NPC-12G-1 (FAS*)

Parameter	Sirolimus Gel N=30	Vehicle Gel N=32	Total N=62
Age (years)			
Mean (SD)	21.6 (11.1)	23.3 (12.6)	22.5 (11.9)
Median	20.5	20.0	20.5
Range	7–48	6–53	6–53
Age Group (years)			
<18	13 (43%)	12 (37%)	25 (40%)
≥18	17 (57%)	20 (62%)	37 (60%)
Sex			
Male	17 (57%)	11 (34%)	28 (45%)
Female	13 (43%)	21 (66%)	34 (55%)
Body Weight (kg)			
Mean (SD)	49.3 (14.6)	53.7 (17.4)	51.6 (16.1)
Median	52.2	53.3	53.3
Range	20.6–79.7	22.0–88.8	20.6–88.8
BSA			
Mean (SD)	1.4 (0.3)	1.5 (0.3)	1.4 (0.3)
Median	1.5	1.5	1.5
Range	0.8–1.9	0.8–2.0	0.8–2.0

* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
Source: Reviewer's analysis
Abbreviations: BSA, body surface area; FAS, full analysis set

8.1.1.4. Results for the Primary Endpoint

The results for the primary endpoint; i.e., composite improvement in AF assessed by the IRC at Week 12, are presented in Table 8. No subjects in the sirolimus gel arm had 'slightly exacerbated' or 'exacerbated' AFs compared to BL, and one subject exhibited 'unchanged' AFs. In the vehicle gel arm, five subjects (16%) had 'slightly improved' AFs, while the remaining subjects exhibited 'unchanged' AFs. It is noted that one subject in the vehicle arm was assessed as 'not evaluable' by the IRC following consensus discussion.

Table 8. Composite Improvement in Angiofibroma at Week 12 Assessed by IRC–Trial NPC-12G-1 (FAS*)

N (%)	Markedly Improved	Improved	Slightly Improved	Unchanged	Slightly Exacerbated	Exacerbated	P-Value**
Sirolimus gel N=30	5 (17%)	13 (43%)	11 (37%)	1 (3%)	0 (0%)	0 (0%)	
Vehicle gel N=32†	0 (0%)	0 (0%)	5 (16%)	26 (81%)	0 (0%)	0 (0%)	<0.001

* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
** P-value obtained by Wilcoxon rank-sum test
† One subject in the vehicle arm was not evaluated
Source: Reviewer's analysis (same as Applicant's analysis)
Abbreviations: FAS, full analysis set; IRC, independent review committee

8.1.1.5. Results for Secondary Efficacy Endpoints

This section presents the results for the secondary endpoints of improvement in AF. As noted in Section 8.1.1.2, the Applicant did not specify any adjustment for multiplicity when testing the secondary efficacy endpoints. Therefore, statistical significance cannot be determined, and p-values are not presented here. Because of the small number of subjects with hypomelanotic

macule (9 subjects) and plaques (29 subjects) of the head at BL, the endpoints for improvement in the hypomelanotic macules and plaques of the head are not discussed in the review.

Table 9 presents the results for the composite improvement in AF at Weeks 4 and 8 for both IRC and Investigator assessments. In addition, the same results are presented for the Investigator assessment at Week 12. The results for composite improvement in AF appear more optimistic in favor of the sirolimus gel based on the IRC assessments compared to those of the Investigator assessments. Specifically, the IRC assessments rated more subjects in the sirolimus gel group towards the higher improvement categories compared to the Investigator assessments.

Table 9. Composite Improvement in Angiofibroma–Trial NPC-12G-1 (FAS*)

N (%)	Markedly Improved	Improved	Slightly Improved	Unchanged	Slightly Exacerbated	Exacerbated
IRC Assessment						
Week 8						
Sirolimus gel N=30	3 (10%)	10 (33%)	15 (50%)	2 (7%)	0 (0%)	0 (0%)
Vehicle gel N=32	0 (0%)	0 (0%)	7 (22%)	25 (78%)	0 (0%)	0 (0%)
Week 4						
Sirolimus gel N=30	0 (0%)	6 (20%)	19 (63%)	5 (17%)	0 (0%)	0 (0%)
Vehicle gel N=32	0 (0%)	0 (0%)	5 (16%)	27 (84%)	0 (0%)	0 (0%)
Investigator Assessment						
Week 12						
Sirolimus gel N=30	3 (10%)	4 (13%)	14 (47%)	9 (30%)	0 (0%)	0 (0%)
Vehicle gel N=32	1 (3%)	1 (3%)	8 (25%)	22 (69%)	0 (0%)	0 (0%)
Week 8						
Sirolimus gel N=30	2 (7%)	4 (13%)	12 (40%)	11 (37%)	1 (3%)	0 (0%)
Vehicle gel N=32	0 (0%)	2 (6%)	6 (19%)	23 (72%)	1 (3%)	0 (0%)
Week 4						
Sirolimus gel N=30	1 (3%)	3 (10%)	13 (43%)	13 (43%)	0 (0%)	0 (0%)
Vehicle gel N=32	1 (3%)	2 (6%)	4 (13%)	25 (78%)	0 (0%)	0 (0%)

* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
Source: Reviewer's analysis (same as Applicant's analysis)
Abbreviations: FAS, full analysis set; IRC, independent review committee

Table 10 and Table 11 provide the results for the improvement in size and color of AF, respectively, assessed by the IRC and the Investigator at Weeks 4, 8, and 12. Again, the IRC assessments rated more subjects in the Sirolimus gel group towards the higher improvement categories compared to the Investigator assessments.

Table 10. Improvement in the Size of Angiofibroma–Trial NPC-12G-1 (FAS*)

N (%)	Markedly Improved	Improved	Slightly Improved	Unchanged	Slightly Exacerbated	Exacerbated
IRC Assessment						
Week 12						
Sirolimus gel N=30	5 (17%)	13 (43%)	10 (33%)	2 (7%)	0 (0%)	0 (0%)
Vehicle gel** N=32	0 (0%)	1 (3%)	2 (6%)	28 (88%)	0 (0%)	0 (0%)
Week 8						
Sirolimus gel N=30	3 (10%)	10 (33%)	12 (40%)	5 (17%)	0 (0%)	0 (0%)
Vehicle gel N=32	0 (0%)	1 (3%)	4 (13%)	27 (84%)	0 (0%)	0 (0%)
Week 4						
Sirolimus gel N=30	0 (0%)	7 (23.3%)	14 (47%)	9 (30%)	0 (0%)	0 (0%)
Vehicle gel N=32	0 (0%)	0 (0%)	3 (9%)	29 (90%)	0 (0%)	0 (0%)
Investigator Assessment						
Week 12						
Sirolimus gel N=30	3 (10%)	5 (17%)	10 (33%)	12 (40%)	0 (0%)	0 (0%)
Vehicle gel N=32	0 (0%)	2 (6%)	4 (13%)	26 (81%)	0 (0%)	0 (0%)
Week 8						
Sirolimus gel N=30	2 (7%)	4 (13%)	9 (30%)	14 (47%)	1 (3%)	0 (0%)
Vehicle gel N=32	0 (0%)	1 (3%)	5 (16%)	26 (81%)	0 (0%)	0 (0%)
Week 4						
Sirolimus gel N=30	1 (3%)	4 (13%)	11 (79%)	14 (34%)	0 (0%)	0 (0%)
Vehicle gel N=32	1 (3%)	1 (3%)	3 (9%)	27 (84%)	0 (0%)	0 (0%)

* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
** One subject in the vehicle arm was assessed as 'not evaluable' by the IRC.
Source: Reviewer's analysis (same as Applicant's analysis)
Abbreviations: FAS, full analysis set; IRC, independent review committee

Table 11. Improvement in the Color of Angiofibroma–Trial NPC-12G-1 (FAS*)

N (%)	Markedly Improved	Improved	Slightly Improved	Unchanged	Slightly Exacerbated	Exacerbated
IRC Assessment						
Week 12						
Sirolimus gel N=30	2 (7%)	10 (33%)	12 (40%)	6 (20%)	0 (0%)	0 (0%)
Vehicle gel** N=32	0 (0%)	0 (0%)	3 (9%)	28 (88%)	0 (0%)	0 (0%)
Week 8						
Sirolimus gel N=30	1 (1%)	8 (27%)	13 (43%)	7 (23%)	1 (3%)	0 (0%)
Vehicle gel N=32	0 (0%)	0 (0%)	2 (6%)	30 (94%)	0 (0%)	0 (0%)
Week 4						
Sirolimus gel N=30	0 (0%)	3 (10%)	17 (57%)	10 (33%)	0 (0%)	0 (0%)
Vehicle gel N=32	0 (0%)	0 (0%)	3 (9%)	29 (91%)	0 (0%)	0 (0%)
Investigator Assessment						
Week 12						
Sirolimus gel N=30	3 (10%)	4 (13%)	8 (27%)	13 (43%)	2 (7%)	0 (0%)
Vehicle gel N=32	1 (3%)	0 (0%)	8 (25%)	23 (72%)	0 (0%)	0 (0%)
Week 8						
Sirolimus gel N=30	2 (7%)	5 (17%)	5 (17%)	17 (57%)	1 (3%)	0 (0%)
Vehicle gel N=32	1 (3%)	0 (0%)	5 (16%)	24 (75%)	2 (6%)	0 (0%)
Week 4						
Sirolimus gel N=30	1 (3%)	3 (10%)	10 (33%)	16 (53%)	0 (0%)	0 (0%)
Vehicle gel N=32	2 (6%)	1 (3%)	4 (13%)	25 (78%)	0 (0%)	0 (0%)

* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
** One subject in the vehicle arm was assessed as 'not evaluable' by the IRC.
Source: Reviewer's analysis (same as Applicant's analysis)
Abbreviations: FAS, full analysis set; IRC, independent review committee

Table 12 presents the proportion of subjects assessed as "Improved" or "Markedly Improved" based on the composite improvement in AF at Week 12 (also designated as improvement rate). Almost twice the subjects in the sirolimus gel were assessed as "Improved" or "Markedly Improved" by the IRC compared to the Investigator for all types of improvement in AF (composite, improvement in size and color). The statistical reviewer notes that if the proportion of subjects assessed as "Improved" or "Markedly Improved," based on composite improvement in AF assessed by the Investigator, was to be tested, the results would have been nonsignificant using the Fisher exact test (p=0.077).

Table 12. Improvement Rate* in Angiofibroma at Week 12–Trial NPC-12G-1 (FAS)**

Improvement	Sirolimus Gel N=30	Vehicle Gel N=32
Composite improvement–IRC	18 (60%)	0 (0%)
Composite improvement–Investigator	7 (23%)	2 (6%)
Improvement in size–IRC	18 (60%)	1 (3%)
Improvement in size–Investigator	8 (27%)	2 (6%)
Improvement in color–IRC	12 (40%)	0 (0%)
Improvement in color–Investigator	7 (23%)	1 (3%)

* The proportion of subjects assessed as "Improved" or "Markedly Improved"
** FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
Source: Reviewer's analysis (same as Applicant's analysis)
Abbreviations: FAS, full analysis set; IRC, independent review committee

8.1.1.6. Patient-Reported Outcomes

The protocol included an assessment of the patient-reported outcomes (PROs) of DLQI and CDLQI. The endpoints based on these PROs were designated as 'secondary endpoints' in the protocol; however, the scales for these PROs were not validated and the endpoints were not adjusted for multiplicity. Therefore, these endpoints are not discussed in this review.

8.1.1.7. Independent Review Committee Assessments

As noted in Section 8.1.1.1 the IRC consisted of three members who assessed the improvements in AF (composite, size and color) independently using photographs. The statistical reviewer explored the inter-rater reliability for composite improvement using data from the Phase 3 trial. In particular, the statistical reviewer considered the pairwise cross-tabulations and pairwise kappa statistics, which are presented in Appendix 15.4.2 of this review (Table 40 and Table 41). The pairwise weighted kappa statistics for the composite improvement ranged from 0.44 to 0.68.

The statistical reviewer also considered the following measures of inter-rater reliability among more than two raters: Fleiss' kappa (Light 1971) and Light's kappa (Light 1971). Fleiss's kappa and Light's kappa are generalizations of Cohen's kappa for multiple raters. Light (1971) suggests computing kappa for all pairs of raters, and then using the arithmetic mean of these estimates to provide an overall index of agreement. Fleiss (1971) extended Scott's pi statistic to account for the case of more than two raters classifying multiple subjects using a scale with more than two categories. Fleiss' kappa is also a function of observed agreement corrected for chance agreement. Both measures yielded a value of 0.35 after incorporating all timepoints.

Caution is needed when interpreting these results because of the concerns raised by CDRH for photograph processing and color adjustment, and the concerns raised by the DCOA regarding the scale and the procedures followed by the IRC (see Section 8.1.1.1 for more information on these concerns).

Sensitivity Analyses for the IRC Assessments

The final IRC score was based on a consensus with concordance of two out of three IRC raters. If none of the independent assessments by the three IRC raters agreed with each other, a consensus discussion was held to resolve (Consensus Discussion 1) with the possibility of a second consensus discussion even if concordance in two out of three raters was achieved. For

composite improvement in AF at Week 12, agreement between all three raters occurred in 26/62 (42%) subjects, agreement in two out of three raters occurred in 29/62 (48%) subjects, and all raters disagreed for 7/62 (11%) subjects. The final IRC scores for composite improvement at Week 12 for the cases included in consensus discussion are presented in Table 13.

Due to the concerns expressed by the DCOA regarding the procedure of the IRC assessments including the consensus discussions, the statistical reviewer conducted sensitivity analyses for the IRC assessments excluding the cases included in Consensus Discussion 1 at Week 12. It should be noted that for the subjects included in Consensus Discussion 2, the score of the second consensus discussion was not used in this analysis; the score based on the consensus of the two out of three raters was adopted instead. The statistical reviewer also analyzed the improvement rate (i.e., the proportion of subjects assessed as "Improved" or "Markedly Improved") based on composite improvement in AF using only the subjects for which all three IRC raters had an agreement. The results for the sensitivity analysis are presented in Table 14 to Table 16. The results are similar between the FAS and after excluding the subjects that went under Consensus Discussion 1; however, caution is again needed when interpreting these results based on the concerns regarding photograph processing and color adjustment.

Table 13. Final Scores for the Composite Improvement in Angiofibroma for Cases Included in Consensus Discussion–Trial NPC-12G-1

Subject ID	Rater 1	Rater 2	Rater 3	Final Score
Consensus Discussion 1				
(b) (6)	2	1	0	0
	3	2	1	3
	2	3	1	2
	1	2	0	1
	1	2	0	1
	3	2	1	2
	1	Not evaluable	0	Not evaluable
Consensus Discussion 2				
(b) (6)	2	2	1	1
	3	1	1	2
	3	2	2	3
	3	3	1	2
	2	0	0	1

Source: Reviewer's analysis

Table 14. Composite Improvement in Angiofibroma at Week 12 for the Full Analysis Set and After Excluding Subjects Included in Consensus Discussion–Trial NPC-12G-1 (FAS*)

N (%)	Markedly Improved	Improved	Slightly Improved	Unchanged	Slightly Exacerbated	Exacerbated
IRC Assessment for the Full Analysis Set						
Sirolimus gel N=30	4 (15%)	11 (42%)	10 (38%)	1 (4%)	0 (0%)	0 (0%)
Vehicle gel** N=32	0 (0%)	0 (0%)	4 (14%)	25 (45%)	0 (0%)	0 (0%)
IRC Assessment–Excluding Subjects Included in Consensus Discussion						
Sirolimus gel N=26	3 (18%)	9 (41%)	9 (18%)	1 (5%)	0 (0%)	0 (0%)
Vehicle gel N=29	0 (0%)	0 (0%)	3 (11%)	25 (89%)	0 (0%)	0 (0%)

* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
** One subject was assessed as "not evaluated" by the IRC and as "Unchanged" by the Investigator.
Source: Reviewer's analysis
Abbreviations: FAS, full analysis set; IRC, independent review committee

Table 15. Improvement Rate* at Week 12 for the Full Analysis Set and After Excluding Subjects Included in Consensus Discussion–Trial NPC-12G-1 (FAS)**

	Full Analysis Set		Excluding Subjects Who Included in Consensus Discussion	
Improvement Assessment	**Sirolimus Gel**	**Vehicle Gel**	**Sirolimus Gel**	**Vehicle Gel**
Composite improvement - IRC	18/30 (60%)	0/32 (0%)	15/26 (58%)	0/29 (0%)
Composite improvement - Investigator	7/30 (23%)	2/32 (6%)	6/26 (23%)	2/29 (4%)

* The proportion of subjects assessed as "Improved" or "Markedly Improved"
** FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
Source: Reviewer's analysis
Abbreviations: FAS, full analysis set; IRC, independent review committee

Table 16. Improvement Rate* at Week 12 for the Full Analysis Set and Only Subjects on Which All IRC Members Agreed–Trial NPC-12G-1 (FAS)**

	Full Analysis Set		Including Only Subjects On Whom All Raters Agreed	
Improvement Assessment	**Sirolimus Gel**	**Vehicle Gel**	**Sirolimus Gel**	**Vehicle Gel**
Composite improvement - IRC	18/30 (60%)	0/32 (0%)	6/8 (75%)	0/18 (0%)
Composite improvement - Investigator	7/30 (23%)	2/32 (6%)	2/8 (25%)	0/18 (0%)

* The proportion of subjects assessed as "Improved" or "Markedly Improved"
** FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
Source: Reviewer's analysis
Abbreviations: FAS, full analysis set; IRC, independent review committee

8.1.1.8. Agreement Between the IRC and Investigator Assessments

This section investigates the degree of agreement between IRC and Investigator assessments. It should be noted that the IRC used both BL and Week 12 photographs (after corrections) for their assessment; while the Investigator assessment was made in person at Week 12, using the BL photograph (before corrections) as a reference. The final IRC score is used in this analysis. The reader is reminded that the final IRC score was based on a consensus with concordance of two out of three IRC raters, as noted in the previous section.

Table 17 presents the cross-tabulation of the IRC and Investigator assessments for composite improvement in AF at Week 12. As noted in Section 8.1.1.2, the Applicant evaluated Kendall's

coefficient of concordance and the rank correlation coefficient (or Kendall's tau) to measure the degree of agreement between the two assessments. Kendall's coefficient of concordance assesses the degree of association for rank assessments made by multiple raters when assessing the same samples. The value of Kendall's coefficient ranges from 0 to 1. The higher the value of Kendall's coefficient, the stronger the association. Kendall's coefficient was corrected for ties between raters. The rank correlation coefficient (or Kendall's tau) is also a nonparametric measure of relationships between variables of ranked data. The tau correlation coefficient returns a value from 0 to 1, where: 0 is no relationship, 1 is a perfect relationship. According to Khamis (2008), for data that have at least one ordinal variable, Kendall's tau is more appropriate.

Since this application deals with ordinal scales rather than ranks, the statistical reviewer also considered Cohen's Kappa statistic to measure the degree of agreement between the two assessments at Week 12 (see Table 17). Cohen's kappa statistic (simple kappa), and related kappa variants, are commonly used for assessing inter-rater reliability for nominal variables for two raters. Weighted Kappa statistics have been introduced in the literature to allow us to differentially penalize disagreements based on the magnitude of the disagreement. A weighted kappa statistic is typically used for ordinal data. Cicchetti and Allison proposed 'linear' weights, whereas Fleiss and Cohen used 'quadratic' weights. Note that the quadratic weights attach greater importance to near disagreements compared to the linear weights. Suppose the column scores are ordered, say $C_1 \leq C_2 \leq \ldots \leq C_r$ and assigned values of 0, 1, …, r. Then, the Cicchetti-Allison and Fleiss-Cohen weights in each cell of the K×K contingency table are computed as follows:

Cicchetti-Allison (C-A) weights: $w_{ij} = 1 - \frac{|C_i - C_j|}{|C_1 - C_r|}$

Fleiss-Cohen (F-C) weights: $w_{ij} = 1 - \frac{(C_i - C_j)^2}{(C_1 - C_r)^2}$

The same analyses were performed for the improvement in size and color of AF. The results are presented in Appendix 15.4.3 (Table 42 and Table 43).

For composite improvement, concordance was observed in 33/61 (54%) subjects (diagonal elements of the table) while discordance within one unit was observed in 19/61 (32%) subjects. Discordance within two or more units is observed for 9/61 (15%) subjects; for 8 of these subjects, the Investigator score was lower (by at least two units) than the IRC score. Kappa statistics appeared with low values (range from 0.31 to 0.4), which may be attributed to many factors referenced in this review, including image processing and color adjustment, the Investigator using a mix of live/photograph assessments while the IRC only assessed photographs, issues related to scale raised by the DCOA team (Section 8.1.1.1), and small sample size.

