23 February 2023
EMA/CHMP/844737/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hyftor

International non-proprietary name: sirolimus

Procedure No. EMEA/H/C/005896/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADME	Absorption, distribution, metabolism, excretion
ADR	Adverse drug reaction
AE	Adverse event
AF	Angiofibroma
ANCOVA	Analysis of covariance
API	Active Pharmaceutical Ingredient
ASMF	Active substance master file
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
BA	Bioavailability
BID	Twice daily
BSA	Body surface area
CDLQI	Children's Dermatology Life Quality Index
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Clearance
Cmax	Maximum blood concentration
CMC	Chemistry, Manufacturing, Controls
CRL	Complete Response Letter
CSR	Clinical study report
CYP	Cytochrome P450
DLQI	Dermatology Life Quality Index
EOT	End of treatment
FAS	Full Analysis Set
FASI	Facial Angiofibroma Severity Index
FT-IR	Fourier transform infrared spectroscopy
GC	Gas chromatography
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
HV	Healthy volunteer
ICC	Intraclass correlation coefficient
ICH	International Council on Harmonisation
IEC	Independent Evaluation Committee
IFA	Index for Facial Angiofibroma
IR	Infrared
IRC	Independent Review Committee

LAM	Lymphangioleiomyomatosis
LC-MS/MS	Liquid chromatography - tandem mass spectrometry
LDL	Low density lipoprotein
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
LSM	Least squares mean
LTS	Long term study
MAA	Marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MPA	Medical Products Agency
MS/MS	Tandem mass spectrometry
mTOR	Mammalian target of rapamycin
ND	Not detected
NDA	New Drug Application
NE	Not evaluated
NF	National Formulary
NF1	Neurofibromatosis type 1
NMR	Nuclear magnetic resonance
NORD	National Organization for Rare Disorders, US
NR	Not reported
OECD	Organisation for Economic Co-operation and Development
PD	Pharmacodynamic
PE	Polyethylene
P-gp	P-glycoprotein
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PSUR	Periodic Safety Update Report
QC	Quality control
QOL	Quality of life
QTPP	Quality target product profile
RE	Relative error
RT	Room temperature
SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
t1/2	Half-life
tmax	Time to maximum concentration

TSC	Tuberous sclerosis complex
US	United States of America
USP	United States Pharmacopeia
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Plusultra pharma GmbH submitted on 26 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Hyftor, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 March 2021.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication

Treatment of angiofibroma associated with tuberous sclerosis complex in adults and children.

Hyftor, was designated as an orphan medicinal product EU/3/17/1910 on 23 August 2017, in the following condition: Treatment of tuberous sclerosis.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Tradename as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/hyftor

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and appropriate non-clinical and clinical data

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Rapamune, 0.5, 1, 2 mg coated tablet; 1 mg/ml oral solution
- Marketing authorisation holder: Pfizer Europe MA EEIG
- Date of authorisation: 13/03/2001
- Marketing authorisation granted by:
  - Union

  Union Marketing authorisation number:

  EU/1/01/171/001 – 1 mg/ml oral solution

  EU/1/01/171/007 – 1 mg coated tablet

EU/1/01/171/008 – 1 mg coated tablet

EU/1/01/171/009 – 2 mg coated tablet

EU/1/01/171/010 – 2 mg coated tablet

EU/1/01/171/013 – 0.5 mg coated tablet

EU/1/01/171/014 – 0.5 mg coated tablet

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Rapamune, 0.5, 1, 2 mg coated tablet; 1 mg/ml oral solution
- Marketing authorisation holder: Pfizer Europe MA EEIG
- Date of authorisation: 13/03/2001
- Marketing authorisation granted by:
  - Union

  Marketing authorisation number:

  EU/1/01/171/001 – 1 mg/ml oral solution

  EU/1/01/171/007 – 1 mg coated tablet

  EU/1/01/171/008 – 1 mg coated tablet

  EU/1/01/171/009 – 2 mg coated tablet

  EU/1/01/171/010 – 2 mg coated tablet

  EU/1/01/171/013 – 0.5 mg coated tablet

  EU/1/01/171/014 – 0.5 mg coated tablet

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

Not applicable

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
26 April 2018 COMP answer 26 July 2018	EMEA/H/SA/3799/1/2018/PA/III	*André Elferink and Brigitte Blöchl-Daum*

The protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Quality: manufacturing, validation, assays, specification setting, container closures systems
- Nonclinical: bridging strategy and nonclinical requirements
- Clinical: clinical development package, QT study, DDI studies, and demonstration of significant benefit

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Blanca Garcia-Ochoa

The application was received by the EMA on	26 November 2021
The procedure started on	24 December 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 March 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	14 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 March 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 September 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	17 October 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 October 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	10 November 2022

The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	24 January 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 February 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Hyftor on	23 February 2023

2. Scientific discussion

2.1. Introduction

Disease or condition

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder, caused by mutations in the TSC genes TSC1 and TSC2, which code for the proteins hamartin and tuberin, respectively (Rosset 2017). The mutations lead to constitutive activation of the mammalian target of rapamycin (mTOR) signalling pathway, resulting in abnormal proliferation, differentiation, and migration of cells (Fogel 2015). This causes the appearance of benign tumours, so-called hamartomas, in different tissues and organs which can, through their continued growth, damage the affected tissues/organs.

Epidemiology

Prevalence of TSC in Europe is estimated as 1 in 25,000 to 1 in 11,300 (National Organization for Rare Disorders, NORD 2019).

Clinical presentation, diagnosis and stage/prognosis

The onset of signs and symptoms of TSC is typically shortly after birth. The signs, symptoms, and severity of TSC vary greatly between patients, in part due to the question which organ systems are affected and how strongly, from patients being symptom-less to patients in whom hamartomas lead to organ obstruction and haemorrhage and affect organ function (NORD 2019). Nearly all patients with TSC develop skin abnormalities, including angiofibromas (AFs), hypomelanotic macules, shagreen patches, fibrous plaques, and ungula fibromas.

AF presents as small papules or red spots primarily on the face, often in a butterfly pattern, and may first appear in patients aged 3 to 5 years. Untreated, the lesions increase in size and number over time and through adolescence. In adulthood, the lesions tend to be stable or to grow more slowly. Facial AFs do not affect physiological functioning. However, case studies of patients with serious disfigurement and impaired physiological functions of breathing, eating, speaking, or vision, have been reported (Earnest 2003; Kacerovska 2012). Thus, although facial AFs are benign they may have a considerable psychological impact on patients, causing emotional distress and social isolation/marginalisation, as well as physiological impact in some patients (Knoepfel 2014).

In 2012, the International Tuberous Sclerosis Complex Consensus Conference developed revised diagnostic criteria for TSC, including 11 major and six minor features. The dermatological features outlined in these criteria include AF, fibrous cephalic plaques, hypopigmented macules, ungual fibromas, and shagreen patches (major) as well as Confetti skin lesions (minor). Hypopigmented macules are seen at birth, while facial AF, fibrous cephalic plaques, and shagreen patches are observed beginning in early childhood. Ungual fibromas manifest during adolescence or adulthood.

Management

The direct implication of the mTOR pathway in the TSC pathogenesis has prompted the use of mTOR inhibitors to palliate skin and systemic manifestations. However apart from mTOR inhibitor use, the existing treatment options are invasive and painful and include dermabrasion, laser therapy, excision of lesions, radiofrequency ablation, and electrocoagulation (Salido-Vallejo 2014b). These modalities can yield good results, especially with severe facial AFs, but they also carry the risk of complications from general anaesthesia, as well as hypertrophic scars, pigmentation disorders, and postoperative infections. AF tends to recur after treatment cessation (Schwartz 2007). Topical sirolimus was started to be used for the treatment of AF after early reports on improvements in AF as 'side-effect' of oral sirolimus treatment.

Given that no commercialised topical sirolimus preparations exist in Europe or North America, compounds of different concentrations have generally been developed by crushing and sifting commercially available sirolimus tablets (Rapamune), later also by using sirolimus in powder form.

About the product

This centralised application concerns a hybrid application according to article 10(3) of Directive 2001/83/EC Hyftor (gel containing 0.2 % sirolimus as active substance). The reference medicinal product is Rapamune (EU/1/01/171), which was first approved in the European Union on 13 March 2001.

Rapamune is authorised for the prevention of rejection reactions to transplanted kidneys as well as treatment of sporadic lymphangioleiomyomatosis. Both indications require systemic availability of the active substance sirolimus, either to inhibit T-cells and in consequence cause suppression of the immune system, or to inhibit the activated mTOR pathway and thus the proliferation of LAM cells.

In contrast, Hyftor is intended for the treatment of angiofibroma in patients with TSC. The product is locally administered and acts locally. Lower levels of systemic exposure with topical sirolimus are observed in comparison to oral formulations. For this reason, only data are referenced that are in context with systemic exposure. These are in particular some PK/PD effects (such as metabolism and excretion of sirolimus) and some safety considerations. All clinical and non-clinical data referring to use in AF/TSC and topical administration in general have been generated by the applicant.

The applicant's bridging approach i.e. the use of data from the reference medicinal product for the evaluation of pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and safety of sirolimus gel, 0.2% is summarised in Table 1 below:

Table 1: Reference data from Rapamune and specific data obtained with** Hyftor **in the clinical development program.

	Reference to data from Rapamune	**Specific data for HYFTOR**
PK	• Distribution, metabolism, elimination • PK in special populations (hepatic and renal impairment, Black patients, paediatric patients) • Drug-drug interactions	PK in the target population including dose linearity; PK in paediatric patients; relative bioavailability based on: • R, DB, PBO-controlled, 12-week Phase III study in AF (NPC-12G-1) • UC, single-arm long-term study in AF (NPC-12G-2)

		• R, DB, PBO-controlled, 12-week Phase I/II study in AF (OSD-001-001) • Phase I relative BA study in HV NPC-12G-4/US • R, DB, PBO-controlled, 52-week Phase II/III study in NF1 (OSD-001-004) • R, DB, PBO-controlled, 24-week Phase II study in NF1 (OSD-001-003)
PD	Rapamune is indicated for the prophylaxis of organ rejection in adult patients who received a renal transplant and for the treatment of patients with LAM. PD data related to the immunosuppressive mechanism of action of Rapamune are not considered relevant for the use of sirolimus gel, 0.2% in AF associated with TSC.	Not available
Efficacy	Not applicable	• R, DB, PBO-controlled, 12-week Phase III study in AF (NPC-12G-1) • UC, single-arm long-term study in AF (NPC-12G-2) • R, DB, PBO-controlled, 12-week Phase I/II study in AF (OSD-001-001)
Safety	The safety profile of Rapamune is referenced. Nevertheless, while sirolimus gel, 0.2% is principally thought to be associated with the same side effects as Rapamune, the potential for systemic side effects with sirolimus gel, 0.2% is considered to be much lower than for Rapamune because of the significantly lower systemic exposure.	• R, DB, PBO-controlled, 12-week Phase III study in AF (NPC-12G-1) • UC, single-arm long-term study in AF (NPC-12G-2) • R, DB, PBO-controlled, 12-week Phase I/II study in AF (OSD-001-001) • Phase I relative BA study in HV NPC-12G-4/US • R, DB, PBO-controlled, 52-week Phase II/III study in NF1 (OSD-001-004) • R, DB, PBO-controlled, 24-week Phase II study in NF1 (OSD-001-003)

Abbreviations: AF= angiofibroma; BA= bioavailability; DB= double-blind; HV= healthy volunteer; NF1= neurofibroma type 1; PBO= placebo; R= randomised; UC= uncontrolled

Mechanism of action

TSC is a result of the constitutive activation of mTORC1 caused by defects, or mutations, of the responsible genes TSC1 or TSC2.

Sirolimus is an mTOR inhibitor, although the exact mechanism of action of sirolimus in the treatment of angiofibroma in the tuberous sclerosis complex is not exactly known.

In general, sirolimus inhibits activation of mTOR which is a serine/threonine protein kinase that belongs to the phosphatidylinositol-3-kinase (PI3K)-related kinase family and regulates cellular metabolism, growth and proliferation. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. This complex binds to and inhibits the activation of mTOR.

Initially, the claimed indication was:

The treatment of angiofibroma associated with tuberous sclerosis complex in adults and children.