Table 17. Cross-Tabulation of the IRC and Investigator Assessments for the Composite Improvement in Angiofibroma at Week 12–Trial NPC-12G-1 (FAS*)

	Investigator Assessment						
IRC Assessment	**Markedly Improved**	**Improved**	**Slightly Improved**	**Unchanged**	**Slightly Exacerbated**	**Exacerbated**	**Total**
Markedly improved	2 (3%)	0 (0%)	2 (3%)	1 (2%)	0 (0%)	0 (0%)	5 (8%)
Improved	1 (2%)	3 (5%)	4 (6%)	5 (8%)	0 (0%)	0 (0%)	13 (21%)
Slightly improved	0 (0%)	2 (3%)	9 (15%)	5 (8%)	0 (0%)	0 (0%)	16 (26%)
Unchanged	1 (2%)	0 (0%)	7 (11%)	19 (31%)	0 (0%)	0 (0%)	27 (44%)
Slightly exacerbated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Exacerbated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	4 (6%)	5 (8%)	22 (35%)	30 (50%)	0 (0%)	0 (0%)	61 (98%)**
Kendall's coefficient of concordance (corrected for ties): W=0.70							
Rank correlation coefficient (Kendall's tau): T=0.37							
Simple kappa: K=0.31							
Weighted C-A kappa: K_{C-A}=0.36							
Weighted F-C kappa: K_{F-C}=0.40							

* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
** One subject was assessed as 'not evaluable' by the IRC and as "Unchanged" by the Investigator.
Source: Reviewer's analysis (same as Applicant's analysis except kappa statistics)
Abbreviations: FAS, full analysis set; IRC, independent review committee

8.1.1.9. Findings in Special/Subgroup Populations

Age and Sex

Table 18 presents the results for composite improvement in AF at Week 12 by age (adults [≥18 years] vs. children/adolescents [<18 years]) and sex (female vs. male) for both the IRC and the Investigator assessments. The corresponding results for improvement in size and color of AF are presented in Appendix 15.4.3 (see Table 44 and Table 45). We note that, as a result of the small sample size, it is difficult to draw meaningful conclusions for subgroup analyses.

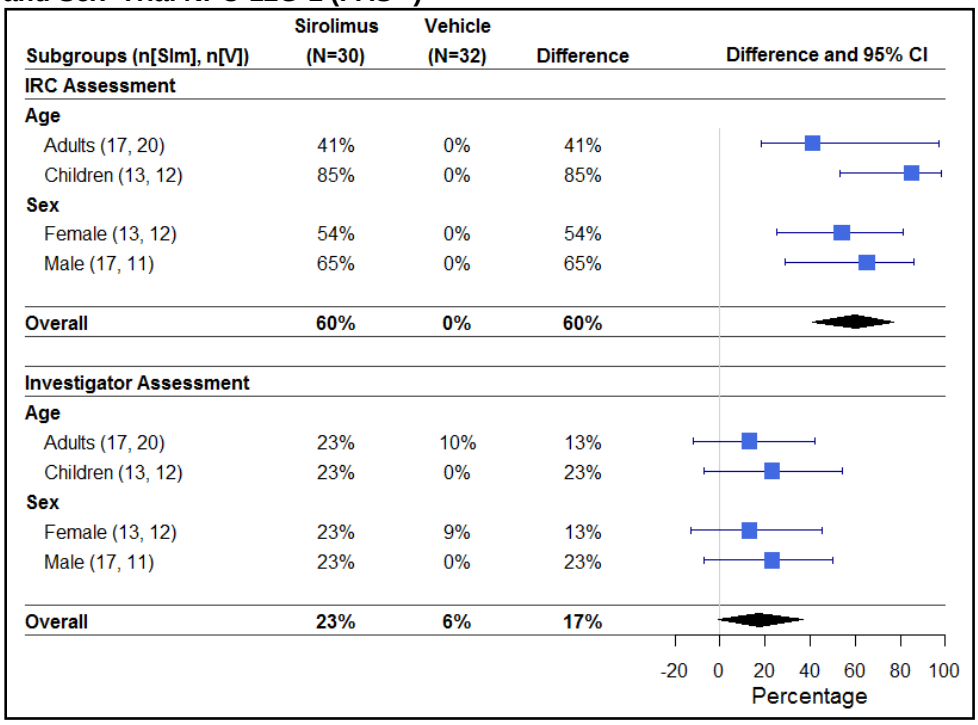
The results for the improvement rate (i.e., proportion of subjects assessed as "Improved" or "Markedly Improved") at Week 12 for the composite improvement is presented in Figure 10. The corresponding results for improvement in size and color of AF are presented in Appendix 15.4.3 (Figure 12 and Figure 13). Again, it is difficult to draw meaningful conclusions due to the small sample size.

Table 18. Composite Improvement in Angiofibroma at Week 12 by Age and Sex–Trial NPC-12G-1 (FAS*)

N (%)	Markedly Improved	Improved	Slightly Improved	Unchanged	Slightly Exacerbated	Exacerbated
IRC Assessment						
By age						
Adults						
Sirolimus gel (N=17)	3 (18%)	4 (24%)	10 (58%)	0 (0%)	0 (0%)	0 (0%)
Vehicle gel** (N=20)	0 (0%)	0 (0%)	2 (10%)	17 (85%)	0 (0%)	0 (0%)
Children/adolescents						
Sirolimus gel (N=13)	2 (15%)	9 (69%)	1 (8%)	1 (8%)	0 (0%)	0 (0%)
Vehicle gel (N=12)	0 (0%)	0 (0%)	3 (25%)	9 (75%)	0 (0%)	0 (0%)
By sex						
Female						
Sirolimus gel (N=13)	1 (8%)	6 (46%)	6 (46%)	0 (0%)	0 (0%)	0 (0%)
Vehicle gel** (N=21)	0 (0%)	0 (0%)	3 (14%)	17 (81%)	0 (0%)	0 (0%)
Male						
Sirolimus gel (N=17)	4 (23%)	7 (41%)	5 (29%)	1 (6%)	0 (0%)	0 (0%)
Vehicle gel (N=11)	0 (0%)	0 (0%)	2 (18%)	9 (82%)	0 (0%)	0 (0%)
Investigator Assessment						
By age						
Adults						
Sirolimus gel (N=17)	2 (5%)	2 (5%)	9 (53%)	4 (23%)	0 (0%)	0 (0%)
Vehicle gel** (N=20)	1 (5%)	1 (5%)	5 (25%)	13 (65%)	0 (0%)	0 (0%)
Children/adolescents						
Sirolimus gel (N=13)	1 (8%)	2 (15%)	5 (38%)	5 (38%)	0 (0%)	0 (0%)
Vehicle gel (N=12)	0 (0%)	0 (0%)	3 (25%)	9 (75%)	0 (0%)	0 (0%)
By sex						
Female						
Sirolimus gel (N=13)	1 (8%)	2 (15%)	7 (54%)	3 (23%)	0 (0%)	0 (0%)
Vehicle gel** (N=21)	1 (5%)	1 (5%)	5 (24%)	14 (67%)	0 (0%)	0 (0%)
Male						
Sirolimus gel (N=17)	2 (12%)	2 (12%)	7 (41%)	6 (35%)	0 (0%)	0 (0%)
Vehicle gel (N=11)	0 (0%)	0 (0%)	3 (27%)	8 (73%)	0 (0%)	0 (0%)

* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
** One female adult was assessed as “Not Evaluable” by the IRC at Week 12
Source: Reviewer’s analysis (same as Applicant’s analysis)
Abbreviations: FAS, full analysis set; IRC, independent review committee

Figure 10. Improvement Rate* for the Composite Improvement in Angiofibroma at Week 12 by Age and Sex–Trial NPC-12G-1 (FAS)**



Source: Reviewer's analysis
* Improvement rate is defined as the proportion of subjects assessed as "Improved" or "Markedly Improved"
** FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
Abbreviations: CI, confidence interval; FAS, full analysis set; n[Slm], subgroup sample size for active arm; n[V], subgroup sample size for vehicle arm

8.1.1.10. Site

The Phase 3 trial was conducted at nine sites in Japan. The majority of the sites enrolled fewer than five subjects and therefore it is not informative for this review to discuss site-to-site variability.

8.1.2. Trial OSD-001-001

8.1.2.1. Trial Design and Endpoints

Trial OSD-001-001 was a single-center, double-blind, randomized, vehicle-controlled, parallel-group, dose-escalation, Phase 1/2 trial. The objective of the trial was to estimate the maximum dose of OSD-001 that can be administered safely within doses ranging from 0.05% to 0.2%, and to explore effective doses using skin-lesion improvement as the indicator in adult and pediatric subjects with facial skin lesions associated with TS. It should be noted that OSD-001 is a different formulation of sirolimus gel (NPC-12G) used in the Phase 3 trial NPC-12G-1. The two formulations of sirolimus gel, NPC-12G and OSD-001, are provided in Table 19.

Table 19. Composition of the Two Sirolimus Gel Formulations

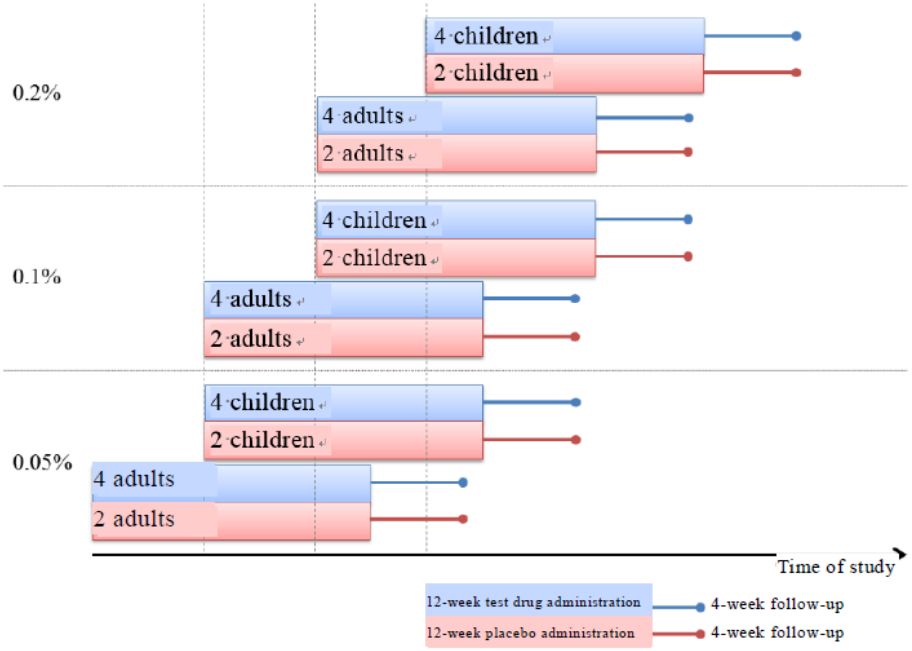
Abbreviation	Definition/Explanation
NPC-12G gel	This contained sirolimus as active ingredient, (b) (4) (b) (4)
OSD-001 gel	This contained sirolimus as active ingredient, (b) (4) (b) (4)

Subjects 3 to 65 years of age with at least three sites of solitary papules (at least 2 mm in longitudinal diameter and red in color) of AF on the face ("red in color" is defined as 2 or more in the evaluation of redness) were enrolled in Trial OSD-001-001.

The trial used the escalation design depicted in Figure 11, where the safety of each concentration was judged by the Investigator based on data collected up to 4 weeks after the start of application in six subjects before moving to the next concentration.

The investigational product was applied to the target sites twice daily for 12 weeks. The target sites of application were facial skin lesions associated with TS (AF, plaque, erythema, and hypomelanotic macule), and the investigational product was applied evenly to facial skin lesions, including a small tumor to be measured for changes in size. The target sites were chosen to be the three largest, discrete, isolated AFs (tumors) at baseline, each of which was at least 2 mm in length and had a score of 'red' on the color scale. Subjects were assessed at Weeks 2, 4, 8, and 12 during treatment, and again at Week 16 (i.e., 4 weeks after the end of treatment).

Figure 11. Study Design for Trial OSD-001-001



Source: Applicant's Figure 9.1-1 in the OSD-001-001 study report

The primary outcome measure was a composite variable of the improvement scores of tumor size reduction and lessening of redness of the target sites relative to BL after 12 weeks. The

composite variable is defined as the sum of 1) improvement scores of tumor volume and 2) improvement scores of redness, based on degree of improvement of the three target tumors specified as the target sites.

The improvement of tumor volume was classified into five levels and scored in accordance with the criteria in Table 20 using the following formulas:

- Tumor volume = longitudinal diameter × transverse diameter × transverse diameter ÷ 2
- Sum of tumor volume = volume of tumor 1 + volume of tumor 2 + volume of tumor 3
- Ratio of sum (%) = $\left(1 - \frac{Sum\ of\ tumor\ volume\ at\ Week\ 12}{Sum\ of\ tumor\ volume\ at\ baseline}\right) \times 100$

Table 20. Improvements in Tumor Volume–Trial OSD-001-001

Score	Improvements	Criteria
-1.0	Exacerbated	Increase by 20% or more in the ratio of sum of the product
0.0	Unchanged	Change by less than ±20% in the ratio of sum of the product
0.5	Mildly improved	Shrinkage by 20% or more to less than 50% in the ratio of sum of the product
1.0	Moderately improved	Shrinkage by 50% or more to less than 80% in the ratio of sum of the product
2.0	Markedly improved	Shrinkage by 80% or more

Source: Applicant's Table 9.5-3 on page 40 of the OSD-001-001 study report

The value of tumor redness was assessed using the scale in Table 21. The change in the sum of the points of redness between BL and Week 12 (i.e., improvement in redness) was classified into five grades and assigned an improvement score according to the criteria shown in Table 22 using the following formulas:

- Sum of assessment values of redness = point of redness of tumor 1 + point of redness of tumor 2 + point of redness of tumor 3
- Change in the sum of assessment values of redness = sum of the points of redness at BL – sum of the points of redness after 12 weeks

Table 21. Assessment Value of Redness of Tumors–Trial OSD-001-001

Assessment value	Number of color sample of PANTONE
1	As dark as or paler than 489C
2	As dark as or paler than 486C
3	As dark as or paler than 7416C
4	As dark as or paler than 485C
5	As dark as or paler than 704C
6	Darker than 704C

Source: Applicant's Table 9.5-4 on page 41 of the OSD-001-001 study report

Table 22. Improvements in Redness of Tumors–Trial OSD-001-001

Score	Improvements	Criteria
-1.0	Exacerbated	Changes in the sum of assessment values are -12 to -3
0.0	Unchanged	Changes in the sum of assessment values are -2 to 2
0.5	Mildly improved	Changes in the sum of assessment values are 3 to 5
1.0	Moderately improved	Changes in the sum of assessment values are 6 to 8
2.0	Markedly improved	Changes in the sum of assessment values are 9 or more

Source: Applicant's Table 9.5-5 on page 41 of the OSD-001-001 study report

8.1.2.2. Subject Disposition, Demographics, and BL Disease Characteristics

Trial OSD-001-001 enrolled and randomized a total of 36 subjects (24 in the active drug group and 12 in the vehicle group). All 36 subjects received the investigational product, and therefore, were included in the efficacy population. All 36 subjects completed their treatment and no subjects discontinued treatment.

Demographics are presented in Table 23. All subjects participating in the trial were Japanese. The majority of the enrolled subjects were female (approximately 70%). The demographics were generally balanced across treatment arms; however, more female subjects were randomized to Sirolimus gel compared to vehicle gel. The BL disease severity characteristics are presented in Table 24. The BL sum of tumor volume was highly variable in all treatment groups. In addition, only one third of the trial population (13/36) presented with erythema at baseline.

Table 23. Demographics–Trial OCS-001-001

	Sirolimus Gel, 0.05% N=8	Sirolimus Gel, 0.1% N=8	Sirolimus Gel, 0.2% N=8	Vehicle Gel (Pooled) N=12	Total N=36
Age (years)					
Mean (SD)	20.9 (13.6)	20.0 (10.8)	19.1 (10.9)	19.0 (12.6)	19.7 (11.6)
Median	19	18	18	16	18.5
Range	6–47	8–42	6–37	6–42	6–47
Age Group (years)					
<18	3 (37%)	4 (50%)	4 (50%)	6 (50%)	17 (47%)
≥18	5 (63%)	4 (50%)	4 (50%)	6 (50%)	19 (53%)
Sex					
Male	2 (25%)	4 (50%)	1 (13%)	6 (50%)	13 (36%)
Female	6 (75%)	4 (50%)	7 (87%)	6 (50%)	23 (64%)
Body Weight (kg)					
Mean (SD)	49.0 (19.3)	47.1 (16.5)	38.4 (13.3)	42.2 (16.1)	44.0 (16.2)
Median	47.8	52.5	39.8	46.9	47.6
Range	23.4–75.4	25.6–65.2	21.2–55.0	17.8–62.0	17.8–75.4

Source: Reviewer's analysis

Table 24. Baseline Disease Characteristics–Study OCS-001-001

	Sirolimus Gel, 0.05% N=8	Sirolimus Gel, 0.1% N=8	Sirolimus Gel, 0.2% N=8	Vehicle Gel (Pooled) N=12	Total N=36
Sum of Tumor Volume					
Mean (SD)	75.9 (78.1)	83.5 (99.2)	60.1 (57.4)	66.9 (74.2)	71.1 (75.2)
Median	48	42.2	32.4	42.2	38.7
Range	16–257	20–316	9.1–158.4	9–262	9–316
Severity of Erythema	**N=5**	**N=1**	**N=1**	**N=6**	**N=13**
Mean (SD)	12.5 (3.0)	15.1	11.64	13.4 (4.1)	13.0 (3.3)
Median	14.4	-	-	14.2	14.4
Range	8.4–15.0	-	-	5.8–17.4	5.8–17.4

Source: Reviewer's analysis

8.1.2.3. Efficacy Results

Table 25 presents the results for the primary outcome measure of the composite variable, which evaluates the size and redness of tumors together. The improvements in the volume and redness of tumors are presented separately in Table 26 and Table 27, respectively. A total of 7/8 (87%) subjects were moderately or markedly improved in tumor volume in the sirolimus 0.2% group versus 3/12 (75%) subjects in the vehicle gel group, while a total of 4/8 (50%) subjects were moderately or markedly improved in tumor redness in the sirolimus 0.2% group versus 3/12 (75%) subjects in the vehicle gel group.

Table 25. Composite Variable at Week 12–Study OSD-001-001

Composite Variable Value	Sirolimus Gel, 0.05% N=8	Sirolimus Gel, 0.1% N=8	Sirolimus Gel, 0.2% N=8	Vehicle Gel (Pooled) N=12
−2	0 (0%)	0 (0%)	0 (0%)	1 (8%)
−1.5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
−1	0 (0%)	0 (0%)	0 (0%)	3 (25%)
−0.5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
0	0 (0%)	1 (13%)	0 (0%)	2 (17%)
0.5	1 (13%)	1 (13%)	0 (0%)	2 (17%)
1	0 (0%)	0 (0%)	0 (0%)	1 (8%)
1.5	1 (13%)	2 (25%)	5 (63%)	2 (17%)
2	1 (13%)	1 (13%)	1 (13%)	0 (0%)
2.5	0 (0%)	0 (0%)	0 (0%)	1 (8%)
3	2 (25%)	0 90%)	2 (25%)	0 (0%)
3.5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Reviewer's analysis (same as Applicant's analysis)

Table 26. Improvements in Tumor Volume at Week 12–Study OSD-001-001

	Sirolimus Gel, 0.05% N=8	Sirolimus Gel, 0.1% N=8	Sirolimus Gel, 0.2% N=8	Vehicle Gel (Pooled) N=12
Markedly improved	2 (25%)	0 (0%)	2 (25%)	1 (8%)
Moderately improved	2 (25%)	4 (50%)	5 (63%)	2 (17%)
Mildly improved	3 (38%)	2 (25%)	1 (12%)	2 (17%)
Unchanged	1 (12%)	2 (25%)	0 (0%)	3 (25%)
Exacerbated	0 (0%)	0 90%)	0 (0%)	4 (33%)

Source: Reviewer's analysis (same as Applicant's analysis)

Table 27. Improvements in Redness of Tumors at Week 12–Study OSD-001-001

	Sirolimus Gel, 0.05% N=8	Sirolimus Gel, 0.1% N=8	Sirolimus Gel, 0.2% N=8	Vehicle Gel (Pooled) N=12
Markedly improved	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Moderately improved	4 (50%)	2 (25%)	4 (50%)	0 (0%)
Mildly improved	3 (38%)	3 (38%)	4 (50%)	5 (42%)
Unchanged	1 (12%)	3 (38%)	0 (0%)	6 (50%)
Exacerbated	0 (0%)	0 (0%)	0 (0%)	1 (8%)

Source: Reviewer's analysis (same as Applicant's analysis)

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety for sirolimus gel, 0.2% for the treatment of FA of TS focuses on data from the Phase 3 Trial, NPC-12G-1. Trial NPC-12G-1 was a multicenter, randomized, double-blind, vehicle-controlled, safety and efficacy trial conducted in subjects with TS 6 years of age and older. The inclusion criteria for this trial specified enrollment of subjects aged 3 years and older; however, the youngest subject enrolled in this trial was 6 years of age. The Phase 3 trial population included a total of 62 subjects with at least three sites of solitary papules of AF (≥2 mm in diameter with redness in each) on the face. Subjects were randomized in a 1:1 ratio to treatment with sirolimus gel, 0.2% or vehicle applied topically twice daily for 12 weeks.

The Applicant submitted long-term safety data from Trial NPC-12G-2. This was a multicenter, open-label, safety trial in subjects 3 years of age and older with FA of TS. Subjects applied sirolimus gel, 0.2% to the affected area twice daily. The Applicant collected efficacy data for 52 weeks; however, subjects could continue treatment after this timepoint. The Applicant planned to continue this trial as a postmarketing safety study after approval in Japan. Treatment with sirolimus gel, 0.2% was to be continued until marketing approval or 09/30/2018, whichever came first. Sirolimus gel, 0.2% was approved in Japan in March 2018.

The Applicant also submitted supportive safety data from a Phase 1/2 PK and dose-finding trial, a PK/comparative BA trial conducted with sirolimus gel, 0.2% and Rapamune tablets, 2 mg, and an ongoing postmarketing safety study.

To determine the safety profile of sirolimus gel, 0.2%, the review team analyzed the following types of pooled data: exposure, demographics, BL characteristics, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, laboratory results, vital signs, and findings from physical examinations.

8.2.2. Review of the Safety Database

Overall Exposure

The primary analysis dataset for the review of safety for sirolimus gel, 0.2% included data from Phase 3 Trial NPC-12G-1. Data from the other studies were not integrated because of dissimilar study designs, or use of a different formulation of sirolimus gel, 0.2%.

The Phase 3 safety population includes the 62 subjects who were enrolled and randomized (30 to sirolimus gel, 0.2% and 32 to vehicle). No subjects discontinued treatment. Furthermore, all 62 subjects enrolled in Phase 3 Trial NPC-12G-1 continued into the open-label long-term safety Trial NPC-12G-2.

The overall safety database comprises subjects who received at least one dose of sirolimus gel, 0.2%. A summary of exposure to sirolimus gel, 0.2% is provided in Table 28.

Table 28. Summary of Exposure during Clinical Trials

Trial	Number of Subjects	Average Daily Dose of Sirolimus Gel, 0.2%	Exposure Period
Phase 1/2(OSD-001-001)	24	<375 mg[1]	12 Weeks
	4	<400 mg	12 Weeks
	7	400–<600 mg	12 Weeks
	10	600–<800 mg	12 Weeks
Phase 3 (NPC-12G-1)	9	≥800 mg	12 Weeks
	30	<400 mg	Over 52 Weeks
	36	400–<600 mg	Over 52 Weeks
	23	600–<800 mg	Over 52 Weeks
Long-term study (NPC-12G-2)	5	≥800 mg	Over 103 Weeks
Comparative bioavailability study (NPC-12G-4/US)	12	800 mg	1 Day

[1] 125 mg of gel extracted for one pump; the maximum application dose was used as the average daily dose.
Source: Applicant's Summary of Clinical Safety, Table 3, p. 14

Relevant Characteristics of the Safety Population

In the Phase 3 safety population, most subjects were female (54.8%). A total of 59.7% was adults (defined as age 18 years and older) and 40.3% were pediatric subjects (defined as age <18 years). It should be noted that although the review team defined the age groups as stated above, the Applicant defined pediatric subjects as those aged 18 years or less. All subjects were Japanese. Demographics for age (Safety Analysis Set) for the Phase 3 and open-label LTS trials are presented in Table 29.

Table 29. Demographics by Age Group, Phase 3 and Open-Label Long-Term Safety Trials

	Phase 3 Trial (NPC-12G-1)		Open-Label Long-Term Safety Trial (NPC-12G-2)
Population	Sirolimus Gel, 0.2% N=30	Vehicle Gel N=32	Sirolimus Gel, 0.2% N=94
3 to 5 years old	0 (0%)	0 (0%)	4 (4%)
6 to 11 years old	6 (20%)	6 (19%)	22 (23%)
12 to 17 years old	7 (23%)	6 (19%)	22 (23%)
≥18 years old	17 (57%)	20 (62%)	46 (49%)

Source: Statistical Reviewer's table by Dr. Marilena Flouri

Adequacy of the Safety Database

The total subject exposure to sirolimus gel, 0.2% applied twice daily for 12 weeks provides sufficient data for the evaluation of safety for treatment of this rare disease. The total exposure of 52 weeks or longer is sufficient to characterize the safety of the product over longer treatment periods. The demographics of the study population are sufficiently representative of

the target population. However, there were no subjects under 6 years of age enrolled in the Phase 3 trial. There were four subjects aged 3 to 5 years in the open-label LTS trial; these included one subject aged 3 years, two aged 4 years, and one aged 5 years. The safety database for subjects less than 6 years of age is not sufficient to support approval for pediatric subjects less than 6 years of age. Therefore, the safety database submitted by the Applicant is sufficient to characterize the safety profile of sirolimus gel, 0.2% for the treatment of FA associated with TS in adults and pediatric patients 6 years of age or older.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is sufficient to characterize the safety and efficacy of sirolimus gel, 0.2% for the treatment of FA of TS. Because the studies were initiated prior to December 2016, the Applicant was not required to submit Clinical Data Interchange Standards Consortium-compliant datasets (i.e., SDTM] and Analysis Data Model datasets). The Applicant was advised during the pre-NDA meeting that the datasets should be submitted in SAS transport format (.xpt). The SAS datasets from Phase 1/2 Trial OSD-001-001, Phase 3 Trial NPC-12G-1, and the open-label LTS Trial NPC-12G-2 were initially not accessible. We sent an information request to the Applicant, and new SAS datasets were submitted. Also, because SDTM datasets were not submitted, Core Data Fitness assessments could not be performed. Nevertheless, we discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

An AE was defined as "any unfavorable and unintended sign (including an abnormal change in laboratory finding), symptom, or disease in subjects who received an investigational product, whether or not causally related to the investigational product." The Applicant defined adverse drug reaction as an AE for which a causal relationship between the study drug and the AE is "at least a reasonable possibility, i.e., the relationship cannot be ruled out."

Investigators monitored subjects for AE by interview and examination. For each AE, the investigator recorded the name of the AE, date of onset, severity, seriousness, presence or absence of intervention, outcome, date of outcome, and causal relationship with study product into the electronic case report form. For dermal AEs, investigators also recorded whether the AE occurred in an area where study drug was applied, and thoroughly examined any AE suggestive of photosensitization. Investigators categorized the severity of the AE according to the following criteria:

- Mild: The symptoms are mild and are easily tolerable.
- Moderate: The symptoms cause discomfort that hinders the activities of daily living and require treatment.
- Severe: The symptoms cause a severe hindrance in the activities of daily living.

Investigators assessed the relationship of the AE to the study drug using the following criteria:

- Not related: There is no temporal pattern that can be associated with the investigational product after administration thereof, or with events that are considered attributable to such factors as disease at the time of onset, other drugs, or environmental factors.
- Related: Events other than "not related."

The Applicant defined an SAE as an AE that met one of the following criteria:

- Death
- Event that may lead to death (defined as "an AE for which a patient may die immediately at the onset of the event, and no inference can be made that a more severe event lead to death.")
- Event that requires hospitalization or prolongation of hospitalization in a hospital or a clinic
- Hindrances (i.e., disability)
- Events that may lead to a hindrance
- Events that are serious in accordance with the preceding criteria*
- Congenital diseases or abnormalities in later generations

*From the Phase 3 Protocol: "Medical and scientific judgement should be exercised in deciding whether expedited reporting described below is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are blood disorders that are considered medically important, renal and hepatic disorder, central nervous system disorders, intensive treatment in an emergency room or at home for allergic bronchospasm; convulsions that do not result in hospitalization; or development of drug dependency or drug abuse."

The Applicant also defined "significant adverse events" as "AEs that are not SAEs and that are judged to be of special interest because of clinical importance" according to the following criteria:

- AEs leading to discontinuation of the investigational product
- Skin irritation symptoms (such as erythema, papules, blisters, erosion, and edema)

If an AE occurred, investigators performed follow-up observation as long as possible until the AE resolved. If pregnancy was confirmed or suspected, study drug was discontinued, and the subject was to be followed until the outcome of the pregnancy was known.

Routine Clinical Tests

During the Phase 3 trial, investigators conducted safety assessments at Screening and BL followed by Weeks 4, 8, and 12. During the open-label LTS trial, subjects returned for clinic visits at Screening and BL, then every 4 weeks from Week 4 to 16, every 5 weeks from Week 16 to 26, then Weeks 39 and 52. In addition, investigators conducted follow-up visits by telephone at Weeks 30, 34, 43, and 47. After Week 52, subjects returned for clinic visits every 13 weeks, with two telephone calls between scheduled visits. The evaluation of safety for these trials included physical examination, vital signs (blood pressure and pulse rate), body weight, clinical laboratory evaluation, and pregnancy testing for females of reproductive potential.

During the Phase 3 trial, investigators conducted clinical laboratory testing at Screening, BL (if Screening occurred >1 week prior to the BL visit), Week 4, and Week 12. Laboratory assessments included hematology, serum chemistry (including lipid parameters), and urinalysis. Pregnancy testing was performed for females of reproductive potential at Screening and Week 12. During the open-label LTS trial, investigators conducted clinical laboratory testing and pregnancy testing at Screening (only for subjects not enrolled in the Phase 3 trial), BL, every 3 months through Week 52, and every 6 months thereafter.

8.2.4. Safety Results

Deaths

No deaths occurred during clinical trials for sirolimus gel, 0.2%. Four deaths were reported in the postmarketing drug use survey (Study RPG01S). These are discussed in Section 8.2.10 of this review.

Serious Adverse Events

In Phase 3 Trial NPC-12G-1, one subject experienced two SAEs. A (b) (6) (Subject (b) (6) (b) (6) with a history of epilepsy treated with valproic acid, lamotrigine, and gabapentin experienced acute pancreatitis and gastric hemorrhage on Day 40 of treatment. (b) (6) continued treatment with sirolimus gel, 0.2% and the SAEs resolved. The investigator considered the gastric hemorrhage not related to treatment with study drug, but that the relationship of acute pancreatitis to study drug "could not be ruled out". Both valproic acid and lamotrigine have been associated with pancreatitis. Oral sirolimus has also been associated with pancreatitis. However, the AE resolved and did not recur, although the subject continued treatment with sirolimus gel, 0.2%. Based on this information, the review team concluded that the SAE of acute pancreatitis was not related to treatment with sirolimus gel, 0.2%.

In the open-label LTS Trial NPC-12G-2, 14 SAEs were reported in nine subjects. Investigators considered none of these SAEs to be related to treatment with sirolimus gel, 0.2%, and no subjects discontinued treatment because of the SAEs. Narrative summaries for these subjects are provided below:

- A (b) (6) (Subject (b) (6)) with a history of LAM had pneumothorax of the left lung on Day 142. (b) (6) underwent surgical treatment and the SAE resolved. The investigator considered the relationship to the study drug as not related.
- A (b) (6) (Subject (b) (6)) was hospitalized for wisdom teeth removal on Day 752 and underwent surgical removal on Day 753. The SAE was resolved on Day 754. The investigator considered the relationship to the study drug as not related.
- A (b) (6) (Subject (b) (6)) with a history of renal angiomyolipoma who discontinued treatment with study drug on Day 84 and was hospitalized for scheduled renal artery embolization on Day 104. The SAE was resolved on Day 106. The investigator considered the relationship to the study drug as not related.
- A (b) (6) (Subject (b) (6)) with a history of enlarged subependymal giant cell astrocytoma associated with TS, and under treatment with oral everolimus, had mycoplasma pneumonia on Day 78. (b) (6) was treated with intravenous and oral

antibiotics and the SAE resolved. The investigator considered the SAE related to immunosuppression from everolimus and the relationship to the study drug as not related.

- A (b) (6) subject (Subject (b) (6)) with a history of infantile spasms experienced the following SAEs:
  - (b) (6) was hospitalized at age (b) (6) and underwent corpus callosotomy on Day 132. The SAE was considered resolved on Day 146. The investigator considered the relationship to the study drug as not related.
  - (b) (6) was hospitalized at age (b) (6) on Day 453 for inpatient management of streptococcal infection with poor oral intake. (b) (6) was discharged to home and the SAE was considered resolved on Day 459. The investigator considered the relationship to the study drug as not related.
  - (b) (6) was hospitalized age (b) (6) and underwent left posterior quadrant disconnection/corpus callosotomy for infantile spasms on Day 637. The SAE was considered resolved and the investigator considered the relationship to the study drug as not related.
  - (b) (6) completed the open-label LTS trial and continued treatment in the postmarketing survey study beginning on (b) (6), during which (b) (6) experienced the following SAEs:
    - (b) (6) was again hospitalized on Day 854 at age (b) (6) for pharyngitis, fever, and poor oral intake and treated with antibiotics. (b) (6) was discharged to home and the SAE was considered resolved on Day 858. The investigator considered the relationship to the study drug as not related.
    - (b) (6) was again hospitalized on Day 927 at age (b) (6) for anorexia, stomatitis, and generalized rash (preferred term [PT] pharyngitis). After intravenous therapy (b) (6) appetite improved, and (b) (6) was discharged on Day 940. The SAE was considered resolved and the investigator considered the relationship to the study drug as not related.
- An (b) (6) (Subject (b) (6)) with a history of West syndrome experienced the following SAEs:
  - On Day 117, (b) (6) accidentally ingested the study drug when his caregiver put approximately 1 cm (200 mg) on his/her finger, which was then placed in the subject's mouth when (b) (6) experienced an epileptic seizure. The subject had no vomiting nor any other apparent ill effect. The SAE of incorrect route of drug administration was considered resolved the same day, and the investigator considered the relationship to the study drug as not related.
  - (b) (6) was hospitalized and underwent corpus callosotomy on Day 302. (b) (6) was discharged on Day 316. The SAE was considered resolved and the investigator considered the relationship to the study drug as not related.
- A (b) (6) (Subject (b) (6)) with a history of refractory West syndrome was hospitalized because of seizures on Day 136. (b) (6) responded to treatment and was discharged the following day. The SAE was considered resolved and the investigator considered the relationship to the study drug as not related.

- A [(b) (6)] (Subject [(b) (6)]) with a history of West syndrome and cerebral arteriovenous malformation underwent cerebral intravascular surgery. The following day (Day 137), [(b) (6)] experienced vomiting, nystagmus, and a feeling of unwellness with right gaze. Magnetic resonance imaging findings were consistent with brain edema in the left cerebellar hemisphere. [(b) (6)] condition improved and [(b) (6)] was discharged on Day 142. The SAE of brain edema was considered resolved and the investigator considered the relationship to the study drug as not related.
- A [(b) (6)] (Subject [(b) (6)]) with a history of divergent strabismus was hospitalized for surgical correction due to worsening strabismus on Day 476. [(b) (6)] was discharged on Day 478 and the SAE of strabismus was considered resolved on Day 484. Treatment with study drug was interrupted from Day 477 until Day 484. The investigator considered the relationship to the study drug as not related.

Dropouts and/or Discontinuations Due to Adverse Events

During Phase 3 Trial NPC-12G-1, no subjects discontinued due to an AE. During the open-label LTS Trial NPC-12G-2, two subjects discontinued due to AEs. Narrative summaries for these subjects are provided below:

- A [(b) (6)] (Subject [(b) (6)]) discontinued because of AEs of eye irritation and erythema (of skin) on Day 1 and 7, respectively. Both of the AEs resolved, and were considered by the investigator to be related to treatment with the study drug.
- A [(b) (6)] (Subject [(b) (6)]) discontinued because of an AE of contact dermatitis on Day 5. The AE resolved, and the investigator considered the event as related to treatment with the study drug.

During the open-label LTS Trial NPC-12G-2, the Applicant also reported five AEs leading to dose reduction to once daily. These included two events of application site hemorrhage, and one event each of “hot flush,” application site paresthesia, and application site irritation. The application site irritation was moderate in severity, and the remaining AEs were mild in severity. Although the investigators did not consider the AEs to be clinically significant, a relationship to treatment with study drug could not be excluded. The AEs resolved during once daily treatment with sirolimus gel, 0.2%.

Significant Adverse Events

During the Phase 3 trial, all TEAEs were mild or moderate in intensity. No severe TEAEs were reported during the Phase 3 trial.

During the open-label LTS trial, six subjects experienced TEAEs of severe intensity. Five of these severe AEs were also classified as SAEs: pneumothorax, therapeutic embolization, pneumonia mycoplasmal, corpus callosotomy, and brain edema. These were discussed earlier in this section. One severe AE was not classified as an SAE. A [(b) (6)] (Subject [(b) (6)]) with a history of epilepsy experienced a severe AE of loss of consciousness on Day 20. The AE resolved the same day and the subject continued treatment with the study drug. The investigator considered the AE not related to treatment with study drug. No further information was provided regarding this AE.

Treatment-Emergent Adverse Events and Adverse Reactions

Treatment-Emergent Adverse Events

During the Phase 3 Trial NPC-12G-1, 27/30 (90%) subjects treated with sirolimus gel, 0.02% and 22/32 (68.8%) subjects treated with vehicle experienced TEAEs. The most frequently reported TEAEs were in the system-organ classes (SOCs) of skin and subcutaneous tissue disorders, and general disorders and administration site conditions. In the SOC of skin and subcutaneous tissue disorders, the most commonly reported PTs were dry skin and pruritus. In the SOC of general disorders and administration site conditions, the most common PT was application site irritation.

The Applicant's assessment for application site reactions included AEs reported by subjects or discovered by the investigator on examination. Investigators recorded whether dermal AEs occurred at the application site or on nontreated skin. TEAEs designated as application site irritation, and AEs in the SOC of skin and subcutaneous disorders, occurred more frequently at the application sites. TEAEs meeting these criteria were reported in 11/30 (36.7%) subjects treated with sirolimus gel, 0.2% and 9/32 (28.1%) subjects treated with vehicle.

TEAEs by SOC are presented in order of descending frequency in Table 30.

Table 30. TEAE by SOC up to Week 12, Phase 3 Trial

System Organ Class	Sirolimus Gel, 0.2% (N=30)	Vehicle (N=32)
Skin and subcutaneous tissue disorders	19 (63.3%)	8 (25.0%)
General disorders and administration site conditions	13 (43.3%)	11 (34.4%)
Infections and infestations	7 (23.3%)	7 (21.9%)
Eye disorders	2 (6.7%)	2 (6.3%)
Injury, poisoning and procedural complications	2 (6.7%)	4 (12.5%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (6.7%)	0 (0.0%)
Gastrointestinal disorders	4 (3.3%)	4 (12.5%)
Investigations	1 (3.3%)	2 (6.3%)
Immune system disorders	1 (3.3%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	1 (3.3%)	0 (0.0%)
Renal and urinary disorders	1 (3.3%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	1 (3.3%)	2 (6.3%)
Nervous system disorders	0 (0.0%)	2 (6.3%)
Psychiatric disorders	0 (0.0%)	1 (3.1%)

Source: Reviewer's table created in JReview
Abbreviations: SOC, system organ class; TEAE, treatment-emergent adverse event

During the open-label LTS Trial NPC-12G-2, the most frequently reported TEAEs were in the SOCs of skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administration site conditions. In the SOC of skin and subcutaneous tissue disorders, the most commonly reported PTs were acne and dry skin. In the SOC of gastrointestinal disorders, the most commonly reported PT was stomatitis. In the SOC of general disorders and administration site conditions, the most commonly reported PT was application site irritation.

Adverse Reactions

The Applicant proposed to include the following information in Section 6.1 (Adverse Reactions/Clinical Trials Experience):

(b) (4)

The review team identified TEAEs occurring in at least 3% of subjects (i.e., one subject) and occurring more frequently in subjects treated with sirolimus gel, 0.2% as adverse reactions (ARs). TEAEs for which a cause could be identified other than treatment with the study drug were excluded.

The following information will be conveyed in Section 6 (Adverse Reactions) in product labeling:

> "The most common adverse reactions reported by ≥(b) (4)% of subjects treated with Hyftor, and more frequently than in subjects treated with vehicle, are presented in Table 1 (b) (4). Adverse reactions occurred with similar frequency in (b) (4)

Table 1: Adverse Reactions (b) (4)

Preferred Term	Hyftor N=30	Vehicle N=32
Dry skin[1]	12 (40%)	4 (13%)
Application site irritation	11 (37%)	9 (28%)
Pruritus	5 (17%)	4 (13%)
Acne	2 (7%)	0 (0%)
Acneiform dermatitis	1 (3%)	0 (0%)
Ocular hyperemia	1 (3%)	0 (0%)
Skin hemorrhage	1 (3%)	0 (0%)
Skin irritation	1 (3%)	0 (0%)

Source: Reviewer's table created in JReview
[1] Dry skin includes dry skin and asteatosis

In a 104-week, open-label safety study, the most common ARs associated with Hyftor application were application site irritation (31%), dry skin (28%), acne (20%), pruritus and eye irritation (9%), erythema (7%), acneiform dermatitis (6%), contact dermatitis (5%), solar dermatitis ((b) (4)%), and photosensitivity reaction (1%). ARs occurred with similar frequency in adult and (b) (4)

Laboratory Findings

Labeling for the LD, Rapamune, includes hyperlipidemia in Section 5 (Warnings and Precautions). This includes increases in serum cholesterol and triglycerides requiring treatment. The Applicant's periodic laboratory monitoring (described in more detail in Section 8.2.3 of this review) included serum lipid parameters. The review team evaluated the laboratory data submitted by the Applicant and found no clinically meaningful trends toward shifts from normal to abnormal in serum lipid parameters related to treatment with sirolimus gel, 0.2%. This was the case with both the Phase 3 and open-label LTS trials.