The final approved indication is:

The treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older

Posology:

This medicinal product should be applied to the affected area twice daily (in the morning and at bedtime). The application should be limited to skin areas with angiofibroma.

A dose of 125 mg gel (or 0.5 cm gel, corresponding to 0.25 mg sirolimus) should be administered per 50 cm^2 lesion in the face.

The maximum recommended daily dose in the face is:

- Patients aged 6-11 years should apply up to 600 mg gel (1.2 mg sirolimus), corresponding to approximately 2 cm gel strand per day.
- Patients aged ≥ 12 years should apply up to 800 mg gel (1.6 mg sirolimus), corresponding to approximately 2.5 cm gel strand per day.

The dose should be equally divided for two administrations.

Type of Application and aspects on development

GMP

No inspections of the drug substance manufacturing site, the drug product manufacturing site or the batch release site are considered necessary.

Satisfactory notification of GMP compliance and a compliance inspection report have been provided by a Japanese authority for the manufacturing site located in Japan, which is responsible for drug product manufacturing, quality control, primary packaging, storage and distribution to secondary packaging site. Accepted following the MRA with the EU.

Satisfactory MA and GMP compliance certificates have been provided for the manufacturing site located in the EU, which is responsible for secondary packaging and batch release.

GLP

The toxicology program followed ICH guideline M3(R2). All pivotal toxicity studies were conducted in compliance with GLP regulations, but the validation of the bioanalytical methods for these pivotal studies was apparently not conducted under GLP conditions. In addition to the nonclinical studies conducted by Nobelpharma, the Applicant relies on nonclinical data for the EU-approved medicinal product Rapamune and on information in the published literature to support a hybrid Marketing Authorization Application (MAA) according to Article 10(3) of Directive 2001/83/EC.

GCP

As stated by the applicant, clinical trials submitted as part of this application, carried out outside the European Union meet the ethical requirements of Directive EC/2001/20/EC and were performed in compliance with the ICH Guideline E6 (R2) for Good Clinical Practice. There are no indications that the conduct of these trials deviated from the principles of GCP

QA statement of audits assuring compliance to GCP/GLP was issued by Head-QA.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a gel containing 2 mg/g of sirolimus.

Other ingredients are: carbomer, anhydrous ethanol, trolamine, purified water.

The product is available in aluminium tube with high density polyethylene closure as described in section 6.5 of the SmPC. Each tube contains 10 g of gel.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of sirolimus (rapamycin) is (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-methyl ethyl)-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido(2,1-C)-(1,4)oxaazacyclo-hentriacontine-1,5,11,28,29-(4H,6H,31H)-pentone corresponding to the molecular formula $C_{51}H_{79}NO_{13}$. It has a relative molecular mass of 914.17 g/mol and the following structure:

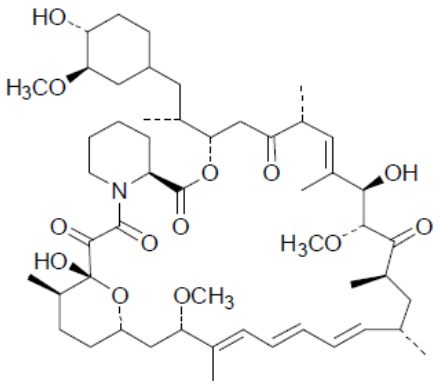


Figure 1: active substance structure

The chemical structure of sirolimus was elucidated by a combination of ^{1}H-NMR Spectrum, ^{13}C-NMR Spectrum, IR Spectrum, UV Spectrum, Mass Spectrum, Elemental Analysis, and X-ray diffraction. The solid state properties of the active substance were measured by XRD.

The active substance is a white to off-white crystalline powder, hygroscopic, freely soluble in acetone, methanol, ethanol, ethyl acetate and isopropyl ether; very sparingly soluble in hexane, practically insoluble in water.

Sirolimus exhibits stereoisomerism due to the presence of 15 chiral centres, but the method of manufacture uniformly produces a single defined stereoisomer in the solid state. The absolute configuration of the stereogenic centres is ensured by the fermentative production. In solution sirolimus interconverts between three tautomers: A, B and C. Enantiomeric purity is controlled routinely in the active substance by specific optical rotation.

Polymorphism has not been observed for sirolimus. Only one form was observed, which was confirmed by XRD.

2.2.2.2. Manufacture, characterisation and process controls

Sirolimus is produced by a single manufacturer. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Sirolimus is produced by fermentation of *Streptomyces hygroscopicus*, using well-defined starting materials with acceptable specifications. After fermentation, sirolimus is extracted and purified.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Eight specified process-related organic impurities are present in the final active substance, all of which can be detected by the HPLC method for chromatographic purity of the active substance.

The existence of tautomeric forms in solution has been suitably discussed.

Possible carry-over of reagents, possible degradants as well as possible impurities from host cells, media and metabolites has been adequately addressed. The company adequately discussed and justified how impurities are removed in different stages of the process.

The active substance is packaged in double Polyethylene (PE) bags, which are placed in aluminium pouches lined with plastic films, together with silica gel desiccant packs. Aluminium pouches are heat sealed and placed in fiber drums.

2.2.2.3. Specification(s)

The active substance specification includes tests for appearance (visual), identity (FT-IR, HPLC), specific optical rotation (Ph. Eur.), water (Ph. Eur., KF), residue on ignition (Ph. Eur.), chromatographic purity (HPLC), assay (HPLC), and residual solvents (GC).

Residual solvents are removed from the product by evaporation and drying steps, and limits comply with the respective ICH Q3C limit, where applicable. .

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for 3 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from 3 batches of active substance, about half the intended commercial scale, from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (2 - 8°C) and for two batches up to 6 months under accelerated conditions (25°C / 60% RH) according to the ICH guidelines were provided. A forced degradation study on one batch demonstrated that the active substance is prone to degradation by acid, base and peroxide, but not to light degradation.

All tested parameters were within the specifications, with no significant decrease in assay or increase in related substances.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

Hyftor 2 mg/g gel is a colourless, transparent gel.

The product is available in aluminium tubes with HDPE closures. Each tube contains 10 g of gel.

The finished product is an aqueous gel manufactured by a standard process consisting of dissolution, gelling, filling and packaging. The gel is packaged in aluminium tubes with high density polyethylene closures.

The active substance has been sufficiently described including relevant characteristics for finished product formulation.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. Functionality-related characteristics of carbomers are considered suitable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Appropriate compatibility studies have been conducted.

Four formulations were developed and subjected to clinical trials.

Considering the uncertainty on representativeness of the clinical batches used in the pivotal studies for the finished product intended for marketing, a major objection (MO) was raised. In the response the applicant provided a comparative overview of physicochemical properties of clinical formulations, a justification on sameness of formulations 2 (Phase III studies) and 3 (final commercial formulation), the totality of which was considered acceptable to resolve the MO.

The finished product is manufactured by a standard process. The manufacturing process development has been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The critical process parameters and in-process controls have been adequately identified.

The primary packaging is an aluminium tube with high density polyethylene closure. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process is a standard process involving dissolution of sirolimus, gelling, filling and packaging.

Suitable holding times were established.

Process validation was performed on three commercial scale batches. Major steps of the manufacturing

process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process for a cutaneous gel.

2.2.3.3. Product specification(s)

The finished product specifications include appropriate tests for cutaneous semi-solid dosage forms: appearance (visual), identification (UV, HPLC), pH, related substances and assay (HPLC), minimum fill weight (USP), apparent viscosity (Ph. Eur.), drug release (USP), and ethanol content (GC).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay (sirolimus) and related substances testing has been presented.

Batch analysis results are provided for three commercial scale batches.

2.2.3.4. Stability of the product

Stability data from 3 commercial scale primary stability batches of finished product, stored for up to 15 months under long term conditions (2-8°C) and for up to 3 months under accelerated conditions (25°C / 60% RH) according to the ICH guidelines were provided.

Accelerated stability studies (25°C/60% RH) have shown that the finished product is stable for up to 1 month.

A MO was raised since the initially proposed shelf life of 18 months with storage at 2 - 8°C was not supported by the stability data provided. The applicant adequately responded to the MO by shortening the shelf life to 15 months.

One of the unspecified impurities which increased in long-term and accelerated stability studies should be discussed in further detail (identity and origin) – this is raised as a recommendation **(REC1).**

In-use stability testing was performed in accordance with EU guidance (CPMP/QWP/2934/99). The finished product was found stable for up to 4 weeks after opening and stored refrigerated.

Freeze - thaw cycle studies on a commercial scale supportive batch demonstrated absence of significant changes after 5 freeze-thaw cycles. The applicant successfully performed additional stability studies with the drug product stored in a freezer at -25°C to -15°C for up to 15 months.

A thermostability study at 40±2°C for two weeks demonstrated that short-term excursions of the refrigerated storage condition result in significant changes in the finished product quality and must therefore be avoided.

In addition, a photostability study conducted on product (directly exposed to light (600,000 lx.h, 25°C) in a tightly stoppered clear glass bottle), demonstrated photosensitivity of the finished product. However, the primary packaging provides sufficient protection against light influence.

Efficacy of antimicrobial preservation in compliance with Ph. Eur. 5.1.3 requirements was demonstrated after 15 months storage at 2-8°C.

Based on available stability data, the proposed shelf-life of 15 months and storage conditions "Store in a refrigerator (2°C – 8°C), Store in the original package in order to protect from light.", as stated in the SmPC (section 6.3) are acceptable.

2.2.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant adequately responded to the two MOs raised during the procedure by providing exhaustive information and justification for representativeness of the clinical batches to the intended commercial product, and by shortening the shelf-life of the finished product to 15 months.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process, however, no design spaces were claimed.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to the need to provide a detailed discussion on one of the unspecified impurities, including possible origin and identity. This point is put forward and agreed as recommendation for future quality development

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

2.3. Commitment to provide a detailed discussion on one of the unspecified impurities in the finished product, including possible origin and identity. Non-clinical aspects

2.3.1. Introduction

TSC is a result of the constitutive activation of mTORC1 caused by defects, or mutations, of the responsible genes TSC1 or TSC2.

Sirolimus is an mTOR inhibitor, although the exact mechanism of action of sirolimus in the treatment of angiofibroma in the tuberous sclerosis complex is not exactly known.

In general, sirolimus inhibits activation of mTOR which is a serine/threonine protein kinase that belongs to the phosphatidylinositol-3-kinase (PI3K)-related kinase family and regulates cellular metabolism, growth and proliferation. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. This complex binds to and inhibits the activation of mTOR.

2.3.2. Pharmacology

As mentioned above, sirolimus binds to the FK binding protein 12. The resulting complex inhibits the activation of mTOR, which in tuberous sclerosis is caused by dysfunctionalities in the hamartin-tuberin protein complex. mTOR inhibition leads to suppression of cytokine driven T-cell proliferation and inhibition of the cell cycle progression from G1 to S phase.

The effects of topically applied sirolimus were investigated in a TS mouse model (Rauktys et al. 2008). Animals received 0.8% (0.16 mg) sirolimus topically on the skin over the tumours (n = 13), 0.8% sirolimus topically on the skin of the back (n = 12), 0.4% sirolimus topically on the skin over the tumours (n = 15), vehicle control topically on the skin over the tumours (n = 12), and 0.16 mg sirolimus intraperitoneally (n = 8) three times per week. On Day 29, the tumour volume was significantly reduced in the 0.4% tumour application group, the 0.8% tumour application group, and the 0.8% back application group, compared with the control. Comparison of tumour volumes between the 0.8% tumour application group and the 0.8% back application group showed no significant difference on either Day 29 or Day 45. However, the p-value on Day 45 was 0.06, suggesting that application of sirolimus on the back may have had higher inhibitory effects on tumour volume than compared with direct application.

For safety pharmacology, the applicant refers to the studies conducted with Rapamune for the systemic use of sirolimus that did not show any effects on central nervous, respiratory and cardiovascular system. The evaluation of the safety pharmacology endpoints in the toxicology studies (FOB in juvenile rats and ECG in monkeys) did not indicate any cause of concern.

Secondary pharmacology and pharmacodynamic drug interaction studies have not been carried out. This is acceptable since this information is available for Rapamune

2.3.3. Pharmacokinetics

The assessment of absorption of sirolimus gel, 0.2% was conducted in an in vitro assay with human skin, and toxicokinetic (TK) assessments in mice, rats and monkeys. No standalone pharmacokinetic (PK) studies have been conducted with sirolimus gel, which is considered adequate. The in vitro skin permeability study with two sirolimus formulations (NPC-12G Gel 0.2% and 0.2% OSD-001) and skin

samples from two human donors mounted on Franz cells showed similar permeability for the two formulations. The sirolimus content in the epidermis and dermis at 24 h after application of NPC-12G Gel 0.2% comprised 0.42% of dose. The recovery amount of sirolimus in the corneum was 2.80% of dose. The sirolimus content in the epidermis and dermis at 24 h after application of 0.2% OSD-001 represented 0.34% of dose. The recovery amount of sirolimus in the corneum in this case was 2.30% of dose. Sirolimus was not detected in the receptor fluid collected at any time point studied up to 24 hours after application for one skin donor suggesting that the in vitro permeability of sirolimus through human skin is very low.

2.3.4. Toxicology

Nobelpharma has developed sirolimus gel, 0.2% (NPC-12G Gel), a topical formulation of sirolimus for the treatment of angiofibroma (AF) associated with tuberous sclerosis (TS). Two formulations of sirolimus gel of slightly different composition, OSD-001 Gel or NPC-12G Gel, have been used in the non-clinical and clinical studies. In order to support the safe chronic use of sirolimus gel in patients with AF associated with TS, one single dose toxicity study was conducted in rats and a number of dermal repeat-dose toxicities were conducted in rats and cynomolgus monkeys. Further studies included a medium-term carcinogenicity in mice, local tolerance studies including skin irritation, eye irritation and skin sensitization studies, as well as photosafety studies evaluating phototoxicity and photoallergy of NPC-12G Gel. In addition to the studies conducted by Nobelpharma, the Applicant relied on non-clinical data for the EU-approved medicinal product Rapamune and on information in the published literature to support a hybrid Marketing Authorization Application (MAA) according to Article 10(3) of Directive 2001/83/EC.

2.3.4.1. Single dose toxicity

The single dose toxicity study evaluated the potential acute toxicity of sirolimus gel (NPC- 12G Gel) in SD rats when administered percutaneously twice within 24 hours (with a 6-hour interval). No death occurred, and no treatment-related abnormalities were noted in the animals' physical condition, body weights or gross pathology. It's therefore agreed that sirolimus gel up to 0.8% (8.0 mg/kg/day) did not induce acute toxicity.

2.3.4.2. Repeat dose toxicity

Repeat-dose toxicity studies were conducted with sirolimus gel (NPC-12G Gel or OSD- 001 Gel). These included studies in SD Rats (13-Week Percutaneous Toxicity Study of Sirolimus in Rats with a 4-Week Recovery Period, 4-Week Percutaneous Toxicity Study of Sirolimus in Juvenile Rats), in HWY/Slc rat (13-Week Repeated Percutaneous Dose Toxicity Study of Sirolimus Gel in Rats with a 7-Week Recovery Period, 7-Week Repeated Percutaneous Dose Toxicity Study of Sirolimus Gel in Juvenile Rats) and Cynomolgus monkeys (13-Week Percutaneous Toxicity Study of Sirolimus in Monkeys with a 4-Week Recovery Period, 39-Week Repeated Percutaneous Dose Toxicity Study of Sirolimus (for external use) in Cynomolgus Monkeys).

Target organs in rats (HWY/SLC and SD rats) were the lungs, adrenals, lymph nodes and thymus predominantly at the highest dose tested. More adverse effects were observed with the OSD-001 gel formation and as a consequence the NOAEL in the study with the OSD-001 Gel formation was marked lower compared to the NPC12G-Gel formation. Since both formulations included 0.2% sirolimus, the effects might be attributed to the different rat strains or to the excipients which were not included in the NPC12G Gel.

No abnormalities were noted after administration of sirolimus gel (NPC12G gel) in monkeys for 13-weeks. However, after 39 weeks of treatment adverse effects were noted in GI tract (soft stool, diarrhoea), kidney (eosinophilic/brown granule in the proximal tubular epithelium of the kidney in males and females at the 4.0 mg/kg/day and in females at 1.0 mg/kg/day group) and adrenals. Further changes such as high glucose content in urine or haematology and clinical chemistry changes showed no dose dependency and occurred in individual animals only.

In cynomolgus monkeys treated twice daily with 2 mg/g and 8 mg/g sirolimus gel for 9 months toxic effects were observed in one male at 8 mg/g gel and one female at 2 mg/g gel at exposure levels similar to clinical exposure levels following systemic administration of sirolimus and with possible relevance to clinical use, were as follows: typhlitis, colitis, and rectitis, vacuolation of the renal proximal tubular epithelium, dilation of distal tubule and collecting ducts, enlargement of the adrenal glands and hypertrophy/eosinophilia of the zona fasciculata, hypocellularity of the bone marrow, atrophy of thymus, lymph nodes and white pulp of the spleen, acinar atrophy of the exocrine pancreas and submandibular gland. These two animals were sacrificed for humane reasons due to deterioration of their general condition.

Following systemic treatment with sirolimus, pancreatic islet cell vacuolation, testicular tubular degeneration, gastrointestinal ulceration, bone fractures and calluses, hepatic haematopoiesis, and pulmonary phospholipidosis were observed.

No skin irritation was observed in either rats or monkeys.

Not all non-clinical findings mentioned in the SmPC were observed after topical administration.

2.3.4.3. Genotoxicity

Studies on the genotoxic potential of Sirolimus (also known as rapamycin) are referred to (SmPC Rapamune). Sirolimus was negative in the standard battery of genotoxicity testing according to ICH S2 (R1) comprising a test for bacterial reverse mutations, chromosomal damage in vitro in Chinese Hamster ovarian cells and a mouse lymphoma assays, and in vivo in a micronucleus test in mice. No further studies were conducted.

2.3.4.4. Carcinogenicity

Long-term oral carcinogenicity studies in mice and rats for rapamycin are referred to (SmPC Rapamune; EPAR Rapamune). The studies with rapamycin were conducted for systemic use of sirolimus with far higher systemic exposures than reached for topical use. In mice, increased incidences of lymphomas (males and females), hepatocellular adenoma and carcinoma (males) and granulocytic leukaemia (females) were observed. In rats, testicular interstitial cell adenomas were observed and considered most likely as indicative of a species dependent response to lutenising hormone levels and are usually considered of limited clinical relevance (SmPC Rapamune). Occurrence of malignancies (lymphoma) are expected as secondary to the chronic use of immunosuppressive agents.

To evaluate any potential for skin tumour promotion of topical application a mid-term (19 weeks of promotor treatment) initiator promotor study for skin carcinogenicity has been performed in Crl:CD mice. Sirolimus gel 0.2 % and 0.8 % applied daily for 19 weeks on initiated skin did not promote skin tumour formation in the initiator promoter model in mice. The positive control TPA, a well know potent skin tumour promoter, induced skin tumour formation in all animals of the TPA group at week 12 instead already with an increasing number of skin nodules per mouse over time. There was no evidence in this study for a skin tumour promoting potential of Sirolimus gel 0.2 % and 0.8 %.

2.3.4.5. Reproduction toxicity and developmental toxicity

Reproductive and developmental toxicity studies conducted for the systemic use of sirolimus, also known as rapamycin, (Rapamune) are referred to (SmPC Rapamune; EPAR Rapamune).

In reproduction toxicity studies using systemic administration of sirolimus, decreased fertility in male rats was observed. Partly reversible reductions in sperm counts were reported in a 13-week rat study. Reductions in testicular weights and/or histological lesions (e.g. tubular atrophy and tubular giant cells) were observed in rats and in a monkey study. In rats, sirolimus caused embryo/foetotoxicity that was manifested as mortality and reduced foetal weights (with associated delays in skeletal ossification).

2.3.4.6. Toxicokinetic data

Systemic exposure increased following twice daily dosing in both rats and cynomolgus monkeys. In rats treated with 0.8% sirolimus gel (to 10% of the total body surface area), AUC values were in the same range as for daily oral dosing of sirolimus (0.25 mg/kg/day). High AUC values were also observed for cynomolgus monkeys treated twice daily with 0.8% sirolimus gel (to 10% of the total body surface area) for 39 weeks. According to FDA/CDER Pharmacology Review(s):Application Number 021083.NDA 21-083 are the observed AUC values in the same range as AUC values reported for treatment of 6 months with a toxic dose of Rapamune. However, since Rapamune was not included as positive control in the monkey studies, this conclusion is regarded as speculative. Further, a direct comparison of Cmax/AUC values between animals and humans is not feasible since specific PK studies in patients have not been conducted. Thus, statements about margins of exposure cannot be given. For clarification, the applicant focuses on Cmax data evaluated in the 39-week and 13-week monkey study. In the 39-week monkey study (and not in the 13-week study) 2 animals died due to inflammatory responses, possibly induced by sirolimus whereas no signs of toxicity could be observed in the 13-week study. The applicant argues that the Cmax value in the 39-week study was similar to or higher than mean and median blood concentrations in any age-group and at any time point in patients.

2.3.4.7. Local tolerance

Sirolimus gels did not show any primary skin irritant effects in rabbits at concentrations under 0.2%. According to the Toxicology Written Summary, 0.2% sirolimus gel deteriorated product containing 14.7% seco-sirolimus also had no skin irritating effects in rabbits. No skin sensitisation potential was noted in guinea pigs up to the concentration of sirolimus gel of 0.8%. Sirolimus gels were classified as moderately irritant to the ocular mucosa but these effects were attributed to an ingredient of the base.

Sirolimus gels showed photosensitivity-inducing properties in guinea pigs, which is mentioned in the SmPC. Photosensitive disease-like skin reactions were dose-dependent. Sunscreen had protective effects when applied at challenge.

2.3.4.8. Other toxicity studies

Juvenile Toxicity

In juvenile rats sirolimus administered percutaneously in repeated dose studies dose-dependent toxic changes such as suppressed body weight gain, decreased food consumption, changes in various haematological parameters and tissue changes in the lymphoid organs were noted. A similar toxicological profile of sirolimus in juvenile rats was seen in the adult rats. The selected age ranges of the juvenile rats at treatment start are considered adequate for the paediatric age group to be treated.

Nevertheless a comparison of Cmax and/or AUC values between the juvenile animals and humans is not feasible since specific PK studies in young patients have not been conducted. The classic approach for risk assessment - comparing exposure margins at the NOAELs with the human exposure is therefore not possible. Instead, the applicant discussed the safety of systemic exposure in juvenile animals; together with the fact that there are no systematic difference between younger and older paediatric patients in sirolimus blood concentrations, this is acceptable.

Phototoxicity

Sirolimus was not phototoxic in a standard in vitro 3T3 NRU test for phototoxicity.

Studies on impurities

Ten impurities, impurity A, B1, B2, C, D, E, F1, F2, seco-rapamycin and rapamycin isomer C, were tested negative with two adequate in silico models and can be considered non-mutagenic based on these models.

The potential mutagenicity of impurities in NPC-12G Gel (impurity A, impurity B1, impurity B2, impurity C, impurity D, impurity E, impurity F1, impurity F2, seco-rapamycin, and rapamycin isomer C) were assessed using in silico tools in compliance with ICH guideline M7.

In silico mutagenicity (Ames test) prediction was performed using knowledge-based Deductive Estimation of Risk from Existing Knowledge (DEREK) and statistical-based CASE Ultra. CASE Ultra used basic modules, GT1_A7B and GT1_AT_ECOLI, and reference modules, PHARM_SALM and PHARM_ECOLI.

In silico prediction indicated no structural alerts of any of the tested structure.

This is considered satisfactory.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant provided an updated environmental risk assessment including a ready biodegradability test of sirolimus according to OECD guideline 301F (Ready Biodegradability: Manometric Respirometry Test) which showed that sirolimus is not readily biodegradable. The stepwise PBT assessment was not continued. Therefore, a final conclusion on PBT is not possible for the active ingredient sirolimus.