The review team also found no treatment-related, clinically meaningful trends toward shifts from normal to abnormal in other parameters including serum chemistry, hematology, and urinalysis.

Vital Signs

During the Phase 3 and open-label LTS trials, investigators assessed vital signs (blood pressure and pulse rate) at clinic visits according to the schedule described in Section 8.1. The Applicant reported no clinically significant changes in vital signs in either of these trials.

During the Phase 3 trial, there were two TEAE PTs related to vital signs. Reduced blood pressure was reported by 1/30 (3.3%) subject treated with sirolimus gel, 0.2% and no subjects in the vehicle group. Pyrexia was reported by one subject each in the sirolimus gel, 0.2% (1/30, 3.3%) and vehicle (1/32, 3.1%) groups.

During the open-label LTS trial, pyrexia was reported by 6/94 (6.4%) subjects. In addition, weight decrease and orthostatic hypotension were each reported by 1/94 (1.1%) subject.

Electrocardiograms/QT

The Applicant did not perform electrocardiograms (ECGs) during the development program, except for during the comparative BA trial (NPC-12G-4/US). During this trial, ECGs were performed at BL, before dosing, then 0, 0.5, 1, 2, 4, 12, and 24 hours postdose after administration of both sirolimus gel, 0.2% and Rapamune. One subject had a TEAE of supraventricular extrasystoles approximately 2 hours after receiving sirolimus gel, 0.2%; this AE was mild in severity and considered not related to treatment. Another subject had clinically significant first degree AV block at the predose ECG on Day 6; this AE was also mild in severity and considered not related to treatment. Per the Applicant, no subject had a corrected QT interval (QTcB and QTcF) greater than 490 msec.

There are no references to QT/QTc prolongation or cardiac arrhythmia in the labeling for LD Rapamune. The Applicant established a clinical bridge to the LD in a Phase 1 relative BA PK trial, in which exposure from the sirolimus gel was demonstrated to be lower than that of oral Rapamune. Therefore, a thorough QT study is not needed per ICH E14. This was confirmed with the Clinical Pharmacology team (email communication, 07/14/2020).

Immunogenicity

Because the proposed product is not a therapeutic protein, the Applicant did not assess the potential for immunogenicity.

8.2.5. Analysis of Submission-Specific Safety Issues

Sirolimus is an inhibitor of mTOR and is available in tablet and oral solution formulations (Rapamune). Rapamune labeling carries the Box Warning: Immunosuppression, use is not recommended in liver or lung transplant patients; increased susceptibility to infection and possible development of lymphoma and other malignancies.

In addition, Section 5 (Warnings and Precautions; 5.1 to 5.20) of labeling includes:

- Increased Susceptibility to Infection and the Possible Development of Lymphoma
- Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis
- Lung Transplantation – Bronchial Anastomotic Dehiscence
- Hypersensitivity Reactions
- Angioedema
- Fluid Accumulation and Impairment of Wound Healing
- Hyperlipidemia
- Decline in Renal Function
- Proteinuria
- Latent Viral Infections
- Interstitial Lung Disease/Non-Infectious Pneumonitis
- *De Novo* Use Without Cyclosporine
- Increased Risk of Calcineurin Inhibitor-Induced Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura/Thrombotic Microangiopathy
- Antimicrobial Prophylaxis
- Embryo-Fetal Toxicity
- Male Infertility
- Different Sirolimus Trough Concentration Reported between Chromatographic and Immunoassay Methodologies
- Skin Cancer Events (including the need for photoprotection)
- Immunizations
- Interaction with Strong Inhibitors and Inducers of CYP3A4 and/or p-gp

During the development program, sirolimus gel, 0.2% for the treatment of FA of TS was evaluated for local and systemic safety. The evaluation of local safety was discussed in Section 8.2.4. Systemic safety of sirolimus gel was evaluated by reporting AEs and systemic BA. Although systemic exposure of sirolimus gel is lower than exposure from oral administration of Rapamune, in the absence of a known exposure threshold for the known ARs described in Section 5 of labeling for Rapamune, known ARs of sirolimus from Rapamune will be included in labeling for sirolimus gel, 0.2%.

Hyperlipidemia was discussed in Section 8.2.4 of this review. Skin cancer events (and need for photoprotection) and hypersensitivity/angioedema will be discussed below. Embryo-fetal toxicity is discussed in detail in Sections 5.5.4 and 8.2.9 of this review. Interaction with Strong Inhibitors and Inducers of CYP3A4 and/or p-gp is discussed in Section 6.3.2 of this review.

Skin Cancer Events/Need for Photoprotection

Labeling for Rapamune states, “Patients on immunosuppressive therapy are at increased risk for skin cancer. Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a broad spectrum sunscreen with a high protection factor.” During the Phase 3 and open-label long-term extension trials, subjects were requested to use sunscreen and avoid direct sunlight.

There were no subjects with the reported AE of skin cancer in the Phase 3 trial and 1/94 (1.1%) in the open-label LTS trial (PT, neoplasm skin). The event of skin neoplasm (not further specified) occurred in an (b) (6) and was first noted on Day 359. Although the AE was not resolved, the subject continued treatment with study drug. Investigators considered this AE mild in severity and not related to treatment with study drug. No further information was provided regarding this AE.

There were no AEs related to photosensitivity reported in the Phase 3 trial. During the open-label LTS trial, the AE of solar dermatitis was reported for 3/94 (3.2%) patients and photosensitivity reaction was reported for 1/94 (1.1%) patient.

Although the systemic exposure after topical application of sirolimus gel, 0.2% is lower than that of sirolimus administered orally, the exposure threshold for the risk for malignancy has not been established. The Applicant did not conduct photosafety studies for sirolimus gel, 0.2% but proposed to include language regarding photoprotection in labeling for the LD. The review team agrees and recommends inclusion regarding photoprotection and risk of skin cancer in Section 5 (Warnings and Precautions) in labeling for sirolimus gel, 0.2%.

Hypersensitivity/Angioedema

Labeling for Rapamune states, "Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis, have been associated with the administration of Rapamune." No AEs related to hypersensitivity were reported during the Phase 3 trial. During the open-label LTS trial, AEs of urticaria were reported by 6/94 (6.4%) subjects, and cold urticaria by 1/94 (1.1%) subjects, respectively. Per the Applicant, investigators considered the urticaria to be related to treatment with study drug in only one subject. There were no reports of angioedema nor anaphylaxis in the Phase 3 or the open-label LTS trial.

Although we found no safety signal for serious hypersensitivity reactions or angioedema, the systemic exposure threshold for these events has not been characterized. Therefore, the review team recommends inclusion of hypersensitivity reactions in Section 5 (Warnings and Precautions) in the labeling for sirolimus gel, 0.2%.

The events in Section 5 of Rapamune labeling pertaining specifically to organ transplant patients will not be included in labeling for sirolimus gel, 0.2%. The review team recommends inclusion of the following in Section 5 (Warnings and Precautions) in the labeling for sirolimus gel, 0.2%:

- Hypersensitivity Reactions
- Infection
- (b) (4) Malignancy
- Hyperlipidemia
- Interstitial Lung Disease/Non-Infectious Pneumonitis
- Immunizations
- Embryo-Fetal Toxicity
- Male Infertility

- (b) (4)

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

No clinical outcome assessments informed the evaluation of safety or tolerability in the Phase 3 or open-label LTS trials. Clinical outcome assessments informing the evaluation of efficacy are discussed in Section 8.1.1 of this review.

8.2.6.1. Safety Analyses by Demographic Subgroups

The review team conducted additional analyses to evaluate the safety profile of sirolimus gel, 0.2% in demographic subgroups. The safety database consists of a single Phase 3 trial and an open-label LTS trial, each of limited size. Therefore, the data should be interpreted with caution. All subjects were Japanese, so a separate analysis of ARs by race was not conducted.

As discussed in Section 8.2.4, ARs occurred with similar frequency in adult and pediatric subjects in both the Phase 3 and open-label LTS trials. ARs by sex are presented in Table 31 and Table 32.

Table 31. AR by Sex, Phase 3 Trial

	Sirolimus Gel, 0.2% (N = 30)		Vehicle (N = 32)	
Preferred Term	**Female (N=13)**	**Male (N=17)**	**Female (N=21)**	**Male (N=11)**
Dry skin[1]	3 (23.1%)	9 (52.9%)	2 (9.5%)	2 (18.2%)
Application site irritation	6 (46.2%)	5 (29.4%)	7 (33.3%)	2 (18.2%)
Pruritus	2 (15.4%)	5 (29.4%)	2 (9.5%)	2 (18.2%)
Acne	2 (15.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acneiform dermatitis	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)
Ocular hyperemia	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)
Skin hemorrhage	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)
Skin irritation	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Reviewer's table created in JReview
[1] Dry skin includes dry skin and asteatosis
Denominator, subjects of the specified sex/treatment arm
Abbreviation: AR, adverse reaction

Table 32. AR by Sex, Open-Label Long-Term Safety Trial

	Sirolimus Gel, 0.2% (N=94)	
Preferred Term	**Female (N=53)**	**Male (N=41)**
Application site irritation	17 (32.1%)	12 (29.3%)
Dry skin	17 (32.1%)	18 (43.9%)
Acne	18 (34.0%)	15 (36.6%)
Pruritus	6 (11.3%)	5 (12.2%)
Eye irritation	6 (11.3%)	2 (4.9%)
Erythema	6 (11.3%)	5 (12.2%)
Acneiform dermatitis	8 (15.1%)	2 (4.9%)
Contact dermatitis	11 (20.8%)	4 (9.8%)
Solar dermatitis	1 (1.9%)	2 (4.9%)
Photosensitivity reaction	1 (1.9%)	0 (0.0%)

Source: Reviewer's table created in JReview
Denominator, subjects of the specified sex/treatment arm
Abbreviation: AR, adverse reaction

Although there was an imbalance between male and female subjects in the frequency with which some ARs occurred, the numbers of subjects of each sex per treatment arm was small. Therefore, these data should be interpreted with caution.

8.2.7. Specific Safety Studies/Clinical Trials

The Applicant submitted supportive safety data from a Phase 1/2 dose-finding trial as well as a comparative BA PK trial. Safety findings from these trials are summarized below.

Trial OSD-001-001

This was a Phase 1/2, randomized, double-blind, placebo-controlled, parallel-group PK and dose-finding trial in subjects 3 years of age and older with TS with ≥3 sites of solitary AF, each ≥2 mm. Subjects were randomized to treatment with sirolimus gel in concentrations of 0.05%, 0.1%, and 0.2%, or vehicle. The dose for each concentration was one "push" from a pump dispenser (approximately 125 mg) per lesion of 50 cm^2 applied to the affected area twice daily for 12 weeks. Adult subjects (age 19 years and older as defined by the Applicant) began treatment with sirolimus gel, 0.05%. Six adult subjects were enrolled per cohort; four were assigned to sirolimus gel and two to vehicle. The next highest concentration was evaluated in a stepwise manner after safety of the preceding concentration was established. Pediatric subjects (age less than 19 years) began evaluation after the safety of each concentration was demonstrated in adult subjects. Six pediatric subjects were enrolled per cohort; four were assigned to sirolimus gel and two to vehicle. A total of 36 subjects (18 adult and 18 pediatric) were enrolled. The formulation of sirolimus gel evaluated in this clinical trial was different than the to-be-marketed formulation. Therefore, the review team did not pool safety data from this trial with data from the Phase 3 and open-label LTS trials.

The evaluation of safety included: AE/SAE monitoring, physical examination, vital signs (temperature, heart rate, and blood pressure), clinical laboratory evaluation (hematology, serum chemistry, and urinalysis), and pregnancy testing.

Per the Applicant, there were no deaths or AEs leading to discontinuation during the trial. The Applicant reported two SAEs. A (b) (6) (Subject (b) (6)) with a history of epilepsy experienced seizures 1 day after completing treatment with vehicle. The AE resolved and the investigator considered the SAE not related to treatment. The other subject was a (b) (6) (Subject (b) (6)) with a history of pulmonary LAM and spontaneous pneumothoraxes, and had two events of pneumothorax during treatment with sirolimus gel, 0.2%. Both episodes of pneumothorax resolved after chest tube placement. (b) (6) continued treatment with sirolimus gel, 0.2% and completed the trial. The investigator considered the SAE not related to treatment with the study drug.

The AEs and AEs considered by investigators as treatment-related are summarized by treatment group in Table 33.

Table 33. Summary of AEs in Trial OSD-001-001

		Placebo Group n/N(%)*1	Test Drug Group n/N(%)*1		
			0.05% group	0.1% group	0.2% group
Patients with adverse events	Adults	4/6(66.7)	3/4(75.0)	4/4(100.0)	3/4(75.0)
	Children	3/6(50.0)	3/4(75.0)	3/4(75.0)	4/4(100.0)
	Combined*2	7/12(58.3)	6/8(75.0)	7/8(87.5)	7/8(87.5)
Patients with adverse events whose causal relationship with the investigational product cannot be ruled out (adverse drug reactions)	Adults	2/6(33.3)	2/4(50.0)	3/4(75.0)	3/4(75.0)
	Children	1/6(16.7)	1/4(25.0)	1/4(25.0)	4/4(100.0)
	Combined*2	3/12(25.0)	3/8(37.5)	4/8(50.0)	7/8(87.5)

*1, n, number of patients with events; N, number of patients analyzed
*2, Adult patients and pediatric patients combined.
Source: OSD-001-001 Clinical Study Report, Table 12.2-2, p.108
Abbreviation: AE, adverse event

The PTs reported by at least two adult subjects in any treatment group were nasopharyngitis (0.05% group, 2/4 subjects, 50.0%), dry skin (0.05% group, 2/4 subjects, 50.0%; 0.1% group, 3/4 subjects, 75.0%), and dermatitis acneiform (0.2% group, 2/4 subjects, 50.0%). In pediatric subjects, the PTs reported by at least two subjects in any treatment group were dry skin (0.2% group, 3/4 subjects, 75.0%).

Trial NPC-12-4/US

This was a Phase 1, open-label, fixed sequence, two-period PK trial which evaluated the comparative BA of a single dose of sirolimus gel, 0.2% given on Day 1 and Rapamune tablet, 2 mg on Day 6 in 12 healthy volunteer subjects. Refer to Section 15.5.1.1 for more details regarding the trial design and PK results. Safety results from this trial are discussed below.

The evaluation of safety included HIV/hepatitis serology and tuberculosis testing at Screening; AE/SAE monitoring, physical examination, vital signs (temperature, heart rate, blood pressure, and respiratory rate), ECGs, clinical laboratory evaluation (hematology, serum chemistry, urinalysis), and pregnancy testing. Investigators also assessed local tolerability 30 minutes after application of sirolimus gel, 0.2%.

Per the Applicant, no deaths or SAEs occurred during the trial. One subject was discontinued from the trial due to an AE. A (b) (6) experienced first-degree AV block prior to administration of Rapamune tablet, 2 mg on Day 6. This AE occurred 5 days after administration of 1.6 mg sirolimus topical gel, 0.2%. The subject was asymptomatic, and the severity of the AE was considered mild. The investigator considered the AE unrelated to treatment with the study drug. Other than this subject, there were no clinically significant changes in ECG parameters.

A total of seven TEAEs was reported by 3/12 (25%) subjects. All TEAEs were mild in severity. The most commonly reported TEAEs were from the SOC of Skin and Subcutaneous Tissue Disorders, consisting of two subjects who reported TEAEs of skin irritation. The Applicant reported that the evaluation of local tolerability revealed no skin reactions to sirolimus gel, 0.2%. However, the evaluation was conducted 30 minutes after administration, so sufficient time may not have elapsed for the development of skin reactions. There were no clinically significant changes in vital signs or clinical laboratory parameters.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct a clinical trial to specifically evaluate human carcinogenicity or tumor development. During the development program, the trial designs did not include specific assessments of carcinogenicity or safety signals related to malignancy. During the Phase 3 trial, AEs from the SOC of Neoplasms Benign, Malignant, and Unspecified were reported in two subjects treated with sirolimus gel, 0.2%. These included one subject with kidney angiomyolipoma and one with lymphangioma. Neither were considered by investigators to be related to treatment with sirolimus gel, 0.2%.

During the open-label LTS trial, AEs from the SOC of Neoplasms Benign, Malignant, and Unspecified were reported in two subjects treated with sirolimus gel, 0.2%. These included one subject with skin neoplasm (not further specified by the Applicant), three subjects with skin papilloma, and one with kidney angiomyolipoma. All of these occurred in the pediatric age group. None were considered by investigators to be related to treatment with sirolimus gel, 0.2%.

The Applicant submitted a 505(b)(2) application, using Rapamune tablets as the LD. The Applicant intends to rely on nonclinical information from the approved labeling for the LD, including carcinogenicity. The carcinogenicity information contained in the labeling for the LD will be conveyed in Section 13.1 (Nonclinical Toxicology) of the labeling for sirolimus gel, 0.2%. In addition, (b) (4) malignancy will be included as class labeling in Section 5 (Warnings and Precautions) for sirolimus gel, 0.2%. Refer to Section 5.5.3 of this review for further information regarding the nonclinical evaluation of carcinogenicity.

Human Reproduction and Pregnancy

During the Phase 3 and open-label long-term safety trials, the Applicant required females of reproductive potential to have a negative pregnancy test at Screening and to use effective forms of contraception. In addition, during the Phase 3 trial urine pregnancy tests were performed on all females of reproductive potential at Screening and Week 12. During the open-label long-term safety trial, investigators conducted pregnancy testing at Screening (only for subjects not previously enrolled in the Phase 3 trial), at BL, then every 3 months through Week 52, then every 6 months thereafter.

In the 120-day safety update (06/09/2020) the Applicant reported three pregnancies. Two were reported from the ongoing postmarketing safety survey and one from a clinical trial being conducted in subjects with neurofibromatosis type I (NF-1). The pregnancy outcomes for these subjects were as follows:

- A (b) (6) female enrolled in the postmarketing study treated with sirolimus gel for 78 days and discontinued treatment at 13 weeks gestation. Outcome: normal delivery of a healthy child.

- A (b) (6) female enrolled in the postmarketing study treated with sirolimus gel for 116 days and discontinued treatment at 4 weeks gestation. Outcome: ongoing (due date (b) (6)).
- A (b) (6) female enrolled in the NF-1 trial treated with sirolimus gel for 126 days and discontinued treatment at 8 weeks gestation. Outcome: spontaneous abortion at 17 weeks gestation. The spontaneous abortion was deemed to be due to cervical insufficiency and unrelated to sirolimus gel, 0.2%. The patient had a history of four prior pregnancies that resulted in no live births prior to treatment with sirolimus.

The Maternal Health Team of the Division of Pediatric and Maternal Health (DPMH) reviewed the proposed labeling for compliance with the Pregnancy and Lactation Labeling Rule and provided recommendations regarding the proposed language for applicable sections of the product labeling (review dated 07/14/2020).

Literature Search

In an animal reproduction study, oral administration of 0.5 mg/kg/day sirolimus caused embryofetal lethality in pregnant rats when administered during the period of organogenesis. The available PK data do not allow the calculation of relevant comparisons between the systemic exposure of sirolimus observed in animal studies to the systemic exposure that would be expected in humans after topical use of sirolimus gel, 0.2%. Although systemic exposure of sirolimus gel is lower than exposure from oral administration of Rapamune, the exposure threshold at which systemic ARs may occur is not known.

The Applicant did not perform a published literature search related to sirolimus use during pregnancy. Dr. Kristie Baisden, the reviewer from DPMH, performed a literature search for relevant articles related to sirolimus use during pregnancy. Dr. Baisden reported that no relevant publications were identified describing the use of topical sirolimus during pregnancy. However, the literature review identified publications describing the use of oral sirolimus during pregnancy. Dr. Baisden concluded that limited published reports of oral sirolimus use in pregnant women do not suggest an increased risk of adverse pregnancy outcomes, but are also insufficient to draw conclusions regarding the safety of sirolimus use during pregnancy. Per Section 8.1 of labeling for Rapamune, based on animal studies and mechanism of action, oral sirolimus can cause fetal harm when administered to a pregnant woman. In addition, limited available PK data for topical sirolimus prevents the calculation of relevant comparisons between the systemic exposure of sirolimus observed in animal studies to the systemic exposure that would be expected in humans after topical use of sirolimus gel, 0.2%. Because these data limitations preclude a clear determination of a safety margin with topical sirolimus administration, the Warning for Embryo-Fetal Toxicity from Section 5 of labeling for the LD will be included in labeling for sirolimus gel, 0.2%.