Instead of further testing on PBT the applicant referred to an European Public Assessment Report for the medicinal product Votubia containing the active ingredient everolimus. For legal reasons it is not allowed to use information published in EPARs of other applicants. Moreover, the assessor does not agree with the approach of the applicant to conclude on environmental behavior of sirolimus by similarities in molecular structure and physicochemical properties to the substance everolimus. According to the CHMP questions & answers document on 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010 Rev. 1) question 14, ‘read-across cannot replace the studies asked for in the guideline on the ERA of medicinal products for human use’. Furthermore, a weight-of-evidence approach is not foreseen in the guideline. Therefore, it is not possible to definitely conclude on the PBT status of the active ingredient sirolimus. Since sirolimus is not readily biodegradable the next step in the stepwise PBT assessment is a study on transformation in water/sediment systems (OECD 308).

Summary of main study results

Substance: Sirolimus			
CAS-number: 53123-88-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log Kow	OECD 123	5.1	Potential PBT Y
PBT-assessment			
Parameter	Result relevant for conclusion		**Conclusion**
Bioaccumulation	log Kow	5.1	Potential PBT
	BCF	pending	
Persistence	Ready biodegradability (OECD 301F)	-3 % (d 28), not readily biodegradable k_{STP} (0 h-1)	*Potential P*
	DT50 (OECD 308)	pending	*P/not P open*
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (prevalence)	0.00008	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

2.3.6. Discussion on non-clinical aspects

Topical application of 0.4 and 0.8% sirolimus to mice with tuberous sclerosis significantly increased survival of animals. Interestingly, indirect application produced significantly better results than direct application of sirolimus over the tumours. This did not correlate with slightly (not significantly) higher sirolimus levels in tumours upon direct application. The applicant concluded that direct and indirect application were equally effective. The contribution of ingestion of sirolimus ointment due to grooming to the systemic exposure cannot be excluded.

LC-MS/MS bioanalytical methods for the determination of sirolimus in mouse skin as well as in whole blood of rats and monkeys were successfully validated. The validation was performed according to the Japanese standards. Although the GLP requirements were not fulfilled in full, the minimal standards were met and the reliability of data was confirmed by the quality assurance.

The in vitro skin permeability study with two sirolimus formulations (NPC-12G Gel 0.2% and 0.2% OSD-001) and skin samples from two human donors mounted on Franz cells showed similar permeability for the two formulations. Sirolimus was not detected in the receptor fluid collected at any time point studied up to 24 hours after application for one skin donor suggesting that the in vitro permeability of sirolimus through human skin is very low.

In order to underline the safety of sirolimus gel after topical administration toxicology studies were performed in rats and cynomolgus monkeys up to 13- and 39-weeks respectively. The NPC12G Gel (0.2% sirolimus) was tolerated in rats and monkeys without major adverse effects on the skin. Monkeys exhibited adverse effects in kidneys and the GI-tract, predominantly at the highest dose tested. However, these changes are known side-effects of Rapamune. Thus, the results are encouraging for a topical administration. However, no margins of exposure could be provided and no information could be provided about the behaviour of the gel in humans with angiofibroma associated with tuberous sclerosis. This makes a scientifically based conclusion on the safety of the gel difficult and the data could only be regarded as supportive.

Sirolimus gels did not show any primary skin irritant effects in rabbits at concentrations under 0.2%. According to the Toxicology Written Summary, 0.2% sirolimus gel deteriorated product containing 14.7% seco-sirolimus also had no skin irritating effects in rabbits. Sirolimus gels were classified as

moderately irritant to the ocular mucosa but these effects were attributed to an ingredient of the base. Sirolimus gels showed photosensitivity-inducing properties in guinea pigs, which is mentioned in the SmPC.

As already known from Rapamune, Sirolimus was not genotoxic in standard battery genotoxicity assays and therefore no further studies were considered necessary. This is also valid for standard 2 years carcinogenicity studies, however according to the scientific advice of CHMP to clarify any skin tumour promoting potential of sirolimus gel a mid-term (19 weeks of promotor treatment) initiator promotor study for skin carcinogenicity has been performed in Crl:CD mice and was considered acceptable. No evidence for a skin tumour promoting potential of Sirolimus gel 0.2 % and 0.8 % was observed in this study.

Effects of sirolimus on the different stages of the reproductive process have been adequately studied. In most studies maximum tolerated doses were reached, but exposure levels were lower than expected clinical levels. Male rats treated had decreased fertility and atrophy of testes. Giant cells in testes and hypospermia in testes as well as in epididymides were evident. These effects on male reproductive organs are not unexpected with an agent with antiproliferative properties. Female fertility was not affected, but early resorptions, decreased uterine and foetal body weights and foetal toxicity were noted. In a rat developmental toxicity study no teratogenic effects of sirolimus were observed. However, vertebral ossification were reduced and vertebral variations were increased. In rabbits, treatment with sirolimus seemed related to an increase in abortions. Interactions of oral applied sirolimus with oral contraceptives are expected due to the involvement of CYP3A in sirolimus metabolism. Special studies in lactating rats showed that the compound-derived radioactivity passes into milk to a large extent.

In the light of the low systemic exposure after topical administration it is not expected that clinical relevant interactions will occur with sirolimus gel, 0.2%. This is adequately expressed in the SmPC.

Since sirolimus is not readily biodegradable. as further step in the stepwise PBT assessment a study on transformation in water/sediment systems (OECD 308). Depending on the outcome, i.e. the P criterium is fulfilled, a bioconcentration study according to OECD guideline 305 would be necessary. If both the P and B criteria are fulfilled, as final step of the PBT assessment a test on toxicity would become necessary

A final conclusion on the environmental risk of sirolimus cannot be drawn based on the data available. A respective letter of recommendation has been provided, including an anticipated time schedule.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data submitted support the marketing authorisation of Hyftor. The response provided by the applicant is acceptable. There are no more issues that need to be clarified.

The CHMP considers the following measures necessary to address the non-clinical issues:

Commitment to provide a study on transformation in water/sediment systems (OECD 308) as next step of the PBT assessment for Sirolimus by Q1-2024. Depending on the outcome further step will be conducted as required, i.e if the P criterium is fulfilled, a bioconcentration study according to OECD guideline 305 will be conducted. lf both the P and B criteria are fulfilled, as final step of the PBT assessment a test on toxicity will be conducted.

2.4. Clinical aspects

This hybrid application concerns a centralised procedure for sirolimus gel, 0.2% according to Article 10(3) of Directive 2001/83/EC. The reference medicinal product is Rapamune (EU/1/01/171).

Rapamune is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant (in combination with ciclosporin microemulsion and corticosteroids, or as maintenance therapy with corticosteroids). Targeted blood concentrations are 4-12 ng/mL during initial therapy (with ciclosporin and corticosteroids) and 12-20 ng/mL during maintenance therapy. It is also indicated for the treatment of patients with sporadic lymphangioleiomyomatosis (LAM) with moderate lung disease or declining lung function. Target blood concentrations for this indication are 5 to 15 ng/mL.

Four clinical studies were performed with sirolimus gel, 0.2% in the AF development programme (Table 3.3.1-1): a randomised, placebo-controlled Phase III study (NPC-12G-1), an uncontrolled, open-label long-term study (NPC-12G-2), a Phase I/II dose escalation study (OSD-001-001), all of them in Japanese AF patients; and a Phase I study in Caucasian healthy volunteers (NPC-12G-4/US).

Based on 3 studies (NPC-12G-1; NPC-12G-2; OSD-001-001), sirolimus gel, 0.2% was approved in Japan on 1 Mar 2018

2.4.1. Introduction

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

To support the application, the applicant has submitted results from 3 clinical studies in patients with angiofibroma and 1 relative bioavailability study in healthy volunteers. All AF studies for sirolimus gel 0.2% included adult and paediatric patients. Study results of studies with patients with other indications have also been submitted.

No results of pharmacodynamic or therapeutic equivalence studies have been submitted.

Table 2.Studies contributing to the evaluation of the PK, efficacy, and safety of sirolimus gel, 0.2% for the treatment of AF associated with TSC in adults and children

Study ID	Study objectives	Study design	Treatment	Population Patients[2], n	
Studies in AF patients					
NPC-12G-1	E, S, PK	R, DB, PBO-controlled	12-w dosing bid, 0.2% sirolimus	AF pts	S0.2%: 30 Placebo: 32
NPC-12G-2	E, S, PK	OL, UC	Continued[1] dosing bid, 0.2% sirolimus	AF pts	Total: 94
OSD-001-001	E, S, PK, dose finding	R, DB, PBO-controlled	12-w dosing bid, 0.05, 0.1, 0.2% sirolimus	AF pts	Sirolimus: 24 Placebo: 12
Studies in HVs					

Study ID	Study objectives	Study design	Treatment	Population	Patients[2], n
NPC-12G-4/US	PK	OL, fixed-sequence, 2-period	Single dose of sirolimus gel, 0.2% containing 1.6 mg sirolimus; Rapamune 2 mg tablet	HV	Total: 12
Studies in other indications					
OSD-001-003	E, S	R, DB, PBO-controlled	24-w dosing BID, 0.2%, 0.4% sirolimus; placebo	NF1 pts	Total: 18 S0.2%: 6 S0.4%: 6 Placebo: 6
OSD-001-004	E, S	R, DB, PBO-controlled	52-w dosing BID, 0.2%, 0.4% sirolimus; placebo	NF1 pts	Total: 76 S0.2%: 25 S0.4%: 24 Placebo: 27

Abbreviations: AF pts= angiofibroma patients; BID= twice daily; E= efficacy; FS= fixed sequence; HV= healthy volunteers; NF1= neurofibromatosis type 1; OL= open-label; PK= pharmacokinetics; S= safety; UC= uncontrolled, w= week

[1] *Until study completion or approval*

[2] *Actual patient number in completed studies, planned number in ongoing studies*

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

To describe the PK of sirolimus after topical application, a mix of own clinical data, literature data and data available for oral sirolimus (RMP product for this hybrid application) have been used as listed in the table below:

Table 3. Data sources for the characterisation of the PK of sirolimus in the MAA

		Data source
Clinical pharmacology	Mechanism of action	Literature
PK	Absorption, distribution, metabolism, elimination	RMP product information (oral sirolimus)
	Bioavailability	RMP product information (oral sirolimus); own clinical data; literature (topical sirolimus)
	Dose linearity	RMP product information (oral sirolimus); own clinical data (topical sirolimus)
	PK in the target population	Own clinical data (topical sirolimus)
PK in special populations	Hepatic impairment	RMP product information (oral sirolimus)
	Renal impairment	RMP product information (oral sirolimus)
	Black patients	RMP product information (oral sirolimus)
	Paediatric patients	RMP product information (oral sirolimus); own clinical data (topical sirolimus)

PK/PD relationship	Effect on cardiac repolarisation/ QT prolongation	Literature (oral rapalogs)
Drug-drug interactions		RMP product information (oral sirolimus)
PD		Literature (topical sirolimus)

Abbreviations: PD= pharmacodynamics, PK= pharmacokinetics, RMP= reference medicinal product

Results

OSD-001-001

Study title Group Titration Study in Facial Skin Lesions Associated with Tuberous Sclerosis Complex to Estimate the Safety and Effective Dose of OSD-001 by a Placebo-controlled, Double-blind, Randomized, Parallel Group Design for Each Dose (Phase I/II)

Treatment The gel (doses ranging from 0.05% over 0.1% to 0.2% and placebo (vehicle only)) was applied to the target site twice daily (morning, evening) for 12 weeks. The amount of application was 1 push (approximately 125 mg) per a lesion of 50 cm^2 as a standard, and an appropriate amount was applied depending on the size of the lesion. However, 1.5 pushes per application and 3 pushes per day were specified as the upper limits.

Results

Table 4: Sirolimus blood concentration by patient

Adults/ Children	Sirolimus Concentration Administered	Patient Number	Concentration of Sirolimus (ng/mL)						
			Day 0		Week 2	Week 4	Week 8	Week 12	
			Before the start of administration	1 hour after administration	Trough	Trough	Trough	Before the start of administration	1 hour after administration
Adults	0.05%	P-001	BQL	BQL	BQL	BQL	BQL	BQL	BQL
		P-002	BQL	BQL	BQL	BQL	BQL	BQL	BQL
		P-004	BQL	BQL	BQL	BQL	BQL	BQL	BQL
		P-006	BQL	BQL	BQL	BQL	BQL	BQL	BQL
	0.1%	P-015	BQL	BQL	BQL	BQL	BQL	BQL	BQL
		P-016	BQL	BQL	BQL	BQL	BQL	BQL	BQL
		P-017	BQL	BQL	BQL	BQL	BQL	0.1481	0.1888
		P-018	BQL	BQL	0.1252	BQL	BQL	BQL	BQL
	0.2%	P-027	BQL	BQL	-	BQL	-	BQL	BQL
		P-028	BQL	BQL	0.1499	0.1667	0.1454	0.1952	0.1045
		P-029	BQL	BQL	BQL	BQL	BQL	BQL	0.1259
		P-030	BQL	BQL	-	BQL	0.1196	0.1088	0.1362
Children	0.05%	P-008	BQL	BQL	BQL	BQL	BQL	BQL	BQL
		P-010	BQL	BQL	BQL	BQL	BQL	0.1066	BQL
		P-011	BQL	BQL	BQL	BQL	BQL	BQL	BQL
		P-012	BQL	BQL	BQL	BQL	BQL	BQL	BQL
	0.1%	P-020	BQL	BQL	BQL	BQL	BQL	BQL	BQL
		P-021	BQL	BQL	BQL	BQL	BQL	BQL	0.1066
		P-022	BQL	BQL	BQL	BQL	BQL	0.1661	0.1626
		P-024	BQL	BQL	BQL	BQL	0.1359	0.1039	0.1343
	0.2%	P-031	BQL	BQL	BQL	0.1686	0.1441	0.1523	0.1271
		P-032	BQL	BQL	BQL	BQL	0.1248	0.1103	BQL
		P-033	BQL	BQL	BQL	0.1357	0.154	0.1541	0.222
		P-036	BQL	BQL	0.1571	0.1986	0.199	0.2118	0.2462

BQL, Below the lower limit of determination (0.1000 ng/mL)

-, Missing value

Data source: Form 11_4_5 List of sirolimus blood concentration (efficacy population)

As outlined in the table above, sirolimus blood concentration was detected in adults in the 0.1% or more groups, and the number of patients with detection tended to increase depending on the application period. The number of patients with detection at 1 hour after application at 12 weeks after the start of application was 1 of 4 patients in the 0.1% group and 3 in the 0.2% group.

In children, sirolimus blood concentration was detected only in 1 of 4 patients in the 0.05% group before application at 12 weeks after the start of application, while it was detected in 2 patients before application at 12 weeks after the start of application and 3 patients at 1 hour after application in the 0.1% group, 3 patients at 4 weeks after the start of application and all of 3 to 4 patients at each measurement time point from 8 weeks after the start of application to 1 hour after application at 12 weeks after the start of application in the 0.2% group.

After application, blood sirolimus concentration was detected in almost no subject at the test drug concentration of 0.05%, but as the concentration became higher to 0.1% and 0.2%, the number of patients in whom blood sirolimus concentration was detected, as well as sirolimus concentration, increased. The blood concentration was higher in children than that in adults at a concentration of 0.2%.

The Applicant concluded, that as the application concentration was higher, the number of patients with detection of sirolimus blood concentration increased, and especially in children, the detected concentration was also higher.

NPC-12G-1

Study title A Phase 3 Study of NPC-12G Gel in Patients with Skin Lesions Associated with Tuberous Sclerosis Complex

Treatment Either NPC-12G gel (containing 2 mg (0.2% w/w) of sirolimus in 1 g) or placebo gel was evenly applied to skin lesions on the face or head twice daily (in the morning and at bedtime). The study medication was to be applied to the lesions of angiofibroma first, followed by the application to both hypomelanotic macules and plaques on the head (above the neck). The duration of treatment was 12 weeks (allowable duration: 11 to 13 weeks). Follow-up observation was performed 4 weeks after the end of the study medication (allowable duration: 3 to 5 weeks).

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 below as a guide, which 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.

For any patient whose body size (body surface area) falls largely outside the reference range specified for the relevant age group, the maximum dose and number of tubes were to be selected based not on age but body surface area of the patient.

Maximum Daily Dose and Maximum Number of Tubes to Dispense until Next Visit for Each Age Group:

Age group	Standard body surface area (m^2)	Maximum daily dose (mg)	Maximum number of tubes to be dispensed for the interval until next visit (number of 10-mg tubes)
5 years and younger	< 0.8	400 (corresponds to approximately to 2 to 3 cm)	2
6 to 11 years	≥ 0.8 , < 1.3	600 (corresponds to approximately to 3 to 4 cm)	3
12 years and older	≥ 1.3	800 (corresponds to approximately to 4 to 5 cm)	4

Results

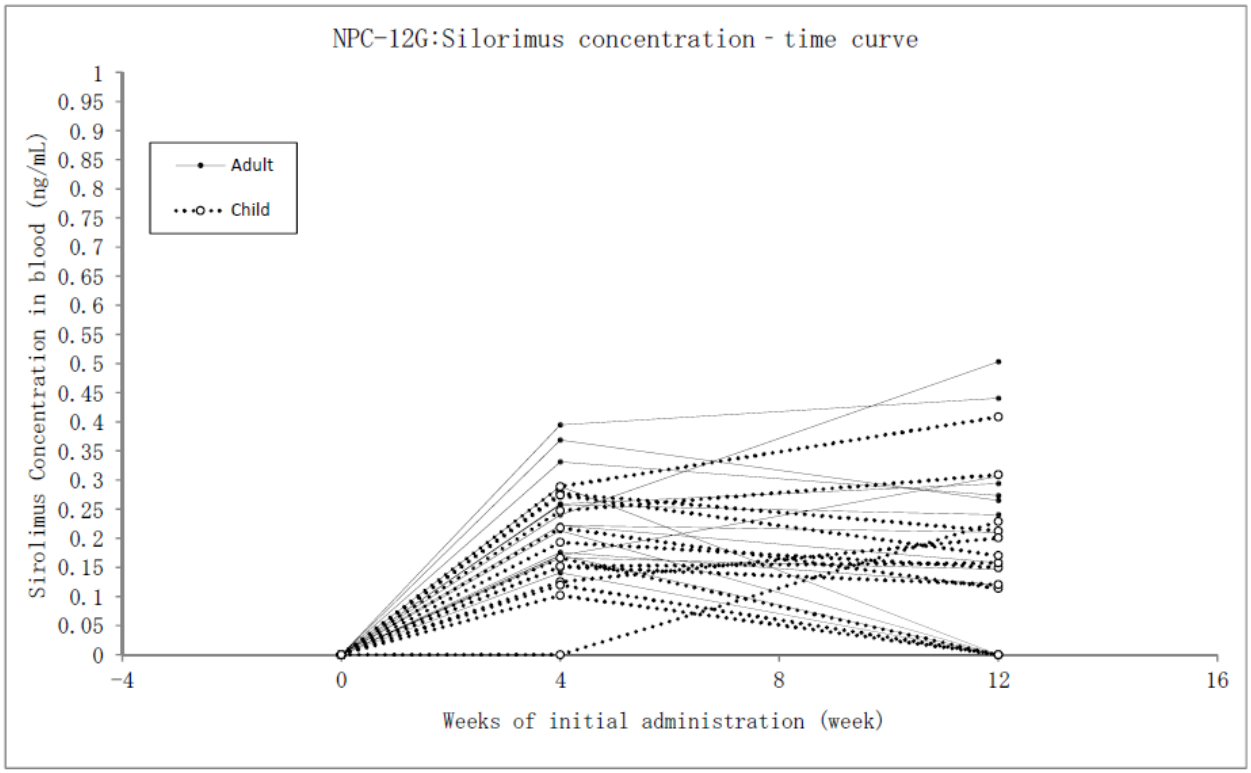
Summary statistics of blood concentration of sirolimus are shown in the table below:

Table 5: Summary Statistics of the Concentration of Sirolimus in Blood

	Items	Baseline (ng/mL)	4W (ng/mL)	12W (ng/mL)
Whole	Number of patients	30	30	30
	Number of patients showing the drug concentration (%)	0(-)	27(90.0)	21(70.0)
	Mean (SD)	-	0.220 (0.0751)	0.239 (0.1083)
	Median (Min, Max)	-	0.218 (0.10,0.39)	0.212 (0.11,0.50)
Adults	Number of patients	17	17	17
	Number of patients showing the drug concentration (%)	0(-)	15(88.2)	11(64.7)
	Mean (SD)	-	0.241 (0.0766)	0.269 (0.1183)
	Median (Min, Max)	-	0.222 (0.14,0.39)	0.265 (0.12,0.50)
Children	Number of patients	13	13	13
	Number of patients showing the drug concentration (%)	0(-)	12(92.3)	10(76.9)
	Mean (SD)	-	0.193 (0.0666)	0.207 (0.0911)
	Median (Min, Max)	-	0.180 (0.10,0.29)	0.185 (0.11,0.41)

Value of lower detection limit = 0.1 ng/mL, Value less than lower detection limit was numerically excluded.

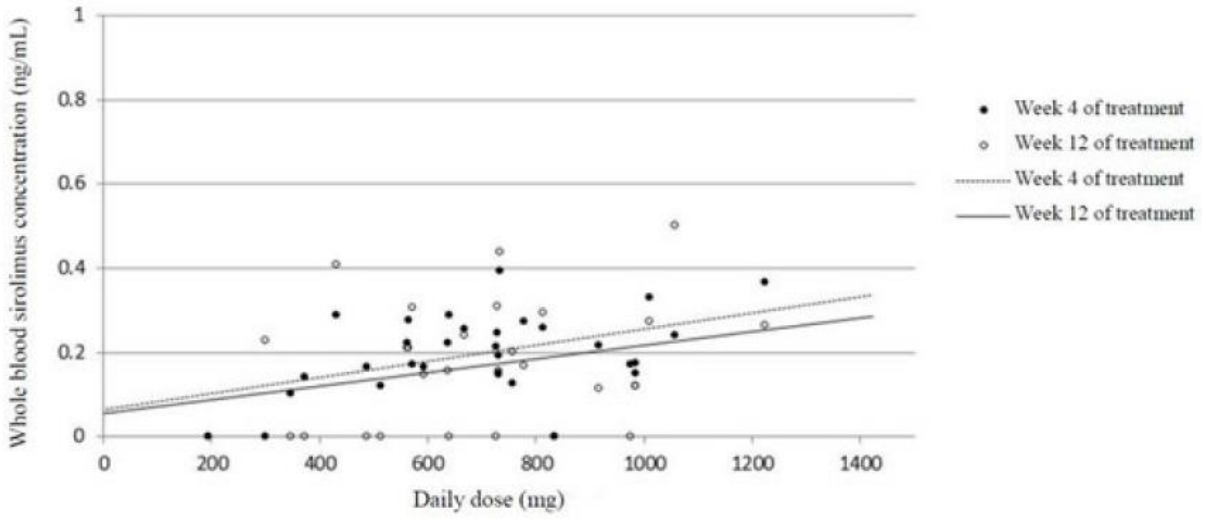
Figure 2 Plot of the concentration of Sirolimus and time by individual patients



Mean blood concentrations of sirolimus in the NPC-12G group at 4 and 12 weeks after the start of the study medication were 0.241 ng/mL (n=15) and 0.269 ng/mL (n=11) in the adult subgroup and 0.193 ng/mL (n=12) and 0.207 ng/mL (n=10) in the children subgroup, respectively.

Dose linearity was investigated by plotting blood concentrations from the pooled study population vs actual total daily dose, see figure below:

Figure 3 Whole blood sirolimus concentration by daily dose after topical administration of sirolimus gel, 0.2%; study NPC-12G-1



Note: The mean daily gel dose was calculated as the mean gel amount/day from the total amount used for 12 weeks for each patient. Concentrations BLQ (0.1 ng/mL) are shown as 0 ng/mL.

Regression curves were determined as Y= 0.2X + 0.07 (p=0.008 for hypothesis that slope=0) at Week 4, and as Y= 0.2X + 0.05 (p=0.140) at Week 12, were Y was the sirolimus concentration (ng/mL) and X the gel amount (g).