Literature searches were also conducted relating to sirolimus use during lactation. Dr. Baisden reported that no relevant publications were identified describing the use of topical sirolimus during lactation. However, the literature review identified publications describing the use of oral sirolimus during lactation. The DPMH review states that "there are no available data on the presence of sirolimus in human milk, the effects on the breastfed infant, or the effects on milk production. Sirolimus was present in the milk of lactating rats. When a drug is present in animal

milk, it is likely the drug will be present in human milk. However, the concentration of drug in animal milk does not necessarily predict the concentration of drug in human milk. Approved Pregnancy and Lactation Labeling Rule labeling for the LD, Rapamune, and other mTOR inhibitors in class (such as everolimus and temsirolimus) states that there is a potential for serious ARs in the breastfed infant. Given such, DPMH recommends including a statement that breastfeeding is not recommended during treatment in labeling for sirolimus gel, 0.2%."

Literature searches were also conducted relating to the effects of sirolimus on fertility. Dr. Baisden reported that no relevant publications were identified describing the effect of topical sirolimus on fertility. However, the literature review identified publications describing the potential effects of oral sirolimus on fertility. The DPMH review states that "there are no available data related to topical sirolimus administration and potential effects on male or female fertility. However, there are case reports and small retrospective studies in male transplant recipients that do suggest oral sirolimus administration may be associated with infertility. Further, fertility was decreased in both male and female rats following oral administration of sirolimus." As with pregnancy, the data limitations described above preclude a clear determination of a safety margin with topical administration of sirolimus. Therefore, the Warning for Male Infertility and information from Section 8.3 (Females and Males of Reproductive Potential) of labeling for the LD will be included in labeling for sirolimus gel, 0.2%.

Pediatrics and Assessment of Effects on Growth

Because sirolimus gel, 0.2% for the treatment of AF associated with TS has been granted Orphan Drug designation, the requirement under the Pediatric Research Equity Act (21 U.S.C. 355c) for assessment of the safety and effectiveness of the product for AF associated with TS in pediatric subjects does not apply. Nevertheless, the Phase 3 trial included six subjects 6 to 11 years of age and seven subjects 12 to 17 years of age who were treated with sirolimus gel, 0.2%. The long-term open-label safety trial included the following numbers of pediatric subjects treated with sirolimus gel, 0.2%: 4 subjects 3 to 5 years of age, 22 subjects 6 to 11 years of age and 22 subjects 12 to 17 years of age. The safety database submitted by the Applicant is sufficient to support approval of sirolimus gel, 0.2% for the treatment of FA associated with TS in adults and pediatric patients 6 years of age and older.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

Per the Applicant, based on the low systemic exposure to sirolimus after topical administration of sirolimus gel, 0.2%, the risk of overdose is low following topical use. The overdose potential of sirolimus gel, 0.2% has not been studied.

Drug Abuse Potential/Withdrawal and Rebound

The Applicant did not evaluate abuse potential of sirolimus gel, 0.2%. However, based on the mechanism of action and low systemic exposure of sirolimus gel, 0.2%, there is no reason to anticipate any potential for abuse or dependency. Therefore, Section 10 will be omitted from the product labeling.

Per the Applicant, no signs of withdrawal or rebound have been observed in non-clinical or clinical studies of sirolimus gel, 0.2%.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Sirolimus gel, 0.2% was approved in Japan in March 2018 for the treatment of "skin lesions including angiofibromas associated with tuberous sclerosis." In the 120-day safety update (06/09/2020) the Applicant submitted safety data from an ongoing postmarketing safety survey (Study RPG01S) in subjects with TS, and a clinical trial being conducted in subjects with NF-1 (Trial OSD-001-004). Safety data from the ongoing postmarketing safety survey are summarized below.

Deaths

The Applicant reported four deaths that occurred during the postmarketing study. Investigators considered none of these to be related to treatment with sirolimus gel, 0.2%. Brief narrative summaries for these patients are provided below.

- A (b) (6) with a history of seizure disorder experienced fatal status epilepticus. (b) (6) had been treated with sirolimus gel, 0.2% for 14 months prior to the event. However, after 2 months of treatment (b) (6) dose was reduced to once daily because of "improvement of the lesions and the adverse event of skin irritation." I concur with the investigator's assessment that the event was related to the underlying disease of TS rather than treatment with sirolimus gel, 0.2%.
- A (b) (6) with a history of carcinoma of the large intestine status post removal in (b) (6) experienced a recurrence on (b) (6) and died 1 month later. (b) (6) began treatment with sirolimus gel, 0.2% 1 day prior to the discovery of the recurrence of (b) (6) tumor. Because this was a recurrence of disease that predated treatment with sirolimus gel, and the limited exposure prior to diagnosis of the recurrent malignancy, I concur with the investigator's assessment that the event was not related to treatment with sirolimus gel, 0.2%.
- A (b) (6) with an extensive medical history remarkable for end-stage renal disease related to TS and hepatitis C died of acute hepatic failure in (b) (6) had begun treatment with sirolimus gel, 0.2% approximately 1 month prior to (b) (6) death. I concur with the investigator's assessment that the event resulted from complications of (b) (6) underlying medical problems and was not related to treatment with sirolimus gel, 0.2%.
- A (b) (6) with a history remarkable for renal impairment and epilepsy died of renal impairment and aspiration pneumonia in (b) (6) had begun treatment with sirolimus gel, 0.2% approximately 1 month prior to (b) (6) death. I concur with the investigator's assessment that the event resulted from complications of (b) (6) underlying medical problems and was not related to treatment with sirolimus gel, 0.2%.

Serious Adverse Events

The Applicant reported that 16/273 (5.9%) subjects experienced 19 SAEs in the postmarketing study at the time of the 120-day safety update. This includes the four subject deaths described

above. One SAE was considered related to treatment with sirolimus gel, 0.2%. A (b) (6) (Subject (b) (6)) experienced application site hemorrhage, which was resolving at the time of the 120-day safety update.

The Applicant reported the following SAEs which were considered not related to treatment with sirolimus gel, 0.2%. A (b) (6) female with a history of cervical incompetence experienced an intrauterine death (PT, abortion late) at 17 weeks. This is described in more detail in Section 8.2.9. Seven SAEs were related to epilepsy; PTs included epilepsy (four subjects), epilepsy aggravated (one subject), status epilepticus (one subject), and seizure (one subject). The remaining SAE PTs, each reported in one subject were pneumothorax, pneumonia, hyperinsulinemic hypoglycemia, hyperammonemia aggravated and hyponatremia (same subject), and neoplasm skin.

Adverse Reactions

The frequency of reported ARs in the 120-day safety update was similar to that observed during the Phase 3 and open-label LTS trials. The most commonly reported ARs were from the SOC of Skin and Subcutaneous Tissue Disorders (28/273, 10.3%); the most common PTs in this SOC were acne (10/273, 3.7%) and dermatitis acneiform (3/273, 1.1%). In addition, 16/273 (5.9%) subjects reported ARs from the SOC of General Disorders and Administration Site Conditions. The most commonly reported PT from this SOC was application site erythema (13/273, 4.8%).

Expectations on Safety in the Postmarket Setting

In the Clinical Overview submitted with the NDA, the Applicant provided information to support the applicability of foreign data to the U.S. population. This information was based on the genetics of TS; mutations in the *TSC1* and *TSC2* genes are not specific to a single race. Although the clinical trials and the postmarketing study were conducted in Japan, the safety profile of sirolimus gel, 0.2% in the United States is expected to be similar to that observed in Japan.

8.2.10. Integrated Assessment of Safety

The safety profile for sirolimus gel, 0.2% was adequately characterized during the development program. The primary safety database consisted of 62 subjects enrolled and randomized in Phase 3 Trial NPC-12G-1. Supportive safety data were provided by 94 subjects enrolled in the open-label LTS Trial NPC-12G-2. The safety data from this population were analyzed according to the treatment received by the subjects.

Based on a review of the safety data, no serious ARs were identified for inclusion in Section 4 (Contraindications) of the labeling for sirolimus gel, 0.2%. Section 4 will include only hypersensitivity to sirolimus or any other component of the gel. Although systemic exposure of sirolimus gel is lower than exposure from oral administration of Rapamune, in the absence of a known exposure threshold for the known AR described in Section 5 (Warnings and Precautions) of the labeling for Rapamune, known ARs of sirolimus from Rapamune will be included in Section 5 of the labeling for sirolimus gel, 0.2%. However, the events in Section 5 of the Rapamune labeling pertaining specifically to organ transplant patients (including the Box Warning) will not be included in the labeling for sirolimus gel, 0.2%.

Treatment with sirolimus gel, 0.2% was not associated with an increased risk of mortality or SAEs. No deaths occurred during the development program. However, a total of four deaths were reported to date in the postmarketing safety study in Japan; none were considered related to treatment with sirolimus gel, 0.2%. During the Phase 3 trial, two SAEs occurred in one subject (acute pancreatitis and gastric hemorrhage). Neither was related to treatment with sirolimus gel, 0.2%. No SAEs were reported in the vehicle group. During the open-label LTS trial, 14 SAEs were reported in nine subjects. The SAEs included pneumothorax, wisdom teeth removal, renal artery embolization, mycoplasma pneumonia, corpus callosotomy (three events in two subjects), streptococcal infection, incorrect route of drug administration, seizures, brain edema, and strabismus. Investigators considered none of these SAEs to be related to treatment with sirolimus gel, 0.2%, and no subjects discontinued treatment because of the SAEs.

The most common ARs were dry skin, application site irritation, pruritus, acne, acneiform dermatitis, ocular hyperemia, skin hemorrhage, and skin irritation. Dry skin was reported by 40% of subjects treated with sirolimus gel, 0.2% and 13% of subjects treated with vehicle, application site irritation was reported by 37% of subjects treated with sirolimus gel, 0.2% and 28% of subjects treated with vehicle, pruritus was reported by 17% of subjects treated with sirolimus gel, 0.2% and 13% of subjects treated with vehicle, acne was reported by 7% of subjects treated with sirolimus gel, 0.2% and no subjects treated with vehicle; acneiform dermatitis, ocular hyperemia, skin hemorrhage, and skin irritation were each reported by 3% of subjects treated with sirolimus gel, 0.2% and no subjects treated with vehicle. ARs were mild or moderate in severity. During the open-label LTS trial, the most common ARs were application site irritation (31%), dry skin (28%), acne (20%), pruritus (9%), eye irritation (9%), erythema (7%), acneiform dermatitis (6%), contact dermatitis (5%), solar dermatitis (3%), and photosensitivity reaction (1%). ARs occurred with similar frequency in adult and pediatric subjects in both of these trials.

8.3. Statistical Issues

Due to the several issues summarized in the review regarding the process of photograph editing and the procedure of the IRC assessments, the designated primary endpoint based on the IRC assessment is not considered appropriate for assessing efficacy for the indication of treatment of facial angiofibroma associated with TS. Therefore, an alternative endpoint, based on the Investigator live assessment, is considered by the review team to be more appropriate than the designated endpoint for assessing efficacy. Thus, the proposed labeling was altered to convey information regarding the proportion of subjects assessed as “Improved” or “Markedly Improved” by the Investigator based on the composite improvement, which was listed as a secondary endpoint in the protocol. Although such an endpoint was not adjusted for multiplicity and did not reach statistical significance, there is an efficacy trend in favor of sirolimus gel compared to the vehicle gel (see Table 12). Given the several issues raised in this review for the Phase 3 trial, one should exercise caution in making a definitive conclusion concerning the results.

Efficacy assessments in the Phase 1/2 Trial OSD-001-001 also showed a trend in favor of sirolimus gel; however, no definitive conclusions can be drawn from this trial because efficacy scales and endpoints (different than those in the pivotal Phase 3 trial) were not validated to be

clinically meaningful, and a different formulation of sirolimus gel was used. Furthermore, many of the concerns raised regarding the IRC could also apply to the Phase 1/2 trial.

8.4. Conclusions and Recommendations

To establish the efficacy and safety of sirolimus gel, 0.2% for the treatment of FA associated with TS, the Applicant submitted data from a multicenter, randomized, double-blind, vehicle-controlled Phase 3 trial. The trial was conducted in subjects 6 years of age and older. The study population included subjects who are diagnosed with TS, with three or more "papules of angiofibroma" (≥2 mm in diameter with redness in each) on the face, as well as subjects who are not suitable for therapy with laser or surgery (including liquid nitrogen therapy and phototherapy) for AF, or who are unwilling to receive such interventions.

Despite the several issues regarding the efficacy assessment summarized in the review, given the evidence for the proportion of subjects assessed as "Improved" or "Markedly Improved" by the Investigator based on the composite improvement, subjects with FA associated with TS appear to benefit from the treatment of sirolimus gel in improving the size and redness of AF in comparison to the vehicle gel.

TS is a serious and rare disease. FA associated with TS may cause hemorrhage, obstruction of facial orifices, and disfigurement, which may lead to emotional distress. Surgical intervention may be indicated for lesions causing impaired function, irritation, bleeding, pain, or disfigurement. However, the benefits of invasive treatments must be weighed against the risk of scarring and the need for general anesthesia, especially in medically complex patients such as those with TS. There are no drug products currently approved in the United States for the treatment of FA associated with TS. The available evidence of safety and efficacy supports the approval of NDA 213478, Hyftor (sirolimus) Topical Gel, 0.2% for the treatment of FA associated with TS in adults and pediatric patients 6 years of age and older.

9. Advisory Committee Meeting and Other External Consultations

The Agency conducted no Advisory Committee Meeting regarding this application.

10. Pediatrics

Because sirolimus gel, 0.2% for the treatment of AF associated with TS has been granted Orphan Drug designation, the requirement under the Pediatric Research Equity Act (21 U.S.C. 355c) for assessment of the safety and effectiveness of the product for AF associated with TS in pediatric subjects does not apply. In the Phase 3 and open-label LTS trials, the Applicant established safety and efficacy for the treatment of AF associated with TS in the pediatric population ages 6 to 17 years. Refer to Pediatrics and Assessment of Effects on Growth in Section 8.2.9 for a discussion regarding enrollment of pediatric subjects in the Phase 3 and long-term open-label safety trials.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed prescribing information (PI), a Medication Guide, and carton/container labels for sirolimus gel, 0.2%. The review team provided recommendations regarding PI, which are provided throughout this review. The review team also decided that a Medication Guide was not necessary, and that patient labeling in the form of a Patient Package Insert (PPI) would be sufficient. Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis reviewed the proposed PI, PPI, container labels, and carton label. Dr. Patel stated "we note the PI can be improved to provide clarity on the package configuration and to facilitate product identification. We also note the container label and carton label can be improved to prominence of important information (e.g., established name, medication guide statement, storage conditions), to prevent wrong dose errors, and to facilitate product identification." Dr. Patel made specific recommendations to address these concerns (refer to the review dated 05/21/2020). The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PI, PPI, and carton/container labeling and label. Refer to the OPDP review by Laurie Buonaccorsi, PharmD, dated 07/15/2020. These comments are reflected in the final labeling. Table 34 provides the location in this review of the discussion of each section of the product labeling.

Table 34. Locations of Discussion of Significant High-Level Labeling Changes

Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Section 1.1
2 DOSAGE AND ADMINISTRATION	Sections 1.1, 6.2.2
4 CONTRAINDICATIONS	Section 8.2.11
5 WARNINGS AND PRECAUTIONS	Section 8.2.4, 8.2.5, 8.2.9, 8.2.11
6 ADVERSE REACTIONS	Section 8.2.4
7 DRUG INTERACTIONS	Section 6.3.2
8 USE IN SPECIFIC POPULATIONS	Sections Error! Reference source not found..4, Error! Reference source not found..8, Error! Reference source not found., 13.1
12 CLINICAL PHARMACOLOGY	Section 6
14 CLINICAL STUDIES	Section 8.1
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling: Labeling Sections 2, 5, and 8

Source: Reviewer's table

11.2. Patient Labeling

The Division of Medical Policy Programs and OPDP reviewed and provided comments regarding the PPI for sirolimus gel, 0.2%. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Jessica Chung, PharmD, MS and Laurie Buonaccorsi, PharmD, dated 07/17/2020.

12. Risk Evaluation and Mitigation Strategies

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and standard postmarketing surveillance are not warranted at this time.

13. Postmarketing Requirements and Commitment

None.

14. Division Director (Clinical) Comments

New drug application (NDA) 213478 for Hyftor (sirolimus) Topical Gel, 0.2% was submitted by the Applicant in support of an indication for the treatment of facial angiofibromas (FA) in patients with tuberous sclerosis (TS). This application was filed under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The listed drug (LD) is Rapamune (sirolimus) Tablets (NDA 021110). The Applicant established a clinical bridge between sirolimus gel, 0.2% and Rapamune Tablets, and proposed to rely upon the Agency's findings of safety for nonclinical toxicology data (reproductive toxicity, carcinogenesis, mutagenesis, and impairment of fertility) for the LD.

TS is a serious and rare genetic multisystem disorder characterized by excess cell growth and proliferation resulting in development of benign tumors and other abnormal tissues in multiple organs. Some TS patients will develop FA, which can be severe and lead to obstruction of facial orifices, disfigurement, and/or hemorrhage. There are no drug products currently approved in the United States for the treatment of FA associated with TS. TS is caused by the inactivity of two tumor suppressor genes which code for hamartin and tuberin. Hamartin and tuberin help control cell proliferation and differentiation through inhibition of the mammalian target of rapamycin (mTOR). mTOR is a serine/threonine protein kinase that regulates cell growth and division.

Sirolimus is an mTOR inhibitor currently approved for prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants, and for the treatment of patients with lymphangioleiomyomatosis (LAM). Case reports and small case series also describe efficacy of sirolimus for treatment of subependymal giant cell astrocytomas (SEGA) and kidney angiomyolipoma; both are manifestations of TS. Everolimus, another mTOR inhibitor, is approved for treatment of SEGA, renal angiomyolipoma, and partial-onset seizures. SEGAs generally shrink in size during treatment with an mTOR inhibitor, but often recur following discontinuation of therapy. In everolimus clinical trials, improvement in skin manifestations of TS were noted. Similarly, off-label use of topical sirolimus has been reported to be effective treatment for FA associated with TS.

In support of this marketing application, the Applicant conducted a pharmacokinetics (PK) trial, one randomized, double-blind, placebo-controlled Phase 3 clinical trial, a long-term safety study, and a population PK analysis. In the Phase 3 clinical trial, 62 subjects aged 6 years or older with TS and at least three FA were randomized to receive blinded sirolimus gel, 0.2% or vehicle twice daily for twelve weeks. The protocol and statistical analysis plan specified the primary endpoint as composite improvement in FA at Week 12 as assessed by an Independent Review Committee (IRC) using photographs of trial subjects. The IRC consisted of three dermatologists who were independent from persons involved in the sponsorship or the conduct of the trial and had no direct conflict of interest with the Applicant. The IRC used a 6-point numeric rating scale which categorized the degree of improvement at Week 12 as compared to Baseline (BL) using ratings ranging from markedly improved to exacerbated. The primary endpoint was found to be statistically significant with a p-value of <.001. Over half of subjects were assessed as having improved or markedly improved FA.

Multiple issues with the assessment of the primary endpoint precluded it's use by the Agency to assess the efficacy of sirolimus gel, 0.2% to treat FA associated with TS. The following list highlights some of the key issues.

- Variability in the photographs of subjects: Instructions for taking photographs recommended using the camera's automatic mode for shutter speed, aperture, white balance and image sensitivity (ISO). No instruction was provided for selecting image background, distance of the camera to the subject, and subject positioning from different angles.
- Intentionally altered photographs: An imaging data center performed image correction, including scale, rotation, and color correction, using Adobe image-editing software "Photoshop".
- No validation testing: No validation testing is provided to adequately demonstrate that the camera's Auto Mode, the image correction, and the Casmatch system do not alter the color or size of skin lesions (which are the components of the primary efficacy endpoint).
- Photographs not reviewed in a blinded manner by IRC (e.g., "before" and "after" treatment)
- Inadequate scale: The Composite Improvement in Angiofibroma scale used to assess treatment effect is subjective relative to the baseline assessment and does not capture absolute severity. The categories of change in the scale have overlapping descriptors and are either double- or triple-barreled. No qualitative evidence was provided to support instrument development or use.

Therefore, the designated primary endpoint, based on the IRC assessment of photographs, is not considered acceptable for efficacy evaluation of sirolimus gel, 0.2% for the indication of treatment of FA associated with TS.