Data were analysed using linear regression separately at Weeks 4 and 12. The slope parameters of the regression curves were identical and low (0.2 ng/mL). However, only at Week 4 (but not Week 12), the slope parameter was statistically significantly different (p=0.008) from 0. Based on these results, dose linearity could not be concluded.

NPC-12G-2

Study title A Long-term Study of NPC-12G Gel in Patients with Skin Lesions Associated with Tuberous Sclerosis Complex

Treatment

Dosage and Administration

NPC-12G gel containing 2 mg (0.2%) of sirolimus in 1 g was evenly applied to skin lesions twice daily (in the morning and at bedtime).If a patient forgot the study medication in the morning, then the patient was to immediately apply the medication whenever realizing the fact, as long as it occurs before dinner on the same day; and the patient was only to applythe medication before sleeping when it was realized after dinner.

Dose

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) 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 shown in the table below:

Age category	Standard body surface area (m^2)	Maximum daily dose* (mg)*		Maximum number of tubes to be dispensed as 1-month supply (Number of 10 mg tubes)
5 years or younger	Less than 0.8	400	(1) Corresponding approximately to 2 to 3 cm	2
			(2) Corresponding approximately to 1 cm	
6 to 11 years	0.8 or more; Less than 1.3	600	(1) Corresponding approximately to 3 to 4 cm	2
			(2) Corresponding approximately to 1.5 to 2 cm	
12 years or older	1.3 or more	800	(1) Corresponding approximately to 4 to 5 cm	3
			(2) Corresponding approximately to 2.5 cm	

If an adverse event occurred, and a dosage modification was deemed necessary by the investigator, then the dosage of NPC-12G gel (0.2%) might be decreased to once daily regimen (at bedtime). Dosage modification, 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.

Results

Statistical summary of blood sirolimus concentrations in patients with detected blood concentrations are shown in the table below:

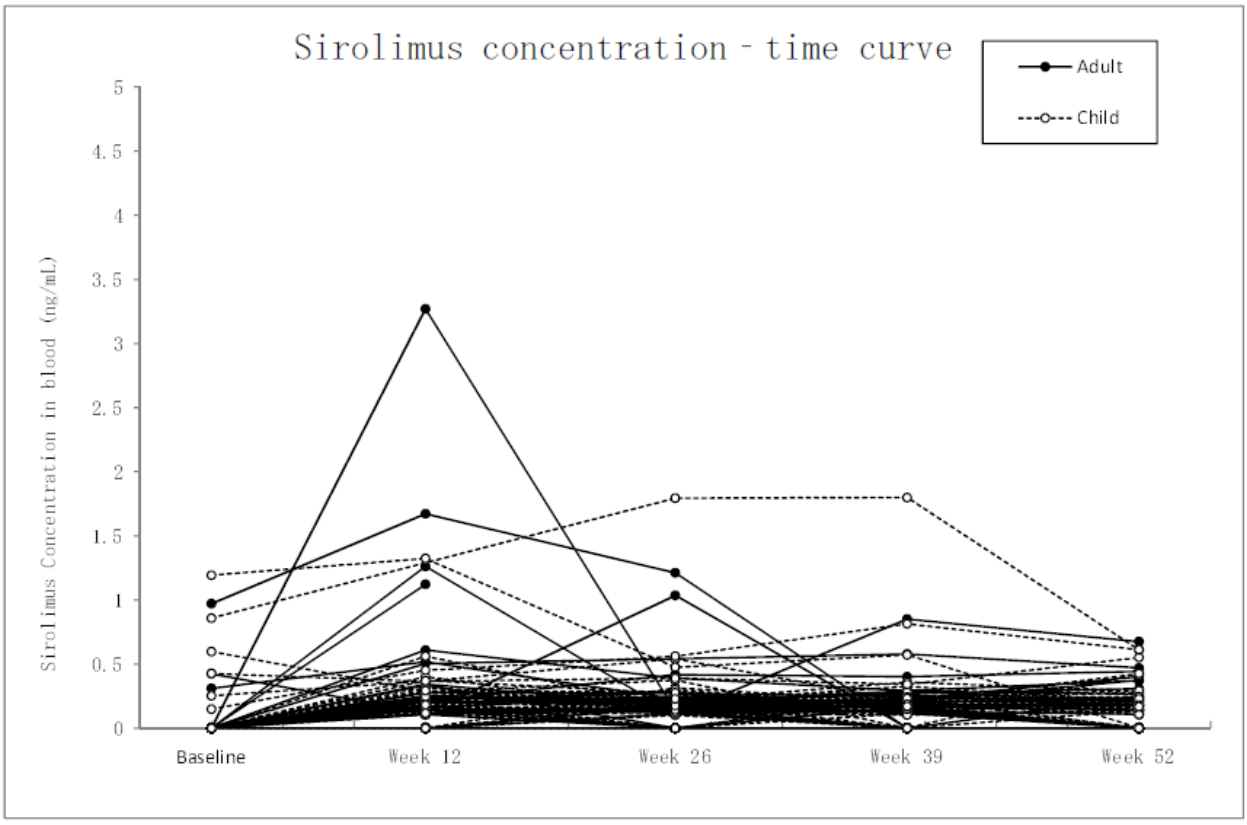
Table 6: Summary Statistics of the Concentration of Sirolimus in Blood

		Baseline (ng/mL)	Week 12 (ng/mL)	Week 26 (ng/mL)	Week 39 (ng/mL)	Week 52 (ng/mL)
All patients	No. of patients	94	89	88	89	88
	n	9	69	64	60	46
	Mean	0.576	0.343	0.278	0.263	0.267
	SD	0.3568	0.4591	0.2708	0.2478	0.1435
	Min	0.15	0.11	0.10	0.10	0.10
	Median	0.427	0.223	0.201	0.203	0.225
	Max	1.19	3.27	1.79	1.80	0.68
Adults	No. of patients	44	41	39	40	39
	n	3	32	29	25	17
	Mean	0.569	0.431	0.276	0.239	0.291
	SD	0.3525	0.6308	0.2550	0.1626	0.1504
	Min	0.31	0.11	0.11	0.11	0.11
	Median	0.425	0.219	0.199	0.178	0.248
	Max	0.97	3.27	1.21	0.85	0.68
Children	No. of patients	50	48	49	49	49
	n	6	37	35	35	29
	Mean	0.580	0.266	0.280	0.280	0.253
	SD	0.3923	0.2063	0.2870	0.2953	0.1400
	Min	0.15	0.11	0.10	0.10	0.10
	Median	0.512	0.223	0.205	0.208	0.213
	Max	1.19	1.32	1.79	1.80	0.61

n: Number of patients with detected levels

□: PK Parameter for maximal values highlighted by the assessor

Figure 4 Plot of the concentration of Sirolimus and time by individual patients



The mean blood sirolimus concentration (range) at baseline in patients with detected blood concentrations was 0.576 ng/mL (0.15 to **1.19** ng/mL) in overall safety population, 0.569 ng/mL (0.31 to 0.97 ng/mL) in adults, and 0.580 ng/mL (0.15 to **1.19** ng/mL) in children. Mean baseline concentrations were numerically higher than mean concentrations at any other assessment time point.

Similarly, the mean blood sirolimus concentration at 12 weeks after the start of administration was 0.343 ng/mL (0.11 to **3.27** ng/mL) in overall safety population, 0.431 ng/mL (0.11 to **3.27** ng/mL) in adults, and 0.266 ng/mL (0.11 to **1.32** ng/mL) in children.

At 26 weeks after the start of administration, it was 0.278 ng/mL (0.10 to 1.79 ng/mL) in overall safety population, 0.276 ng/mL (0.11 to **1.21** ng/mL) in adults, and 0.280 ng/mL (0.10 to **1.79** ng/mL) in children.

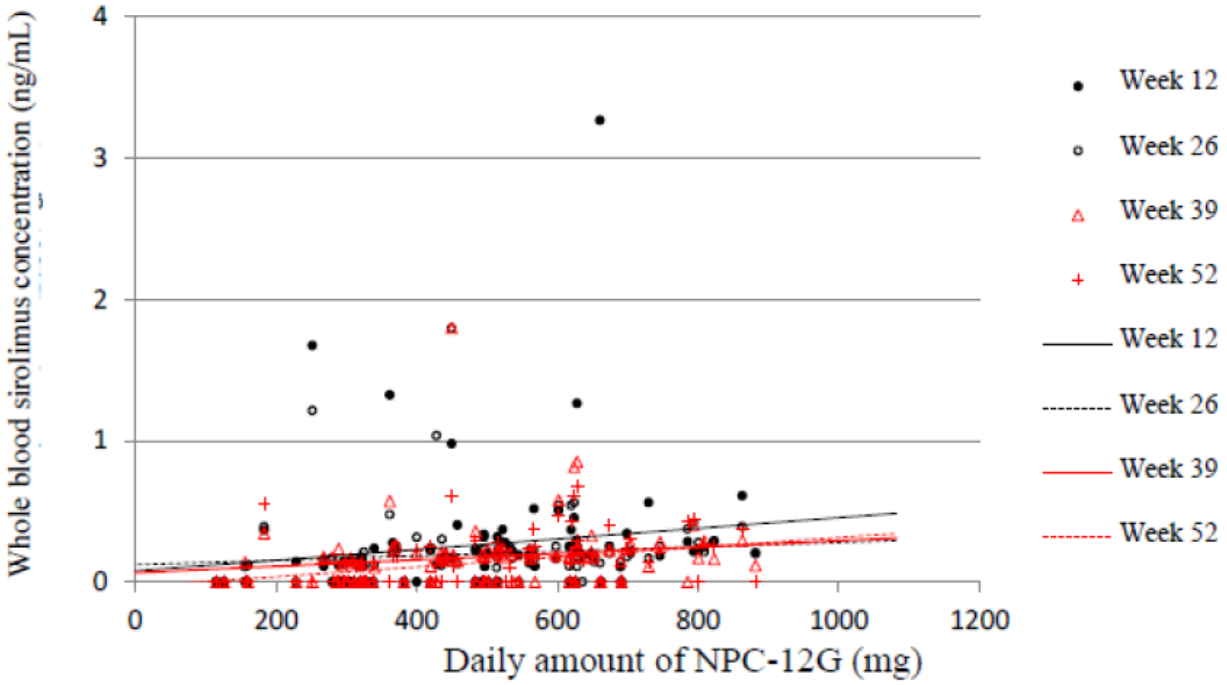
At 39 weeks after the start of administration, it was 0.263 ng/mL (0.10 to **1.80** ng/mL) in overall safety population, 0.239 ng/mL (0.11 to 0.85 ng/mL) in adults, and 0.280 ng/mL (0.10 to **1.80** ng/mL) in children.

At 52 weeks after the start of administration, it was 0.267 ng/mL (0.10 to 0.68 ng/mL) in overall safety population, 0.291 ng/mL (0.11 to 0.68 ng/mL) in adults, and 0.253 ng/mL (0.10 to 0.61 ng/mL) in children.

The Applicant´s CSR concludes that there were no major differences between adults and children and that detected concentrations were extremely low in the majority of patients.

Dose linearity was investigated by plotting sirolimus concentrations vs actual total daily dose. Additionally, data were analysed using linear regression separately at Weeks 12, 26, 39, and 52. See figure below:

Figure 5 Whole blood sirolimus concentration by daily dose after topical administration of sirolimus gel, 0.2%; study NPC-12G-1



Note: The mean daily gel dose was calculated as the mean gel amount/day from the total amount used for 52 weeks for each patient. Concentrations BLQ (0.1 ng/mL) are shown as 0 ng/mL.

Regression curves were determined as Y= 0.48X - 0.03 at Week 12 (p=0.043 for hypothesis that slope=0); Y=0.25X + 0.02 (p=0.028) at Week 26; Y= 0.28X + 0.01 at Week 39 (p=0.029), and Y= 0.38X - 0.05 at Week 52 (p<0.001), where Y was the sirolimus concentration (ng/mL) and X the gel amount (g)..

Slope parameters of the regression curves were low (range: 0.25-0.48) and were all significantly (p<0.05) different from a slope of 0. The data indicate dose linearity, with a flat dose-concentration relationship.

Blood concentrations of more than 1 ng/mL

Blood concentrations of more than 1 ng/mL were detected in 9 patients even at baseline before the start of administration of NPC-12G gel. These 9 patients were all newly enrolled in this long-term study.

The Summary of Pharmaceutic Studies (module 2.7.1) states the following about blood concentrations of more than 1 ng/mL:

Individual patients had values >1 ng/mL, information on these patients is summarised in the following (where all available values are given for each of the patients). Of the 7 patients, 5 were adult, 3 were female. The group included the 2 patients using oral sirolimus ((paediatric),) and 3 patient ((paediatric)) using everolimus. It is noteworthy that most of the patients had concentrations >1 ng/mL at some time points but values <LOQ at other time points, indicating high intraindividual variability in exposure.

• Patient (31 years; female) with 0.9707 ng/mL at baseline and **1.672 and 1.212 ng/mL** at Weeks 12 and 26; values <LOQ at Week 39 and 52;

• Patient no. (19 years, male) with sirolimus <LOQ at baseline; 1.262 ng/mL at Week 12, and lower values at Week 26 (0.1071 ng/mL); Week 39 (0.8510 ng/mL); and Week 52 (0.6756 ng/mL);

• Patient no. (35 years, male) with values <LOQ at baseline, no measurement at Week 12, and **1.122 ng/mL** at discontinuation;

• Patient no. (paediatric: 10 years, male) with 0.8581 ng/mL at baseline, and high values at Week 26 (**1.794 ng/mL**), Week 39 (**1.798 ng/mL**), and Week 52 (0.6099 ng/mL);

• Patient no. (39 year, female) with 0.4248 ng/mL at baseline, 0.1209 ng/mL at Week 12, **1.036 ng/mL** at Week 26, and values <LOQ at Weeks 39 and 52;

• Patient no. (32 years, male) with sirolimus <LOQ at baseline, a single high value of **3.269 ng/mL** at Week 12; 0.1337 ng/mL at Week 26; and values <LOQ at Weeks 39 and 52;

• Patient no. (paediatric: 17 years, female) with 1.193 ng/mL at baseline; **1.323 ng/mL** at Week 12; 0.4756 and 0.5724 at Weeks 26 and Week 39, respectively; and sirolimus <LOQ at Week 52.

NPC-12G-4/US

Study design

This was a Phase 1, single centre, 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. A total of 12 healthy adult male or female, non-smokers were 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).

Subjects might have outings permitted during confinement at the discretion of the site staff. Outings were not allowed until at least 24 hours after the gel application in Period 1. Any outings from Day 2 to Day 8, the subjects would have avoided direct sunlight exposure to the gel application site. If not possible, they would have used sunscreen or worn a hat as measures to prevent direct sunlight exposure to the gel application site. Outings were supervised at all times by the clinical staff to ensure compliance with protocol and were limited to the grounds surrounding the site, as per site's specific procedures for supervised outings.

There was an in-house washout period of 5 days or more between doses. Participation of each subject in the study lasted approximately 8 days.

Treatments

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 central face on Day 1 (period 1).

Treatment B (Reference): Rapamune® 2 mg Tablet (sirolimus) (Distributed by Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc, USA) Dose 1 x 2 mg tablet was administered orally on Day 6 as a single dose (period 2).

For standardization purposes, no food was allowed from at least 10 hours before each dosing until at least 4 hours after dosing.

For Treatment B only, except for water given with study medication, no fluids were allowed from 1 hour before dosing until 1 hour post-dose.

Results

The primary objective of this study was to compare the systemic exposure to sirolimus following topical application (NPC-12G Gel) to the central face (cheeks, forehead, chin, nose) to that observed from oral dosing (Rapamune® Tablet), following single administration in healthy volunteers under fasting conditions.

Table 7: Summary of Pharmacokinetic Parameters for Sirolimus - PK Population

	NPC-12G					Sirolimus Tablet				
Parameter (unit)	N	Mean	SD	CV%	Geometric Mean	N	Mean	SD	CV%	Geometric Mean
AUC_{0-48} (h*pg/mL)	0	-	-	-	-	11	74550.99	11306.83	15.17	73775.38
AUC_{0-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.
CV%: Coefficient of Variation; Min: Minimum; Max: Maximum; N: Number of observations; SD: Standard deviation; '-': Not calculated.

[pg/ml values as stated in the CSR and the table above were transformed to ng/ml in the written text below by the Assessor]

As indicated in the table above, PK parameters could not be calculated for Treatment A (NPC-12G Gel 0.2% [2 mg of sirolimus in 1 g of gel]) due to an insufficient number of detectable whole blood concentrations (all but 3 concentrations are BLQ).

The three concentrations observed to be above the LLOQ for Treatment A (NPC-12G Gel 0.2%) were:

- Subject 01 at 12 hrs (0.116 ng/ml), and at 24 hrs (0.102 ng/ml);

- and Subject 04 at 12 hrs (0.102 ng/ml).

All observed concentrations were at least 40-fold lower than the mean C_{max} from the tablet.

Exploratory PPK analysis

An exploratory PPK analysis was carried out based on blood concentration data from four clinical studies (OSD-001-001, NPC-12G-1, NPC-12G-2, and 192003). Data of 114 adults and 90 paediatric subjects were included in the current analysis (age range 3 to 61 years).

A large number (56.2%) of concentrations was below the lower limit of quantification, the M3 method was used to handle BQL data. The inclusion of data below the quantification limit is appreciated in order to get a more unbiased estimation of the population PK parameters.

The final model was a 1-compartment model with first-order absorption and IIV on CL and an additive (fixed) and proportional residual error. Interindividual variability of the clearance was high with 91%. Due to more than half of the samples being below the lower limit of quantification, it was not possible to conduct a proper covariate analysis. Nevertheless, allometric scaling had been implemented in the model with fixed exponents.

Overall, the final population PK model is able to describe the observed data and final parameter estimates were precisely estimated. An over-estimation of the IIV random effects was observed, which may be expected based on the limited experimental data available.

2.4.2.2. Pharmacodynamics

No specific studies have been performed to evaluate patient PD and/or PK/PD.

Sirolimus gel, 0.2% is a new formulation of sirolimus, designed to deliver targeted topical therapy for the treatment of angiofibroma (AF) in patients with tuberous sclerosis (TS). Sirolimus is a macrocyclic lactone fermentation product of *Streptomyces hygroscopicus* with mammalian target of rapamycin (mTOR) inhibitory action.

Pharmacodynamics (i.e. mechanism of action) of the sirolimus is described on data obtained from literature sources. This approach is considered in principle acceptable. However, Pharmacodynamic section of the proposed SmPC is not adequate and requires further amendments.

2.4.3. Discussion on clinical pharmacology

To describe the PK of sirolimus after topical application, a mix of own clinical data and literature data have been used. In addition, the applicant makes reference to the reference product Rapamune with regard to distribution, metabolism and elimination as well as drug-drug-interactions and PK in special populations of systemically absorbed sirolimus.

As a consequence, the PK data presented in section 5.2 of the SmPC are mainly in line with what is stated in the Rapamune SmPC, where applicable. This approach is considered acceptable, as no differences in PK could be reasonably expected between sirolimus from oral or topical administration once it reached the systemic circulation.

Different formulations have been used during clinical development and further changes to the formulation are proposed for the commercial product. Differences between formulations were judged by the Applicant to not change formulation characteristics. The justification provided is based on a comparison of quality attributes and assessed in the Quality part of this report.

The results of the provided clinical pharmacokinetic data obtained in clinical studies NPC-12G1-1, NPC-12G1-2, OSD-001-001 (patients with AF) and NPC-12G-4/US (healthy volunteers) have been cited above, these four studies were also the ones used to carry out exploratory population pharmacokinetic (PPK) analysis.

The study design of study OSD-001-001 ("Group Titration Study in Facial Skin Lesions Associated with Tuberous Sclerosis Complex to Estimate the Safety and Effective Dose of OSD-001 by a Placebo-controlled, Double-blind, Randomized, Parallel Group Design for Each Dose (Phase I/II)"), is described in the clinical part of this report. One of the secondary objectives was to assess the "presence or absence of transfer of sirolimus into the blood and the degree thereof". To do so "blood sirolimus concentration before the start of application (day 0), on the first day of application (1 h), and 2 weeks (0 h), 4 weeks (0 h), 8 weeks (0 h), and 12 weeks (0 h, 1 h) after the start of application as well as its time-course changes were evaluated."

Of note, the maximum applied daily dose was 375 mg of the gel ("3 pushes per day") which is less than the maximum applied dose in the pivotal study and its extension (NPC-12G-1 and NPC-12G-2), which was up to 800 mg, depending on the body surface area.

Regarding the results, the number of patients with detection of sirolimus blood concentration increased with increasing concentrations of the gel administered and detected concentrations tended to increase with increasing concentrations of the gel administered, especially in children.

The highest measured concentration was approximately 0.20 ng/ml and 0.25 ng/ml in adults and children, respectively.

Trough concentration seem not to differ markedly from concentrations at 1 h after treatment in week 12, which is in line with the results of studies NPC-12G-1 and NPC-12G-2 and NPC-12G-4 showing no obvious correlation between "sirolimus concentration vs. time after administration" (see assessment below).

The discussion on the potential impact of the measured sirolimus concentrations found in the pharmacokinetic studies is placed in the safety section below.

The design of the pivotal phase III study NPC-12G-1 ("A Phase 3 Study of NPC-12G Gel in Patients with Skin Lesions Associated with Tuberous Sclerosis Complex") is outlined in the clinical section of this Report. One of the secondary objectives was to assess the "sirolimus concentration in blood". To do so "the blood concentrations of sirolimus were measured by the method of LC/MS/MS at Baseline, 4 weeks and 12 weeks after the start of administration, and at the time of withdrawal."

The results of this study show that the mean and median sirolimus blood concentrations found at 4 and 12 weeks stayed below 0.3 ng/ml and maximum sirolimus blood concentrations at 4 and 12 weeks were approximately 0.5 ng/ml and 0.4 mg/ml in adults and children, respectively.

No clear trend regarding significant changes over time of sirolimus blood concentrations was seen; in addition, no clear relationship of sirolimus blood concentrations to the time after administration of the sirolimus gel was obvious.

During the procedure, the Applicant provided an assessment of sirolimus concentrations in study NPC-12G-1 by age categories of 3-5, 6-11, 12-18, and ⩾19 years. As expected, the sample size in the age categories 6-11 and 12-18 was rather small, limiting the informative value of these data. Patients aged 6-11 years had somewhat higher mean and median sirolimus concentrations than patients aged 12-18 years but concentrations comparable to patients aged ⩾19 years old. The data do not suggest an age-effect on systemic sirolimus concentrations, following topical treatment with sirolimus gel, 0.2% for children aged 6 years and older.

One of the secondary objectives of the long term extension study NPC-12G-2 (see clinical efficacy section) was to assess the sirolimus concentration in blood at baseline, at 12, 26, 39, and 52 weeks after the start of administration, and at the time of withdrawal. Notably, only 4 children in the age category 3 to 5 years have been included in the study population and therefore pharmacokinetic data in this study population is very limited. As structure and physiology of the skin and consequently its permeability for sirolimus could be reasonably expected to differ in very young children, the Applicant was asked to thoroughly justify the absence of PK data in the very young children below 3 years of age and the limited study population for the age range 3-6 years. The limited amount of paediatric patients below the age of 6 years is also generally of concern as further discussed in the efficacy and safety sections below. This issue is resolved further to the restriction of indication to patients aged 6 years and older.

Blood sirolimus concentrations were detected in 9 patients already at baseline, i.e., before the start of administration of NPC-12G gel. Two of the 9 patients used also oral sirolimus and 8 of the 9 patients additionally used oral everolimus.

Mean and median sirolimus blood concentrations found after administration of sirolimus gel stayed below approximately 0.3 ng/ml. Maximum sirolimus blood concentrations well above 1 ng/ml (up to 3.269 ng/ml) were seen in 9 patients. In these patients, concentrations did not markedly increase over time, rather a high intraindividual variability (fluctuating profile) was seen. At 52 weeks, no patient had sirolimus concentrations above 0.68 ng/ml (N=88). For two of the nine patients with sirolimus concentrations above 1 ng/ml, concomitant use of oral sirolimus was described which could clearly explain their higher systemic sirolimus concentrations. Regarding everolimus, the Applicant described that deethoxylation of the 40th position of the chemical structure generates sirolimus and cited

literature that reported that sirolimus (rapamycin) at a level of 3.0-5.2% of everolimus concentration was detected when everolimus 25 mg was given as single dose to patients. Therefore, everolimus use may also have contributed to the systemic sirolimus concentrations measured.