Due to the issues which precluded use of the primary efficacy endpoint, the Agency relied on a protocol-specified secondary efficacy endpoint, the composite improvement in FA assessed by the Investigator. The assessments by the Investigator were conducted separately from the IRC

assessments using the same scale. According to the protocol, these were in-person assessments using unaltered BL photographs as reference. The proportion of subjects assessed in person by the investigator as 'Improved' or 'Markedly Improved' at Week 12 was 23% for subjects treated with sirolimus gel, 0.2%, and 6% for subjects treated with vehicle. Although this result did not reach statistical significance and the Composite Improvement in Angiofibroma scale was used for assessment, the review team concluded that the result was clinically meaningful, and that some subjects with FA associated with TS appear to benefit from treatment.

The safety profile for sirolimus gel, 0.2% was adequately characterized during the development program. The most common adverse reactions (ARs) were dry skin, application site irritation, pruritus, acne, acneiform dermatitis, ocular hyperemia, skin hemorrhage, and skin irritation. ARs were mild or moderate in severity. The Applicant also submitted long-term safety data from a 104-week, open-label, long-term safety trial and a postmarketing study conducted in Japan.

Based on the PK data obtained across the submitted clinical trials, the Agency concluded that sirolimus gel, 0.2% produces low systemic exposure of sirolimus after topical application for the treatment of FA compared to oral sirolimus tablets. However, in the absence of a known exposure threshold for the ARs described in the Warnings/Precautions section of the Rapamune label, those ARs will be included in labeling for sirolimus gel, 0.2%, with the exception of labeling specifically pertaining to organ transplant patients. The following adverse reactions will be included in the Warnings/Precautions section of the sirolimus gel, 0.2% label; hypersensitivity reactions, infection, (b) (4) malignancy, hyperlipidemia, interstitial lung disease/non-infectious pneumonitis, immunizations, embryo-fetal toxicity, and male infertility.

About 40,000 to 80,000 people in the United States are estimated to have TS. By adolescence, about 80% of patients with TS will have FA. Sirolimus gel, 0.2% will provide a treatment option for FA with low systemic exposure, thereby minimizing risk to patients and offering potential therapeutic benefit. While the data provided by the Applicant did not meet the prespecified threshold for establishing efficacy, I considered the evidence that was provided, along with data supporting the use of mTOR inhibitors for other manifestations of TS, in my decision to support the review teams recommendation to approve sirolimus gel, 0.2%, for the treatment of FA associated with TS.

Although the review team generally supported approval of this application, the Office of Pharmaceutical Quality noted deficiencies in the CMC information provided by the Applicant regarding assurance of identity, strength, purity, and quality of the drug product. Additionally, facilities have not been cleared because of pending required preapproval inspections of the manufacturing facility, and travel restrictions imposed by the ongoing COVID-19 pandemic. A Complete Response is being recommended by the review team due to these deficiencies and I concur with their recommendation.

15. Appendices

15.1. References

Ebrahimi-Fakhari, D, S Meyer, T Vogt, C Pfohler, and CSL Muller, 2017, Dermatological manifestations of tuberous sclerosis complex (TSC), J Dtsch Dermatol Ges, 15(7):695-700.

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NORD, NOfRD, 2019, Tuberous Sclerosis, National Organization for Rare Disorders, accessed July 6, 2020, https://rarediseases.org/rare-diseases/tuberous-sclerosis/.

Randle, S, 2020, Tuberous sclerosis complex: Genetics, clinical features, and diagnosis, accessed August 3, 2020, https://www.uptodate.com/contents/tuberous-sclerosis-complex-genetics-clinical-features-and-diagnosis?search=tuberous-sclerosis-complex-genetics-clinical-features-and&source=search_result&selectedTitle=1~105&usage_type=default&display_rank=1.

15.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and subinvestigators who participated in covered clinical studies for sirolimus gel, 0.2%. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements, or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were Trials NPC-12G-1 and NPC-12G-2 which provided the primary data to establish effectiveness and safety of this product. Refer to Section 8.1.1 for the trial designs.

Covered Clinical Study (Name and/or Number): NPC-12G-1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 12		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable-N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NPC-12G-2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 12		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable-N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

Recommended Revisions to the Nonclinical Portions of Labeling

Revisions to the Applicant's proposed wording for the nonclinical and related sections of the label are provided below. Reviewer-proposed deletions are annotated as ~~double strikeout~~ text and reviewer-proposed additions are annotated as double-underlined text.

(b) (4) Pharmacology/Toxicology recommends deletion of the last sentence in Section 7 (Drug Interactions).

Only nonclinical edits are provided below for the Risk Summary subsection of Section 8.1 (Pregnancy) and for Section 8.2 (Lactation).

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Hyftor (b) (4) is a mTOR inhibitor immunosuppressant indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and (b) (4) pediatric patients 6 years of age and older. (1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

Animal reproduction studies have not been conducted with HYFTOR (b) (4) In an animal reproduction study, oral administration of 0.5 mg/kg/day sirolimus caused embryofetal lethality in pregnant rats when administered during the period of organogenesis *(see Data).* The available data do not allow the calculation of relevant comparisons between the systemic exposure of sirolimus observed in animal studies to the systemic exposure that would be expected in humans after topical use of HYFTOR (b) (4)

Data

Animal Data

(b) (4)

In embryofetal development studies in rats, oral administration of sirolimus to pregnant rats during the period of organogenesis (gestation days 6 -15) induced embryofetal lethality at 0.5 mg/kg/day, reduced fetal body weight at 1.0 mg/kg/day and caused maternal toxicity at 2.0 mg/kg/day. No treatment related embryofetal developmental effects were observed at 0.1 mg/kg/day. (b) (4)

In embryofetal development studies in rabbits, oral administration of sirolimus to pregnant rabbits during the period of organogenesis (gestation days 6 -18) induced maternal toxicity (decreased body weight) at 0.05 mg/kg/day, which was associated with embryofetal loss or early resorption. No treatment related developmental effects were observed at 0.025 mg/kg/day.

In a pre- and postnatal development toxicity study, oral administration of sirolimus to pregnant rats during gestation and lactation (gestation day 6 through lactation day 20) increased the incidence of dead pups, resulting in reduced live litter size at 0.5 mg/kg/day. No treatment related developmental effects were observed at 0.1 mg/kg/day.

Sirolimus did not cause maternal toxicity or affect developmental parameters in the surviving offspring (morphological development, motor activity, learning, or fertility assessment) at 0.5 mg/kg/day, the highest dose tested.

8.2 Lactation

Risk Summary

After oral administration, sirolimus was present in the milk of lactating rats.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of sirolimus in the treatment of angiofibroma associated with tuberous sclerosis (TS) is unknown. TS is associated with genetic defects in TSC1 and TSC2 which leads to the constitutive activation of mammalian target of rapamycin (mTOR). Sirolimus inhibits mTOR activation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4) Oral carcinogenicity studies were conducted in mice and rats. In an oral carcinogenicity study conducted in (b) (4) female mice, (b) (4) sirolimus administered once daily for 86 weeks was associated with (b) (4) a statistically significant increase in malignant lymphoma at all dose levels compared with control animals. In a second oral mouse carcinogenicity study, sirolimus-related (b) (4) hepatocellular adenoma and carcinoma were induced in male mices (b) (4) . In (b) (4) an oral carcinogenicity study conducted in (b) (4) rats (b) (4) with sirolimus (b) (4) there were no significant findings.

Sirolimus was not genotoxic in the in vitro bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the in vivo mouse micronucleus assay.

(b) (4) Fertility was (b) (4) decreased in both male and female rats following oral administration of sirolimus at 2.0 and 0.5 mg/kg, respectively. (b) (4) In male rats, atrophy of testes, epididymides, prostate, seminiferous tubules and/or reduced (b) (4) sperm counts were observed. In female rats, decreased ovarian and uterine weights and decreased implantation (b) (4) were (b) (4) observed. (b) (4) Testicular tubular degeneration was also seen in a 4-week intravenous study of sirolimus in monkeys at 0.1 mg/kg. (b) (4)

15.4. Biostatistics

15.4.1. Scales for Assessing Efficacy

Table 35. Cross Table for Assessing Composite Improvement in Angiofibromas–Trial NPC-12G-1

		← Exacerbating **Score of Improvement in Size** Improving→					
		-2	**-1**	**0**	**1**	**2**	**3**
Exacerbating↑	**-2**	Exacerbated	Exacerbated	Exacerbated	*	*	*
Improvement	**-1**	Exacerbated	Slightly exacerbated	Slightly exacerbated	Unchanged	*	*
	0	Exacerbated	Slightly exacerbated	Unchanged	Slightly improved	Slightly improved	Improved
	1	*	Unchanged	Slightly improved	Slightly improved	Improved	Improved
Redness Score	**2**	*	*	Slightly improved	Improved	Improved	Markedly Improved
Improving↓	**3**	*	*	Improved	Improved	Markedly Improved	Markedly Improved

* To be assessed by considering each improvement in the size and the intensity of the redness of angiofibroma.
Source: Applicant's Table 3-1 in "Instructions for Completing Assessments of Efficacy Outcomes in Accordance with the Protocol Specified Assessment Criteria."

Table 36. Criteria of Improvement in the Size of Angiofibroma–Trial NPC-12G-1

Score	Degree of improvement	Criteria
3	Markedly Improved	Shrinkage, flattening, or disappearance of tumors is observed overall.
2	Improved	Shrinkage or flattening of tumors is observed nearly overall. Or, disappearance of tumors is observed.
1	Slightly Improved	Shrinkage or flattening of tumors is partially observed.
0	Unchanged	There is no definite change in the size of tumors.
-1	Slightly Exacerbated	Enlargement or new formation of tumors is partially observed.
-2	Exacerbated	An enlargement or new formation of tumors is observed nearly overall, or a huge enlargement of tumors is partially observed. Or, more severe exacerbation is observed.

[Definition of terms]

Overall	: Not less than about 75% of the extent of the lesion at baseline
Nearly overall	: About 50% to 75% of the extent of the lesion at baseline
Partially	: About 25% to 50% of the extent of the lesion at baseline

Source: Applicant's Table 9-6 on page 45 of the study report

Table 37. Criteria of Improvement in the Color of Angiofibroma–Trial NPC-12G-1

Score	Degree of improvement	Criteria
3	Markedly Improved	A large decrease in intensity of redness is observed nearly overall. Or, a change in redness to the level equal to that of the normal region is observed nearly overall.
2	Improved	A decrease in intensity of redness is observed nearly overall. Or, a large decrease in intensity of redness is partially observed.
1	Slightly Improved	A slight decrease in intensity of redness is observed nearly overall. Or, a decrease in intensity of redness is partially observed.
0	Unchanged	There is no definite change in redness of tumors.
-1	Slightly Exacerbated	A slight increase in intensity of redness is observed nearly overall. Or, an increase in intensity of redness is partially observed.
-2	Exacerbated	A decrease in intensity of redness is observed nearly overall. A large increase in intensity of redness is partially observed. Or, more severe exacerbation is observed.

[Definition of terms]

Nearly overall	Not less than about 50% of the extent of the lesion at baseline
Partially	About 25% to 50% of the extent of the lesion at baseline
Large decrease in intensity of redness	Changes of 3 levels or more in redness in accordance with the Pantone® color sample
Decrease/increase in intensity of redness	Changes of 2 levels in redness in accordance with the Pantone® color sample
Slight decrease/increase in intensity of redness	Changes of 1 level in redness in accordance with the Pantone® color sample

Source: Applicant's Table 9-7 on page 48 of the study report

Table 38. Criteria of Improvement in Hypomelanotic Macule on the Head–Trial NPC-12G-1

Score	Degree of improvement	Criteria
3	Markedly Improved	A change in color tone to substantially the same level as the skin in a normal region (difficult to distinguish from a normal region). A decrease in size by about 75% or more.
2	Improved	A change in color tone toward the tone of the skin in a normal region (distinguishable from a normal region). A decrease in size by about 50% to 75%.
1	Slightly Improved	A slight change in color tone toward the tone of the skin in a normal region. A decrease in size by about 25% to 50%.
0	Unchanged	There is no definite change in color tone or size.
-1	Slightly Exacerbated	The difference in color tone from the skin in a normal region is slightly more distinct. An increase in size by about 25% to 50%.
-2	Exacerbated	The difference in color tone from the skin in a normal region is more distinct. An increase in size by about 50% or more.

Source: Applicant's Table 9-8 on page 48 of the study report

Table 39. Criteria of Improvement in Plaques on the Head–Trial NPC-12G-1

Score	Degree of improvement	Criteria
3	Markedly Improved	A shrinkage of eminence by about 75% or more.
2	Improved	A shrinkage of eminence by about 50% to 75%.
1	Slightly Improved	A shrinkage of eminence by about 25% to 50%.
0	Unchanged	There is no definite change in the degree of eminence.
-1	Slightly Exacerbated	An enlargement of eminence by about 25% to 50%.
-2	Exacerbated	An enlargement of eminence by about 50% or more.

Source: Applicant's Table 9-9 on page 49 of the study report

15.4.2. Appendix for Independent Review Committee Assessments and Inter-Rater Reliability

Table 40. Pairwise Cross-Tabulation of the Three IRC Raters for Composite Improvement in Angiofibroma at Week 12–Study NPC-12G-1 (FAS*)

			IRC Rater 2				
IRC Rater 1	**Markedly Improved**	**Improved**	**Slightly Improved**	**Unchanged**	**Slightly Exacerbated**	**Exacerbated**	**Total**
Markedly Improved	3 (5%)	5 (8%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	10 (16%)
Improved	1 (2%)	8 (13%)	2 (3%)	2 (3%)	0 (0%)	0 (0%)	13 (21%)
Slightly Improved	0 (0%)	2 (3%)	8 (13%)	3 (5%)	0 (0%)	0 (0%)	13 (21%)
Unchanged	0 (0%)	0 (0%)	3 (5%)	18 (29%)	3 (5%)	0 (0%)	24 (39%)
Slightly Exacerbated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Exacerbated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	4 (6%)	15 (24%)	15 (24%)	23 (37%)	3 (5%)	0 (0%)	60 (97%)**

Weighted C-A Kappa: $K_{C\text{-}A}$=0.63
Weighted F-C: $K_{F\text{-}C}$=0.76

			IRC Rater 3				
IRC Rater 1	**Markedly Improved**	**Improved**	**Slightly Improved**	**Unchanged**	**Slightly Exacerbated**	**Exacerbated**	**Total**
Markedly Improved	1 (2%)	3 (5%)	6 (10%)	0 (0%)	0 (0%)	0 (0%)	10 (16%)
Improved	0 (0%)	7 (11%)	3 (5%)	3 (5%)	0 (0%)	0 (0%)	13 (21%)
Slightly Improved	0 (0%)	1 (2%)	6 (10%)	8 (13%)	0 (0%)	0 (0%)	15 (24%)
Unchanged	0 (0%)	0 (0%)	3 (5%)	21 (34%)	0 (0%)	0 (0%)	24 (39%)
Slightly Exacerbated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Exacerbated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	1 (2%)	11 (18%)	18 (29%)	32 (52%)	0 (0%)	0 (0%)	62 (100%)

Weighted C-A Kappa: $K_{C\text{-}A}$=0.47
Weighted F-C: $K_{F\text{-}C}$=0.58

	IRC Rater 3						
IRC Rater 2	**Markedly Improved**	**Improved**	**Slightly Improved**	**Unchanged**	**Slightly Exacerbated**	**Exacerbated**	**Total**
Markedly Improved	0 (0%)	1 (2%)	3 (5%)	0 (0%)	0 (0%)	0 (0%)	4 (6%)
Improved	1 (2%)	8 (13%)	4 (6%)	2 (3%)	0 (0%)	0 (0%)	15 (24%)
Slightly Improved	0 (0%)	2 (3%)	7 (11%)	6 (10%)	0 (0%)	0 (0%)	15 (24%)
Unchanged	0 (0%)	0 (0%)	3 (5%)	20 (32%)	0 (0%)	0 (0%)	23 (37%)
Slightly Exacerbated	0 (0%)	0 (0%)	0 (0%)	3 (5%)	0 (0%)	0 (0%)	0 (0%)
Exacerbated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	1 (2%)	11 (18%)	17 (27%)	31 (50%)	0 (0%)	0 (0%)	60 (97%)**

Weighted C-A kappa: $K_{C\text{-}A}$=0.51
Weighted F-C: $K_{F\text{-}C}$=0.63

* FAS is defined as all enrolled subjects who received the investigational product and those for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
** One subject was assessed as “Not Evaluable” by Rater 2, “Slightly Improved” by Rater 1, and “Unchanged” by Rater 3; one subject was assessed as “Not Evaluable” by Rater 2 and as “Slightly Improved” by Rater 1 and Rater 3.
Source: Reviewer’s analysis
Abbreviations: FAS, full analysis set; IRC, independent review committee

Table 41. Summary of Pairwise Kappa Statistics of the Three IRC Raters by Timepoint for the Composite Improvement in Angiofibroma–Trial NPC-12G-1 (FAS*)

	Overall	Week 4	Week 8	Week 12
Rater 1 vs Rater 2	K_{C-A}=0.54 K_{F-C}=0.68	K_{C-A}=0.40 K_{F-C}=0.48	K_{C-A}=0.51 K_{F-C}=0.70	K_{C-A}=0.63 K_{F-C}=0.76
Rater 1 vs Rater 3	K_{C-A}=0.44 K_{F-C}=0.58	K_{C-A}=0.37 K_{F-C}=0.49	K_{C-A}=0.44 K_{F-C}=0.59	K_{C-A}=0.47 K_{F-C}=0.58
Rater 2 vs Rater 3	K_{C-A}=0.51 K_{F-C}=0.58	K_{C-A}=0.32 K_{F-C}=0.46	K_{C-A}=0.48 K_{F-C}=0.61	K_{C-A}=0.51 K_{F-C}=0.63

* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
Source: Reviewer's analysis
Abbreviations: FAS, full analysis set; IRC, independent review committee

15.4.3. Appendix for Agreement Between the IRC and the Investigator Assessments

Table 42. Cross-Tabulation of the IRC and Investigator Assessments for the Improvement in Size of Angiofibroma at Week 12–Study NPC-12G-1 (FAS*)

	Investigator Assessment						
IRC Assessment	**Markedly Improved**	**Improved**	**Slightly Improved**	**Unchanged**	**Slightly Exacerbated**	**Exacerbated**	**Total**
Markedly Improved	1 (2%)	0 (0%)	1 (2%)	3 (5%)	0 (0%)	0 (0%)	5 (8%)
Improved	2 (3%)	3 (5%)	3 (5%)	6 (10%)	0 (0%)	0 (0%)	14 (22%)
Slightly Improved	0 (0%)	2 (3%)	5 (8%)	5 (8%)	0 (0%)	0 (0%)	12 (19%)
Unchanged	0 (0%)	2 (3%)	5 (8%)	23 (37%)	0 (0%)	0 (0%)	30 (48%)
Slightly Exacerbated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Exacerbated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	3 (5%)	7 (11%)	14 (23%)	38 (61%)	0 (0%)	0 (0%)	61 (98%)**

Kendall's coefficient of concordance: W=0.66
Rank correlation coefficient (Kendall's tau): T=0.29
Simple K=0.24
Weighted C-A kappa: K_{C-A}=0.28
Weighted F-C kappa: K_{F-C}=0.31

* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
** One subject was assessed as "not evaluated" by the IRC and as "Unchanged" by the Investigator.
Source: Reviewer's analysis (same as Applicant's analysis except kappa statistics)
Abbreviations: FAS, full analysis set; IRC, independent review committee

Table 43. Cross-Tabulation of the IRC and Investigator Assessments for Improvement in Color of Angiofibroma at Week 12–Study NPC-12G-1 (FAS*)

	Investigator Assessment						
IRC Assessment	**Markedly Improved**	**Improved**	**Slightly Improved**	**Unchanged**	**Slightly Exacerbated**	**Exacerbated**	**Total**
Markedly Improved	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Improved	2 (3%)	1 (2%)	3 (5%)	4 (6%)	0 (0%)	0 (0%)	10 (16%)
Slightly Improved	0 (0%)	2 (3%)	4 (6%)	8 (13%)	1 (2%)	0 (0%)	15 (24%)
Unchanged	1 (2%)	0 (0%)	9 (15%)	23 (37%)	1 (2%)	0 (0%)	34 (55%)
Slightly Exacerbated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Exacerbated	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	4 (6%)	4 (6%)	16 (26%)	36 (58%)	2 (3%)	0 (0%)	61 (98%)**

Kendall's coefficient of concordance: W=0.67
Rank correlation coefficient (Kendall's tau): T=0.30
Simple K=0.13
Weighted C-A kappa: K_{C-A} =0.28
Weighted F-C kappa: K_{F-C}=0.43

* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
** One subject was assessed as "not evaluated" by the IRC and as "Unchanged" by the Investigator.
Source: Reviewer's analysis (same as Applicant's analysis except kappa statistics)
Abbreviations: FAS, full analysis set; IRC, independent review committee

Subgroup Analyses Appendix for Analyses by Age and Sex

Table 44. Improvement in Size of Angiofibroma at Week 12 by Age and Sex–Study NPC-12G-1 (FAS*)

N (%)	Markedly Improved	Improved	Slightly Improved	Unchanged	Slightly Exacerbated	Exacerbated
IRC Assessment						
By age						
Adults						
Sirolimus gel (N=17)	2 (12%)	5 (29%)	9 (53%)	1 (6%)	0 (0%)	0 (0%)
Vehicle gel** (N=20)	0 (0%)	0 (0%)	1 (5%)	18 (90%)	0 (0%)	0 (0%)
Children/adolescents						
Sirolimus gel (N=13)	3 (23%)	8 (61%)	1 (8%)	1 (8%)	0 (0%)	0 (0%)
Vehicle gel (N=12)	0 (0%)	1 (8%)	1 (8%)	10 (83%)	0 (0%)	0 (0%)
By sex						
Female						
Sirolimus gel (N=13)	1 (8%)	6 (46%)	5 (15%)	1 (3%)	0 (0%)	0 (0%)
Vehicle gel** (N=21)	0 (0%)	0 (0%)	2 (9%)	18 (86%)	0 (0%)	0 (0%)
Male						
Sirolimus gel (N=17)	4 (23%)	7 (41%)	5 (29%)	1 (6%)	0 (0%)	0 (0%)
Vehicle gel (N=11)	0 (0%)	1 (9%)	0 (0%)	10 (91%)	0 (0%)	0 (0%)
Investigator Assessment						
By age						
Adults						
Sirolimus gel (N=17)	2 (12%)	2 (12%)	7 (41%)	6 (35%)	0 (0%)	0 (0%)
Vehicle gel** (N=20)	0 (0%)	2 (10%)	3 (15%)	15 (75%)	0 (0%)	0 (0%)
Children/adolescents						
Sirolimus gel (N=13)	1 (8%)	3 (23%)	3 (23%)	6 (46%)	0 (0%)	0 (0%)
Vehicle gel (N=12)	0 (0%)	0 (0%)	1 (8%)	11 (92%)	0 (0%)	0 (0%)
By sex						
Female						
Sirolimus gel (N=13)	1 (3%)	3 (23%)	4 (31%)	5 (39%)	0 (0%)	0 (0%)
Vehicle gel** (N=21)	0 (0%)	2 (9%)	4 (19%)	15 (71%)	0 (0%)	0 (0%)
Male						
Sirolimus gel (N=17)	2 (12%)	2 (12%)	6 (35%)	7 (41%)	0 (0%)	0 (0%)
Vehicle gel (N=11)	0 (0%)	0 (0%)	0 (0%)	11 (100%)	0 (0%)	0 (0%)

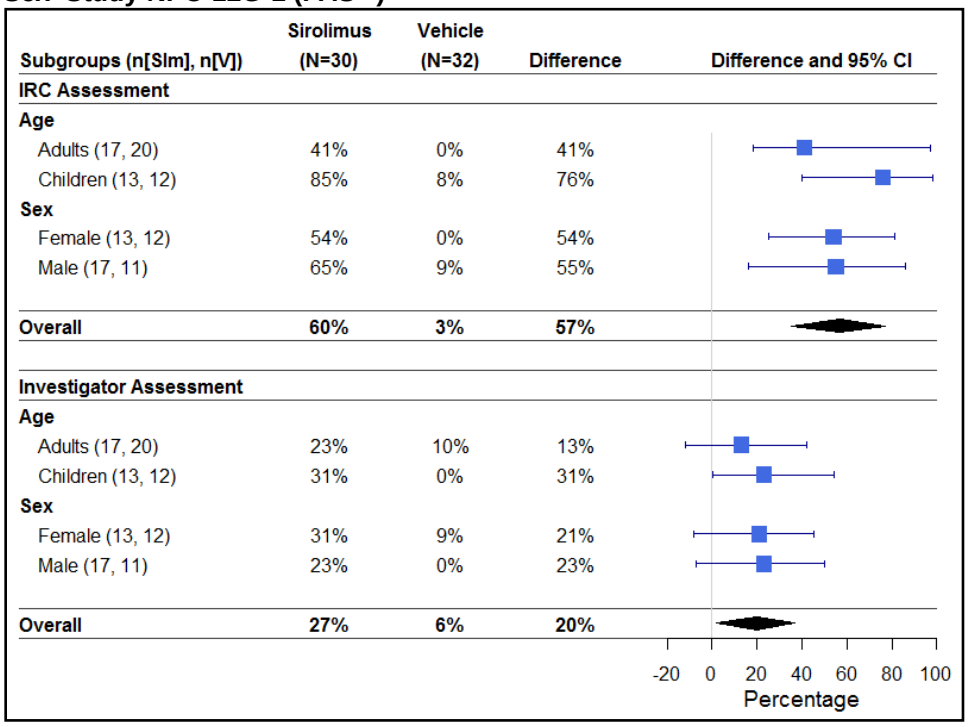
* FAS is defined as all enrolled subjects who received the investigational product and those for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
** One female adult was assessed as “not evaluable” by the IRC at Week 12
Source: Reviewer’s analysis (same as Applicant’s analysis)
Abbreviations: FAS, full analysis set; IRC, independent review committee

Table 45. Improvement in Color of Angiofibroma at Week 12 by Age and Sex–Study NPC-12G-1 (FAS*)

N (%)	Markedly Improved	Improved	Slightly Improved	Unchanged	Slightly Exacerbated	Exacerbated
IRC Assessment						
By age						
Adults						
Sirolimus gel (N=17)	1 (6%)	5 (29%)	7 (41%)	4 (23%)	0 (0%)	0 (0%)
Vehicle gel** (N=20)	0 (0%)	0 (0%)	1 (5%)	18 (90%)	0 (0%)	0 (0%)
Children/adolescents						
Sirolimus gel (N=13)	1 (8%)	5 (38%)	5 (38%)	2 (15%)	0 (0%)	0 (0%)
Vehicle gel (N=12)	0 (0%)	0 (0%)	2 (17%)	10 (83%)	0 (0%)	0 (0%)
By sex						
Female						
Sirolimus gel (N=13)	0 (0%)	4 (23%)	10 (59%)	0 (0%)	0 (0%)	0 (0%)
Vehicle gel** (N=21)	0 (0%)	0 (0%)	2 (10%)	17 (85%)	0 (0%)	0 (0%)
Male						
Sirolimus gel (N=17)	2 (15%)	9 (69%)	1 (8%)	1 (8%)	0 (0%)	0 (0%)
Vehicle gel (N=11)	0 (0%)	0 (0%)	3 (25%)	9 (75%)	0 (0%)	0 (0%)
Investigator Assessment						
By age						
Adults						
Sirolimus gel (N=17)	3 (18%)	1 (6%)	5 (13%)	6 (35%)	2 (5%)	0 (0%)
Vehicle gel** (N=20)	1 (5%)	0 (0%)	5 (25%)	14 (70%)	0 (0%)	0 (0%)
Children/adolescents						
Sirolimus gel (N=13)	0 (0%)	3 (23%)	3 (23%)	7 (54%)	0 (0%)	0 (0%)
Vehicle gel (N=12)	0 (0%)	0 (0%)	3 (25%)	9 (75%)	0 (0%)	0 (0%)
By sex						
Female						
Sirolimus gel (N=13)	2 (15%)	1 (8%)	4 (31%)	6 (46%)	0 (0%)	0 (0%)
Vehicle gel** (N=21)	1 (5%)	0 (0%)	5 (24%)	15 (71%)	0 (0%)	0 (0%)
Male						
Sirolimus gel (N=17)	1 (6%)	3 (18%)	4 (23%)	7 (41%)	2 (12%)	0 (0%)
Vehicle gel (N=11)	0 (0%)	0 (0%)	3 (27%)	8 (73%)	0 (0%)	0 (0%)

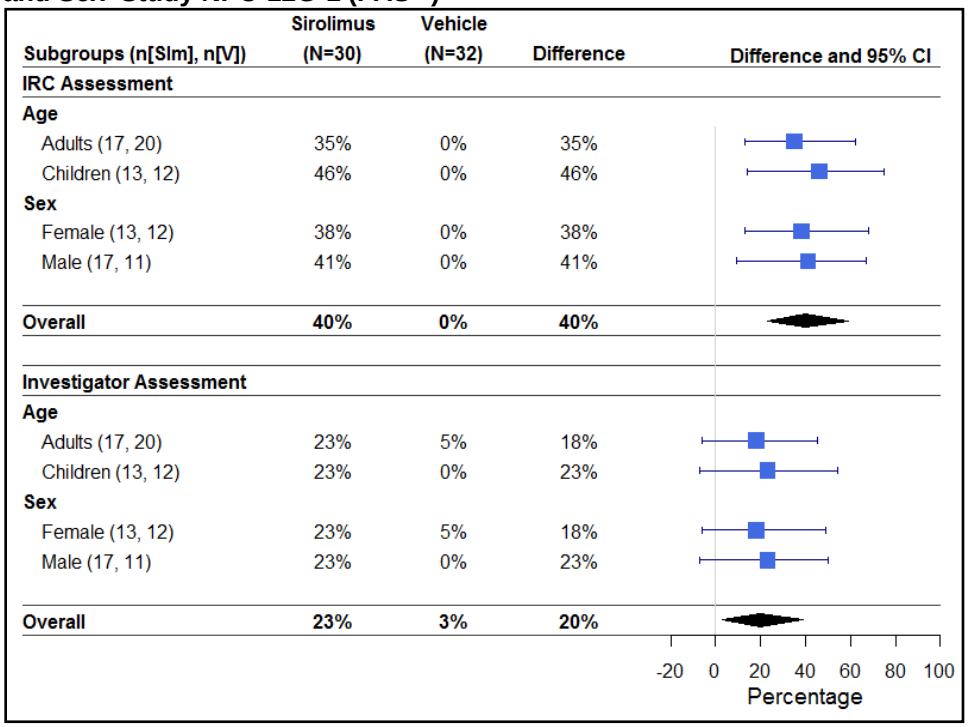
* FAS is defined as all enrolled subjects who received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
** One female adult was assessed as “not evaluable” by IRC at Week 12
Source: Reviewer’s analysis (same as Applicant’s analysis)
Abbreviations: FAS, full analysis set; IRC, independent review committee

Figure 12. Improvement Rate* for the Improvement in Size of Angiofibroma at Week 12 by Age and Sex–Study NPC-12G-1 (FAS)**



Source: Reviewer's analysis
* Improvement rate defined as the proportion of subjects assessed as "Improved" or "Markedly Improved"
** FAS is defined as all enrolled subjects who have received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
Abbreviations: CI, confidence interval; FAS, full analysis set; n[Slm], subgroup sample size for active arm, n[V], subgroup sample size for vehicle arm

Figure 13. Improvement Rate* for the Improvement in Color of Angiofibroma at Week 12 by Age and Sex–Study NPC-12G-1 (FAS)**



Source: Reviewer's analysis
* Improvement rate defined as the proportion of subjects assessed as "Improved" or "Markedly Improved"
** FAS is defined as all enrolled subjects who have received the investigational product and for whom information on efficacy was obtained after the start of administration; the FAS included all 62 enrolled subjects.
Abbreviations: CI, confidence interval; FAS, full analysis set; n[Slm], subgroup sample size for active arm, n[V], subgroup sample size for vehicle arm

15.5. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.5.1. Individual Study Summary

The Applicant submitted the current New Drug Application (NDA) pursuing the approval of NPC-12G, 0.2% (sirolimus) gel through a 505(b)(2) regulatory pathway using Rapamune® (sirolimus) tablets as a listed drug to support the treatment of subjects with angiofibroma (AF) associated with tuberous sclerosis (TS). The Clinical Pharmacology review focused on the bioavailability (BA) assessment of sirolimus gel using the NPC-12G 0.2% formulation (to-be-marketed formulation) in the following studies:

- NPC-12G-4/US (Phase 1 pharmacokinetics [PK] study)
- NPC-12G-1 (Phase 3 study)
- NPC-12G-2 (long-term safety study)
- Population pharmacokinetic (PPK) study (Report NOBE-PMX-NPC12G-1635)

15.5.1.1. Study NPC-12G-4/US

Title

Open-label, fixed-sequence, two-period comparative BA study of sirolimus from topical application of NPC-12G gel (0.2% sirolimus gel) to oral Rapamune® 2 mg tablet following single administration in healthy subjects

Methods

This was a Phase 1, single-center, open-label, fixed-sequence, two-period, PK study in healthy volunteers to compare systemic exposure following topical and oral dosing of sirolimus, and to evaluate the safety and tolerability following topical dosing (Table 46). This study was intended for filing under Food and Drug Administration (FDA) regulations. A total of 12 healthy adult male or female, nonsmokers was planned to be included in this study.

Prior to entering the trial, subjects had a screening visit to establish eligibility within 28 days before study drug administration. Subjects were confined from at least 10 hours before the first dosing in period 1 until after the last PK blood draw in period 2 (on the morning of Day 8). There was an in-house washout period of 5 days between doses. Participation of each subject in the study lasted approximately 8 days.

Table 46. Treatment Scheme

Treatment		
	Treatment A	**Treatment B**
Product	NPC-12G (Sirolimus)	Rapamune® (Sirolimus)
Strength	0.2% (2 mg of sirolimus in 1 g of gel)	2 mg
Dosage form	Gel	Tablet
Dose administered	1 x 800 mg quantity weight (equivalent to 1.6 mg of sirolimus)	1 x 2 mg
Route of administration	Topical	Oral

Duration of Treatment

Each subject was administered the following treatments:

- Treatment A (Test): NPC-12G Gel 0.2% (2 mg of sirolimus in 1 g of gel) for topical application (Nobelpharma Co., Ltd., Japan)
  - Dose: A single 800 mg quantity weight (1.6 mg sirolimus) dose was applied to the face on Day 1 (period 1).
- Treatment B: Rapamune® 2 mg Tablet (sirolimus) (Distributed by Wyeth (Reference) Pharmaceuticals LLC, a subsidiary of Pfizer Inc., USA)
  - Dose: 1×2 mg tablet was administered orally on Day 6 as a single dose (period 2).

PK Assessment

In each period, a total of 10 blood samples was drawn from each subject for PK analyses of sirolimus. Blood samples were collected prior to drug administration (predose) and 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 24.0, and 48.0 hours postdose (3 mL for each sampling time).

Results

In this Phase 1 single-dose PK study (NPC-12G-4/US) comparing 2 mg oral Rapamune® tablet and NPC-12G Gel, 0.2% (800 mg NPC-12G gel, 0.2% corresponds to 1.6 mg sirolimus applied to the face) in 12 healthy subjects, the PK profiles from oral sirolimus were as expected. In contrast, in subjects dosed with NPC-12G Gel, 0.2%, sirolimus blood concentrations in all but three samples were below the lower limit of quantification (100 pg/mL), with a maximum concentration of 116 pg/mL. Therefore, the PK parameters for subjects dosed with sirolimus gel, 0.2% could not be determined in the comparative BA study (Table 47).

The administration of sirolimus was safe and well tolerated in healthy subjects following a single dose of 2 mg administered either topically or orally with water under fasting conditions.

Table 47. Summary of PK Parameters for Sirolimus

	NPC-12G					Sirolimus Tablet				
Parameter (unit)	N	Mean	SD	CV%	Geometric Mean	N	Mean	SD	CV%	Geometric Mean
$AUC_{0\text{-}48}$ (h*pg/mL)	0	-	-	-	-	11	74550.99	11306.83	15.17	73775.38
$AUC_{0\text{-}inf}$ (h*pg/mL)	0	-	-	-	-	11	97795.05	17924.19	18.33	96335.05
Residual Area (%)	0	-	-	-	-	11	23.32	4.04	17.33	23.00
C_{max} (pg/mL)	0	-	-	-	-	11	5463.10	1401.44	25.65	5299.01
$T_{1/2\ el}$ (h)	0	-	-	-	-	11	23.27	2.85	12.26	23.11
K_{el} (/h)	0	-	-	-	-	11	0.0302	0.0037	12.11	0.0300

	NPC-12G				Sirolimus Tablet			
Parameter (unit)	N	Median	Min	Max	N	Median	Min	Max
T_{max} (h)	0	-	-	-	11	1.983	1.017	3.983

The PK parameters could not be calculated for NPC-12G due to an insufficient number of detectable whole blood concentrations
Source: Table 1, NPC-12G-4/US NPC-12G Gel 0.2% Sirolimus PK Bridging Study Report
Abbreviations: -, not calculated; AUC, area under the concentration-time curve; CV, coefficient of variation; C_{max}, maximum concentration; K_{el}, elimination rate constant; max, maximum; min, minimum; N, number of observations; PK, pharmacokinetics; $t_{1/2}$, half life; T_{max}, time to C_{max}

Reviewer's comments:

Topical application of 800 mg sirolimus gel, 0.2% (1.6 mg sirolimus) resulted in blood levels that were too low to fully assess the PK properties. It should be noted that this was a single dose study conducted in healthy subjects, and hence not under maximal use conditions.

Per a pre-NDA communication in the Document Archiving, Reporting and Regulatory Tracking System dated 06/04/2019, the following FDA recommendations were conveyed to the Applicant:

"In this particular case, we believe it is not necessary to conduct a relative bioavailability study comparing your proposed topical product with the listed drug. You intend to rely solely on the listed drug to support the safety of your 505(b)(2) product, and the systemic exposure of your topical product is expected to be significantly lower than the systemic exposure of the listed drug. Based on the total estimated topical dose and the bioavailability of the oral dose, the exposure of your proposed product cannot exceed the exposure of the listed drug. We recommend you conduct a maximal-use pharmacokinetic (PK) study with the final to-be-

marketed formulation in adults, as well as, pediatric subjects where you assess the full PK profile of your product at steady state. We recommend you record the amount of formulation used by each subject."

Although a dedicated maximal-use PK study was not conducted, a clinical bridge with Rapamune tables is considered established based on the fact that the highest topical dose was lower than the highest oral bioavailable dose. Hence, even if there was 100% absorption following topical administration, the systemic exposure would not be higher than that produced following the highest labeled oral daily dose of 40 mg (see Section 6.2).

15.5.1.2. Study NPC-12G-1 (Pivotal Phase 3 Trial)

Title

A Phase 3 study of NPC-12G gel in patients with skin lesions associated with tuberous sclerosis

Methods

Either NPC-12G gel or placebo gel was evenly applied to skin lesions on the face or head twice daily (in the morning and at bedtime) for 12 weeks. The study medication was to be applied to the lesions of AF first, followed by application to both hypomelanotic macules and plaques on the head (above the neck). The maximum daily dose and number of tubes to be dispensed for the interval until next visit (about 1 month) were established by age group, as indicated in Table 48, which was based on the assumption that the dose is 125 mg (approximately 0.5 to 1 cm as the length of gel extruded from the tube) per affected skin area of 50 cm^2.

Table 48. Maximum Daily Dosage

Age group	Maximum daily dose (mg)	Maximum number of tubes to be dispensed for the interval until next visit (number of 10-mg tubes)
5 years or younger	400 (corresponds to approximately 2 to 3 cm)	2
6 to 11 years	600 (corresponds to approximately 3 to 4 cm)	3
12 years or older	800 (corresponds to approximately 4 to 5 cm)	4

PK Assessment

In this Phase 3 study, blood samples were collected at baseline, Week 4 and Week 12 visits, at various times postdose, and the time of dose application and blood collection recorded.

Results

The efficacy of sirolimus gel, 0.2% in patients with AF associated with TS, was demonstrated in the pivotal Phase 3 study (NPC-12G-1), with supporting evidence in the long-term safety (LTS) study (NPC-12G-2). Demographic and baseline characteristics of the patients from active treatment and placebo arms of study NPC-12G-1 are shown in Table 49. The maximum daily

dose of the gel applied was 400 mg (0.8 mg sirolimus) for pediatrics aged 5 years and younger, 600 mg (1.2 mg sirolimus) for pediatrics aged 6 to 11 years, and 800 mg (1.6 mg sirolimus) for pediatrics aged 12 years and older and for adults. The mean blood sirolimus concentrations are summarized in Table 50.

Table 49. Demographics of the Patients in Study NPC-12G-1

Item	Category	NPC-12G group (n=30)	Placebo group (n=32)	P-value [a]
Sex	Men	17(56.7%)	11(34.4%)	P=0.125
	Women	13(43.3%)	21(65.6%)	
Age (year)	3 to 5 years	0(0.0%)	0(0.0%)	P=1.000
	6 to 11 years	6(20.0%)	6(18.8%)	
	12 to 18 years	7(23.3%)	8(25.0%)	
	19 years or older	17(56.7%)	18(56.3%)	
	Child (18 years ≤)	13(43.3%)	14(43.8%)	P=1.000
	Adult (19 years ≥)	17(56.7%)	18(56.3%)	
	Mean (SD)	21.6(11.15)	23.3(12.61)	P=0.574
	Median (Min, Max)	20.5(7,48)	20.0(6,53)	
Body height (cm)	Mean (SD)	156.83(14.652)	156.21(14.002)	P=0.865
	Median (Min, Max)	160.50 (120.8,175.8)	158.55 (111.9,174.0)	
Body weight (kg)	Mean (SD)	49.34(14.646)	53.67(17.394)	P=0.294
	Median (Min, Max)	52.15(20.6,79.7)	53.30(22.0,88.8)	
Presence or absence of genetic diagnosis	Presence	0(0.0%)	1(3.1%)	P=1.000
	Absence	30(100.0%)	31(96.9%)	
Presence or absence of TSC1 mutation	Presence	NA	0(0.0%)	-
	Absence	NA	1(100.0%)	
Presence or absence of TSC2 mutation	Presence	NA	0(0.0%)	-
	Absence	NA	1(100.0%)	
Complication (intellectual disability) [b]	Presence	14(46.7%)	12(37.5%)	P=0.607
	Absence	16(53.3%)	20(62.5%)	
Complication (epilepsy) [c]	Presence	21(70.0%)	16(50.0%)	P=0.128
	Absence	9(30.0%)	16(50.0%)	
Presence or absence of prior medication (mTOR inhibitor)	Presence	7(23.3%)	11(34.4%)	P=0.408
	Absence	23(76.7%)	21(65.6%)	
Presence or absence of prior medication (external preparation of tacrolimus)	Presence	0(0.0%)	0(0.0%)	-
	Absence	30(100.0%)	32(100.0%)	

Source: Table 11-2, NPC-12G-1 Clinical Study Report
Abbreviation: mTOR, mammalian target of rapamycin

Table 50. Sirolimus Blood Concentrations in Study NPC-12G-1

Study Time	N	Number of Patients with Quantifiable Sirolimus Concentrations (%)	Sirolimus Mean ± SD (ng/mL)	Maximum Sirolimus (ng/mL)
Baseline	30	0	ND	ND
Week 4 (all patients)	30	27 (90%)	0.22±0.08	0.39
Week 4 pediatric patients	13	12 (92%)	0.19±0.07	0.29
Week 4 adults	17	15 (88%)	0.24±0.08	0.39
Week 12 all patients	30	21 (70%)	0.24±0.11	0.50
Week 12 pediatric patients	13	10 (77%)	0.21±0.09	0.41
Week 12 adults	17	11 (65%)	0.27±0.12	0.50

ND, below the lower limit of quantification (0.1 ng/mL). The mean ± SD was calculated in patients with quantifiable sirolimus concentrations.
Source: Table 6, 2.7.2 Summary of Clinical Pharmacology Studies
Abbreviation: ND, not detected

Reviewer's comments:

Blood sirolimus concentrations were quantifiable in 90% of patients at week 4 and in 70% of patients at week 12. Mean sirolimus concentrations at any time, ranged from 0.22 to 0.24 ng/mL, with a maximum concentration of 0.50 ng/mL. There were no apparent differences in the concentration of sirolimus between Week 4 and Week 12, or between adult and pediatric patients based on the limited data available; however, concrete conclusions could not be made due to lack of PK data from a dedicated maximal use study.

15.5.1.3. Study NPC-12G-2 (Long-Term Safety Trial)

Title

A long-term study of NPC-12G gel in patients with skin lesions associated with tuberous sclerosis

Methods

NPC-12G gel 0.2% was evenly applied to AFs on the face and hypomelanotic macules and plaques on the head (above the neck) twice daily (in the morning and at bedtime) for 52 weeks. The dose administered was 125 mg (approximately 0.5 to 1 cm as the length of gel extruded from the tube, or approximately 0.3 cm for investigational products with a manufacturing number of NP12G1741 or later) per affected skin area of 50 cm^2, as a rough standard, and should not exceed the predefined maximum daily dose for each age category as in Table 51.

If an adverse event occurred, and a dosage modification was deemed necessary by the principal investigator or subinvestigator (hereinafter referred to collectively as "investigator"), then the dosage might be decreased to once daily (at bedtime).

Dosage modifications, including a case of dose escalation after the previous reduction, were allowed as appropriate at the discretion of the investigator, only when the reason for the modification was specified. For safety reasons, the maximum daily dose and maximum number of tubes to be dispensed as 1-month supply were established for each age category (Table 51).

Table 51. Maximum Daily Dosage

Age category	Maximum daily dose* (mg)	Maximum number of tubes to be dispensed as 1 month supply (number of 10-mg tubes)
5 years or younger	400 (1) Corresponding approximately to 2 to 3 cm (2) Corresponding approximately to 1 cm	2
6 to 11 years	600 (1) Corresponding approximately to 3 to 4 cm (2) Corresponding approximately to 1.5 to 2 cm	2
12 years or older	800 (1) Corresponding approximately to 4 to 5 cm (2) Corresponding approximately to 2.5 cm	3

* (1) Investigational product with a manufacturing number of NP12G1591, NP12G1631, NP12G16X1, orNP12G16Y1.
(2) Investigational product with a manufacturing number of NP12G1741 or NP12G17X1

PK Assessment

In this LTS study, blood samples were collected at baseline (first visit), and at Weeks 12, 26, 39, and 52 at each visit at various times after dose application, and the times of dose application and blood draw recorded.

Results

The results from the LTS study (NPC-12G-2) supported the efficacy of sirolimus gel, 0.2% in patients with AF associated with TS. In this study, study drug was administered topically BID for 52 weeks to 94 adult and pediatric patients. The maximum daily amount of the gel administered was 400 mg (0.8 mg sirolimus) for pediatrics aged 5 years and younger, 600 mg (1.2 mg sirolimus) for pediatrics aged 6 to 11 years, and 800 mg (1.6 mg sirolimus) for adults and for pediatrics aged 12 years and older. The mean blood sirolimus concentrations are summarized in Table 52. The mean blood sirolimus concentrations at 12, 26, 39, and 52 weeks after the start of administration were similar in adults and pediatrics, 0.239 to 0.431 ng/mL in adults, and 0.253 to 0.280 ng/mL in pediatrics (Table 52). The maximum concentration of sirolimus measured at any time, across the two populations ranged from 0.68 to 3.27 ng/mL. The percentage of patients with sirolimus concentrations above the lower limit of quantification ranged from 43.6% to 78.0% in the adult population and 59.2% to 77.1% in the pediatric population.

Table 52. Sirolimus Blood Concentrations in Study NPC-12G-2

Population	Blood Collection Time	N	Number of Patients with Quantifiable Sirolimus Concentrations (% of Patients)	Mean [Sirolimus] ± SD (ng/mL)	Maximum [Sirolimus] (ng/mL)
All Patients	Baseline	94	9 (9.6%)[a]	0.576±0.3568	1.19
	Week 12	89	69 (77.5%)	0.343±0.4591	3.27
	Week 26	88	64 (72.7%)	0.278±0.2708	1.79
	Week 39	89	60 (67.4%)	0.263±0.2478	1.80
	Week 52	88	46 (52.3%)	0.267±0.1435	0.68
Adult Patients	Baseline	44	3 (6.8%)	0.569±0.3525	0.97
	Week 12	41	32 (78.0%)	0.431±0.6308	3.27
	Week 26	39	29 (74.4%)	0.276±0.2550	1.21
	Week 39	40	25 (62.5%)	0.239±0.1626	0.85
	Week 52	39	17 (43.6%)	0.291±0.1504	0.68
Pediatric Patients	Baseline	50	6 (12.0%)	0.580±0.3923	1.19
	Week 12	48	37 (77.1%)	0.266±0.2063	1.32
	Week 26	49	35 (71.4%)	0.280±0.2870	1.79
	Week 39	49	35 (71.4%)	0.280±0.3953	1.80
	Week 52	49	29 (59.2%)	0.253±0.1400	0.61

Reviewer's comments:

There was a total of four pediatric patients age 3 to 5 years being investigated in the LTS trial (NPC-12G-2) with some measurable low sirolimus concentrations, as summarized in Table 53.

Table 53. Measurable Low Sirolimus Concentrations in Study NPC-12G-2

ID	Age (yrs.)	BSA (m^2)	Dose (mg/day)	Sirolimus Concentration (ng/mL)				
				Baseline	WK12	WK26	WK39	WK52
(b) (6)		0.64	400	ND	ND	0.106	0.1389	ND
		0.62	400	ND	ND	ND	0.1155	ND
		0.74	400	ND	ND	ND	ND	ND
		0.70	400	ND	0.1177	ND	ND	ND

Source: Generated by this reviewer based on Table 14.2.17.3 in NPC-12G-2 Clinical Study Report
Abbreviations: BSA, body surface area; ID, identification; wk, week

The maximum sirolimus concentration of 3.27 ng/mL observed in this LTS trial was from an adult population and not from patients in the lowest age range (3 to 5 years).

15.5.2. Population Pharmacokinetic Analysis

An exploratory PPK analysis was conducted (Report NOBE-PMX-NPC12G-1635) using the PK data from the four clinical studies:

- OSD-001-001–PK samples at predose and 1 hour using 0.05%, 0.1%, and 0.2% sirolimus gel (OSD-001 gel) in adult and pediatric patients
- NPC-12G-1–PK samples using sirolimus gel, 0.2% (NPC-12G gel) in adult and pediatric patients
- NPC-12G-2–PK samples using sirolimus gel, 0.2% (NPC-12G gel) in adult and pediatric patients
- NPC-12G-4/US–PK samples at predose and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose using sirolimus gel, 0.2% (NPC-12G gel) in healthy adults

The demographic data of adult (N=114) and pediatric subjects (N=90) were used in the analysis. The adult mean body mass index (BMI) ranged from 21 to 26.6, mean weight ranged from 54.2 to 71.8 kg, and age ranged from 18 to 61 years. The pediatric mean BMI ranged from 17.1 to 17.8, mean weight ranged from 32.5 to 39.9 kg, and age ranged from 3 to 17 years. The observed mean NPC-12G gel concentration was 0.142 ng/mL, whereas the maximum observed concentration was 3.27 ng/mL.

The PPK model of NPC-12G gel was used in the conduct of model-based PK simulations to obtain AUC at steady state and NPC-12G gel covariate analysis to evaluate the impact of age, body weight, sex, and race. Either a first-order conditional estimation method of NONMEM with between subject variability and residual variability interaction (FOCE INTER) or stochastic estimation methods were used for PK model development. A one-compartment disposition model for sirolimus with linear absorption into the central compartment with below the limit of quantification samples being described by the M3 method was identified as an adequate PPK model to describe systemic exposure of sirolimus. The final PPK model had no identified covariates and was the same as the base PPK model. The final PPK estimates are presented in Table 54.

Table 54. Parameter Estimates for the Final Population Pharmacokinetic Model

Parameter (Unit)	Estimate	%RSE	IIV% (%RSE)
NONMEM Model estimates			
θ1: CL/F (L/h)	314.5	10.02	91 (9.6)
θ2: Vc/F (L)	171.6	28.8	-
θ3: k_a (1/h)	0.00139	28.5	-
Residual error			
Additive error (ng/L)	0.025	FIX	-
Proportional error (%)	52.6	12.7	-

Source: Table 8. 2.7.2 Summary of Clinical Pharmacology Studies
Abbreviations: CL/F, apparent clearance; IIV, interindividual variability; k_a, absorption rate constant; NONMEM, nonlinear mixed-effects modeling software; PPK, population pharmacokinetic; RSE, relative standard error; Vc/F, apparent central volume of distribution

Reviewer's comments:

The combined PPK data from four clinical studies showed that 56.2% of the PK samples are below the limit of quantification. Therefore, a one-compartment PPK model was developed using the M3 BQL handling method.

This PPK model is considered exploratory and the model results will not be discussed in detail in this review.

15.5.3. Bioanalytical Method and Validation

15.5.3.1. Determination of Sirolimus in Human Whole Blood Using Liquid Chromatography Tandem Mass Spectrometry (Study NPC-12G-1, Report: PRD15-309)

A bioanalytical method was developed (Table 55) and validated for measuring sirolimus blood concentrations to support the clinical development of sirolimus gel, 0.2% for study NPC-12G-1. The analytical samples, reference standard substances, calibration standards, and quality control (QC) samples were stored under suitable conditions. The reference standard, calibration standards, and QC samples were used within the period of established stability. The incurred sample reanalysis met the criteria of reproducibility. Analytical runs were performed with calibration standards prepared in surrogate matrix. QC samples were prepared in the sample matrix, and the QC results met the preset QC acceptance criteria.

Table 55. Summary of Bioanalytical Method (Study NPC-12G-1)

Clinical study title	NPC-12G Phase III Study for Skin Lesions with Tuberous Sclerosis[1)]
Protocol number	NPC-12G-1
Study design	Placebo control, multicenter collaboration, stratified randomization, double-blind group comparison study The result report was conducted after key opening.
Subject number	62 subjects
Matrix	Human blood
Anticoagulant	EDTA 2Na
Sampling point	Baseline (before application) 4 weeks after application 12 weeks after application Unscheduled 1
Received number	189 samples
Analyzed number	188 samples*
Storage condition after received	Frozen −20°C
Stability	9 months (295 days)[3)] after collection, 3 freeze-thaw cycles[3)] The assay was conducted within period and cycles for validated stability.
Residual analytical samples	Residual analytical samples after analyzed were refrozen. The residual analytical samples will be discarded under instruction of the sponsor.

Abbreviation: EDTA, ethylenediaminetetraacetic acid

15.5.3.2. Determination of Sirolimus in Human Whole Blood Using LC-MS/MS (Study NPC-12G-2, Report: PRD15-310)

A bioanalytical method was developed (Table 56) and validated for measuring sirolimus blood concentrations to support the clinical development of sirolimus gel, 0.2% for study NPC-12G-2. The analytical samples, reference standard substances, calibration standards, and QC samples were stored under suitable conditions. The reference standard, calibration standards, and QC samples were used within the period of established stability. The incurred sample reanalysis

met the criteria of reproducibility. Analytical runs were performed with calibration standards prepared in surrogate matrix. QC samples were prepared in the sample matrix, and the QC results satisfied the acceptance criteria.

Table 56. Summary of Bioanalytical Method (Study NPC-12G-2)

Title of Clinical Trial	A Long-term Study of NPC-12G Gel in Patients with Skin Lesions Associated with Tuberous Sclerosis Complex
Protocol number	NPC-12G-2
Study design	Open-label, multicenter study
Target sample size	≥80 patients
Matrix	Human blood
Anticoagulant	EDTA 2Na
Sampling points	Baseline (before application) 12 weeks after the start of application 26 weeks after the start of application 39 weeks after the start of application 52 weeks after the start of application At discontinuation
Planned number of samples	5 points × ≥80 patients = ≥400
Storage condition after received	Frozen at -20°C
Stability	9 months (295 days)[3)] after collection, 3 freeze-thaw cycles[2)] Samples will be analyzed within the time period and the number of cycles for which stability has been confirmed.
Planned number of analytical samples	≥400
Residual analytical samples	Residual analytical samples will be re-frozen after the completion of analysis. After the end of the study, the sponsor will be contacted regarding disposal.

15.5.2.3 Bioanalytical Method Validation for Determination of Sirolimus in Human Whole Blood (Study NPC-12G-1 and Study NPC-12G-2, Report: PRD14-414)
Abbreviation: EDTA, ethylenediaminetetraacetic acid

The objective of this study was to validate the liquid chromatography-tandem mass spectrometry bioanalytical method to quantify concentrations of sirolimus in human whole blood. The bioanalytical method validation for determination of sirolimus in human whole blood is summarized in Table 57.

Table 57. Bioanalytical Method Validation for Determination of Sirolimus in Human Whole Blood (Study NPC-12G-1 and Study NPC-12G-2)

Analyte	Sirolimus		
Blank matrix	Blank human whole blood		
Results	Selectivity		No interfering peak
	Linearity of Calibration Curve (0.1 to 100 ng/mL)		%RE: –9.7 to 7.6%
	Carryover		No interfering peak
	Lower Limit of Quantification (0.1 ng/mL)		%RE: 17.4% %CV: 4.4%
	Within-run Accuracy and Precision		%RE: –10.2 to –5.3% %CV: 1.7 to 5.0%
	Between-run Accuracy and Precision (3 Days)		%RE: –9.7 to –3.0% %CV: 3.1 to 6.5%
	Recovery	Sirolimus	0.2 ng/mL: 55.4% 80 ng/mL: 65.1%
		IS	75.3%
	Matrix Effect		0.2 ng/mL %CV: 3.7% 80 ng/mL %CV: 1.5%
	Post-preparative Stability (4°C, 24h)		0.2 ng/mL: 104.5% 80 ng/mL: 96.4%
	Post-preparative Stability (4°C, 48h)		0.2 ng/mL: 96.9% 80 ng/mL: 90.9%
	Stability of Standard Solutions (Room temperature, 24 h)		100 µg/mL: 100.1% 1 ng/mL: 98.1%
	Stability of Standard Solutions (4°C, 1 month)		100 µg/mL: 100.5% 1 ng/mL: 97.0%
	Stability of Standard Solutions (4°C, 3 months)		100 µg/mL: 102.4% 1 ng/mL: 100.4%

15.5.2.4 Determination of Sirolimus in Human Whole Blood Using LC-MS/MS and Bioanalytical Method Validation (Study NPC-12G-4/US)

A bioanalytical method was developed (Table 58) and validated for measuring sirolimus blood concentrations to support the clinical development of sirolimus gel, 0.2% for study NPC-12G-4/US. The calibration standards and QC samples were successfully tested prior to sample analysis. A total of 50 samples were selected for the incurred sample reproducibility test to demonstrate that results obtained from study sample analysis are reproducible. A total of 94% of the reanalyzed samples met the criteria of assay reproducibility. The performance of the analytical method was successfully demonstrated during the validation (Table 59).

Table 58. Summary of Bioanalytical Method (Study NPC-12G-4/US)

Method SOP Title:	Determination of Sirolimus in Human EDTA K_2 Whole Blood over a Concentration Range of 100 to 20000 pg/mL using High Performance Liquid Chromatographic Method with Tandem Mass Spectrometry Detection and using Automated Extraction
Analyte:	Sirolimus
Internal Standard:	Sirolimus-d_3
Calibration Range:	100 to 20000 pg/mL
Biological Matrix:	Human EDTA K_2 Whole Blood
Assay Volume Required:	0.150 mL
Sample Extraction:	Automated Liquid-Liquid Extraction
Type of Assay:	LC/MS/MS (API 5000)
Column:	Zorbax SB-CN, 50 x 4.6 mm, 3.5 µm
Column Temperature:	60°C
Mobile Phase A:	Milli-Q Type Water / Methanol with Ammonium Formate and Formic Acid
Mobile Phase B:	Methanol
Chromatographic Mode:	Gradient
Flow Rate:	1.000 mL/min
Chromatographic Integration / Acquisition Data System:	Analyst 1.6.3, AB Sciex
LIMS:	Watson version 7.4.1, Thermo Fisher Scientific Corporation
Quantitation Method:	Peak area ratio
Calibration Regression:	Linear
Weighting Factor:	$1/C^2$ [Peak area ratios (analyte/internal standard) versus the nominal concentration of the calibration standards]
Calibration equation:	$y = mx + b$
Coefficient of determination:	r^2

Abbreviations: EDTA, ethylenediaminetetraacetic acid; LC/MC/MS, liquid chromatography-tandem mass spectrometry; LIMS, laboratory information management system; SOP, standard operating procedure

Table 59. Bioanalytical Method Validation for Determination of Sirolimus in Human Whole Blood (Study NPC-12G-4)

Full Validation Report No.:	125035AFOT
Full Validation Report Title:	Validation of a High Performance Liquid Chromatographic Method using tandem Mass Spectrometry Detection and Automated Extraction for the Determination of Sirolimus (100 to 20000 pg/mL) in Human EDTA K_2 Whole Blood
Full Validation Report Effective Date:	29-OCT-2012
Validation Calibration Range:	100.00 to 20000.00 pg/mL (refer to the validation report in section 16.2.5.3 including the raw numerical data)
Between-Run Accuracy and Precision:	Biases: -5.34 to -2.17% CV: 3.66 to 5.83%
Within-Run Accuracy and Precision:	Biases: -9.02 to -3.68% CV: 1.51 to 4.12%
Freeze and Thaw Stability:	4 cycles at -20°C
Short-Term Stability of Analyte in Matrix:	23h11min at room temperature
Long-Term Stability of Analyte in Matrix:	90 days at -20°C
Post-Preparative Stability:	71h20min at 4°C and 48h01min at room temperature
Maximum Run Size:	192 samples

Abbreviations: CV, coefficient of variation; EDTA, ethylenediaminetetraacetic acid

15.6. Additional Clinical Outcome Assessment Analyses

N/A

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STROTHER D DIXON
08/12/2020 05:54:52 PM

HAMID R SHAFIEI
08/12/2020 06:18:25 PM

JILL C MERRILL
08/13/2020 07:35:30 AM

BARBARA A HILL
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DA ZHANG
08/13/2020 09:23:41 AM

CHINMAY SHUKLA
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MARILENA FLOURI
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MOHAMED A ALOSH
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LAURA L JOHNSON
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KEVIN L CLARK
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Signing also on behalf Dr. Patricia Brown

KENDALL A MARCUS
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