Based on an assessment of sirolimus concentrations in study NPC-12G-2 by age according to age categories of 3-5, 6-11, 12-18, and ⩾19 years, it is agreed that there is no apparent difference in mean/median sirolimus concentrations for children aged 6 years and older.

Based on an assessment of sirolimus concentrations in study NPC-12G-2 by age according to age categories of 3-5, 6-11, 12-18, and ⩾19 years, it is agreed that there is no apparent differences in mean/median sirolimus concentrations for children aged 6 years and older.

Study NPC-12G-4/US was a Phase 1, single centre, open-label, fixed-sequence, two-period, PK study in 12 healthy volunteers to compare systemic exposure following topical and oral dosing of sirolimus and to evaluate the safety and tolerability following topical dosing. This study was not designed to show bioequivalence, as bioequivalence would reasonably not be expected and is not intended - on the contrary, systemic levels of sirolimus are intended to be markedly decreased or even absent with the topical formulation.

The chosen dose of an 800 mg quantity weight of NPC-12G Gel 0.2% (1.6 mg of sirolimus) is higher than the proposed adult single dose of NPC-12G Gel 0.2% which is 400 mg (twice daily, however). Using a 800 mg single dose (the amount normally divided into 2 administrations in the morning and the evening) is regarded to be "closer to a worst case scenario" and acceptable to estimate maximal sirolimus concentrations expected after topical dosing of NPC-12G Gel 0.2%. Dosing of 2 mg the reference product oral Rapamune 2 mg tablets based on the US FDA recommended initial dose of sirolimus indicated for treatment of lymphangioleiomyomatosis (LAM) according to the CSR. This dose is in line with posology authorised in Europe and regarded acceptable for the intended comparison (comparison of bioavailability).

Blood samples were drawn prior to drug administration (pre-dose) and 0.5, 1, 2, 4, 6, 8, 12, 24 and 48 hours post-dose. The three blood concentrations values above the LLOQ were only slightly above the LLOQ and found after 12 and 24 hours post dose. As concentrations were never substantially above the LLOQ at any time point based on these results, it could be concluded that the timing of sirolimus concentration measurements in relation to administration is not critical, which is in line with the results for studies NPC12G-1 and NPC-12G-2. In these studies, based on the figures provided, no clear relationship of sirolimus blood concentrations to the time after administration of the sirolimus gel was obvious.

Systemic exposure to sirolimus following topical administration of NPC-12G Gel 0.2% was found to be far below that observed from oral administration of Rapamune 2 mg tablets in this study.

Sirolimus is extensively metabolised by the CYP3A4 isoenzyme, and it is a substrate for the multidrug efflux pump P-glycoprotein (P-gp). In addition, sirolimus has been shown to inhibit human liver microsomal cytochrome P450 CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 in vitro. In the light of the low systemic exposure after topical administration it is not expected that clinical relevant interactions will occur, but Hyftor should be used with caution in patients taking respective concomitant medications. Potential adverse reactions should be monitored and in case observed, treatment should be interrupted.

No interactions studies with Hyftor and oral contraceptives have been performed. Low systemic exposure to sirolimus during topical treatment with Hyftor makes pharmacokinetic drug interactions unlikely. The possibility of changes in the pharmacokinetics that might affect the efficacy of the oral contraceptive during long-term treatment with Hyftor cannot be fully excluded. For this reason,

patients should be advised to use non-hormonal contraceptive measures during treatment (see section 4.5 of the SmPC).

Regarding drug drug interaction (DDIs) with concomitant topical treatments, the results of the provided inter patient comparison are not considered adequate and as a consequence, Except for sunscreens, no other topical treatments should be used on the facial angiofibroma lesions while treatment with Hyftor is ongoing (see section 4.5 of the SmPC).

No new DDI studies have been performed and none are regarded necessary, as possible mechanism for drug interactions for sirolimus have been well described, e.g. in the SmPC of Rapamune.

In summary, the provided studies seem overall adequate to give a reasonable estimate of the maximal exposure to sirolimus that can be expected after topical administration. Although, with the sensitive bioanalytical methods developed, sirolimus can be measured in the systemic circulation after topical treatment with the sirolimus gel applied for, the serum concentrations are unsurprisingly much lower than after oral sirolimus intake.

Sirolimus concentrations after topical administration were found to be mostly below 1 ng/ml, values above 1 ng/ml have only been seen in the open label extension study NPC-12G-02. Whereas dose linearity could not be concluded based on the results of study NPC-12G-1, study data from NC-12G-2 indicated dose linearity with a flat dose-concentration relationship. Based on a visual comparison provided, no clear increase of sirolimus blood concentration in individual patients with concentrations above the LLOQ with increasing doses of sirolimus gel applied was observed. The Applicant hypothesised that most of these values in study NPC-12G-02 might be possibly explained by concomitant use of oral sirolimus and everolimus, which was further justified and seems plausible. When comparing the results of the different studies, it needs to be kept in mind that the study design and the study population is not completely comparable between studies: in study OSD-001-001 a different (lower) total dose was administered and in study NPC-12G-4/US a different dose (higher) was administered to healthy volunteers and not patients. Also, different formulations have been used (which seems acceptable, see Quality AR).

The safety aspects related to the sirolimus concentrations found in the study population are discussed in the safety section below.

Exploratory PPK analysis

An exploratory PPK analysis was carried out based on blood concentration data from four clinical studies (OSD-001-001, NPC-12G-1, NPC-12G-2, and 192003). the final population PK model is able to describe the observed data and final parameter estimates were precisely estimated. An over-estimation of the IIV random effects was observed, which may be expected based on the limited experimental data available.

2.4.4. Conclusions on clinical pharmacology

The provided studies seem overall adequate to give a reasonable estimate of the maximum exposure to sirolimus after topical administration. Regarding distribution, metabolism excretion, DDIs, PK in special populations and safety of systemically absorbed sirolimus, reference is made to data generated with the reference product Rapamune and to published literature. This is considered appropriate as no differences in PK could be reasonably expected between sirolimus from oral or topical administration once it reached the systemic circulation. In addition, the systemic exposure to sirolimus from the applied gel is much lower than that obtained from orally administered sirolimus, as shown in the comparative bioavailability study NPC-12G-4/US.

2.4.5. Clinical efficacy

The clinical data package to support efficacy of 0.2% sirolimus gel for the topical treatment of AF associated with TSC is based on the results of the pivotal study NPC-12G-1, long-term safety study NPC-12G-2 and dose finding study OSD-001-001.

NPC-12G-1 was a two-arm, randomized, placebo-controlled, 12-week study in 62 paediatric and adult patients with TSC who had facial angiofibromas and/or other cutaneous TSC associated lesions. This is considered to be the **pivotal study** for this application.

NPC-12G-2 was a single-arm study to primarily assess the long-term safety of NPC-12G in 94 paediatric and adult patients with AF associated with TSC (62 of which came from Study NPC-12G-1). All patients received NPC-12G 0.2% twice daily as topical application to angiofibromas. Efficacy was assessed as a secondary outcome.

OSD-001-001 was a phase I/II, randomised, placebo–controlled, parallel-group, double-blind dose escalation study in 36 paediatric and adult patients with AF associated with TSC.

All three clinical studies were performed in Japan, in a Japanese population with TSC.

Table 8 Tabular summary of studies contributing to the assessment of efficacy of Sirolimus Gel, 0.2%

Study ID	Study centres	Study start[1] and completion[2]	Study design, type of control Main inclusion criteria	Study and control drugs	Study objectives	Number of patients	Planned treatment duration	Results for primary endpoints
NPC-12G-1	9 Japanese centres		Randomised, parallel-group, double-blind Patients (≥3 years) with AF associated with TSC	Sirolimus gel, 0.2% Placebo	E, PK, S	S0.2: n=30 P: n=32	12 weeks	Composite AF response rate[3] (IRC): Sirolimus gel, 0.2% 60.0% vs 0% with placebo; p<0.001 (Wilcoxon rank sum test).
NPC-12G-2	10 Japanese centres		Long-term study; open-label, single-arm Patients (≥3 years) with AF associated with TSC	Sirolimus gel, 0.2%	E, PK, S	n=94	Until study completion or approval. Collection of efficacy data through W52	Composite AF improvement[3] (IRC): Week 12 composite AF improvement rate: 59% Week 52 composite AF improvement rate: 78%
OSD-001-001	1 Japanese centre		Randomised, parallel-group, double-blind Patients (3-65 years) with AF associated with TSC	Sirolimus gel, 0.05, 0.1, 0.2% Placebo	E, PK, S	S0.05: n=8 S0.1: n=8 S0.2: n=8 P: n=12	12 weeks	Composite AF improvement at 12 weeks: Shirley-Williams' multiple comparison test indicated significant differences between placebo and sirolimus 0.2% (p<0.001), 0.1% (p=0.028), and 0.05% (p=0.011).

Abbreviations: E= efficacy, IRC= independent review committee; PK= pharmacokinetics; S= safety

[1] First patient in

[2] Last patient last visit

[3] Including patients with composite AF improvement rated as markedly

2.4.5.1. Dose response study

Study OSD-001-001 was a single-centre, randomised, double-blind, placebo-controlled phase II study in patients aged 3 to 65 years with a definite diagnosis of TSC according to the Japanese Dermatological Association, who had ≥3 facial, red AF lesions ≥2 mm in diameter, and who were not suitable for or did not want to undergo laser therapy or surgery.

Three sirolimus concentrations were tested i.e. 0.05%, 0.1%, and 0.2%. The total planned sample size was 36, with 12 patients at each sirolimus concentration, with 2:1 randomisation to sirolimus or placebo for both adults and children. Patients were treated in a group titration design. At first, 6 adults were treated in the 0.05% group (2:1 randomisation to active drug or placebo). When the safety of the 0.05% concentration had been ascertained, the 0.1% concentration was applied to 6 adult patients (2:1 randomisation). If safety of the 0.1% concentration could be shown, the 0.2% adult cohort was opened (2:1 randomisation). Safety of each concentration was judged by the investigator on the basis of data up to 4 weeks after the start of treatment. In paediatric patients, the same dose escalation regimen was applied, but each concentration cohort was only opened after safety of this concentration had been shown in adult patients.

The primary endpoint was a composite endpoint of the degree of shrinkage and the change in redness of 3 AF target lesions at 12 weeks, compared with baseline. Change from baseline to 16 weeks in the primary endpoint, and changes in AF lesion volume and AF lesion redness were analysed as secondary endpoints. The tumour volume of 3 target lesions was calculated and redness of the 3 target lesions was estimated at baseline and week 12. The investigator or subinvestigator comprehensively assessed improvements in facial lesions, and the results were determined in accordance with 5 levels of markedly improved, moderately improved, mildly improved, unchanged, and exacerbated. All efficacy assessments were made by the investigator; central assessment was not in place.

Overall, 36 patients were included (18 adults, 18 paediatric patients). Demographics and baseline characteristics in the study OSD-001-001 were assessed separately for adult and paediatric patients. As for adult patients, most patients receiving sirolimus (75%) were female and half of the adult patients were affected by epilepsy. In paediatric patients receiving sirolimus, age range was 6-18 years. The majority (67%) of paediatric patients receiving sirolimus were female and 83% of patients were affected by epilepsy.

According to the exclusion criteria, treatment with sirolimus, everolimus (mTORC1 inhibitor), or temsirolimus (mTORC1 inhibitor) within 12 months before patient registration was not allowed.

Sirolimus gel applied to target AF lesions in the face BID for 12 weeks. Based on the application specifications (about 125 mg gel per 50 cm2 lesion surface; ≤3 pushes/day from the gel container), the total daily amount of sirolimus applied at dose concentrations of 0.05%, 0.1% and 0.2% was 0.19 mg, 0.38 mg, and 0.75 mg, respectively.

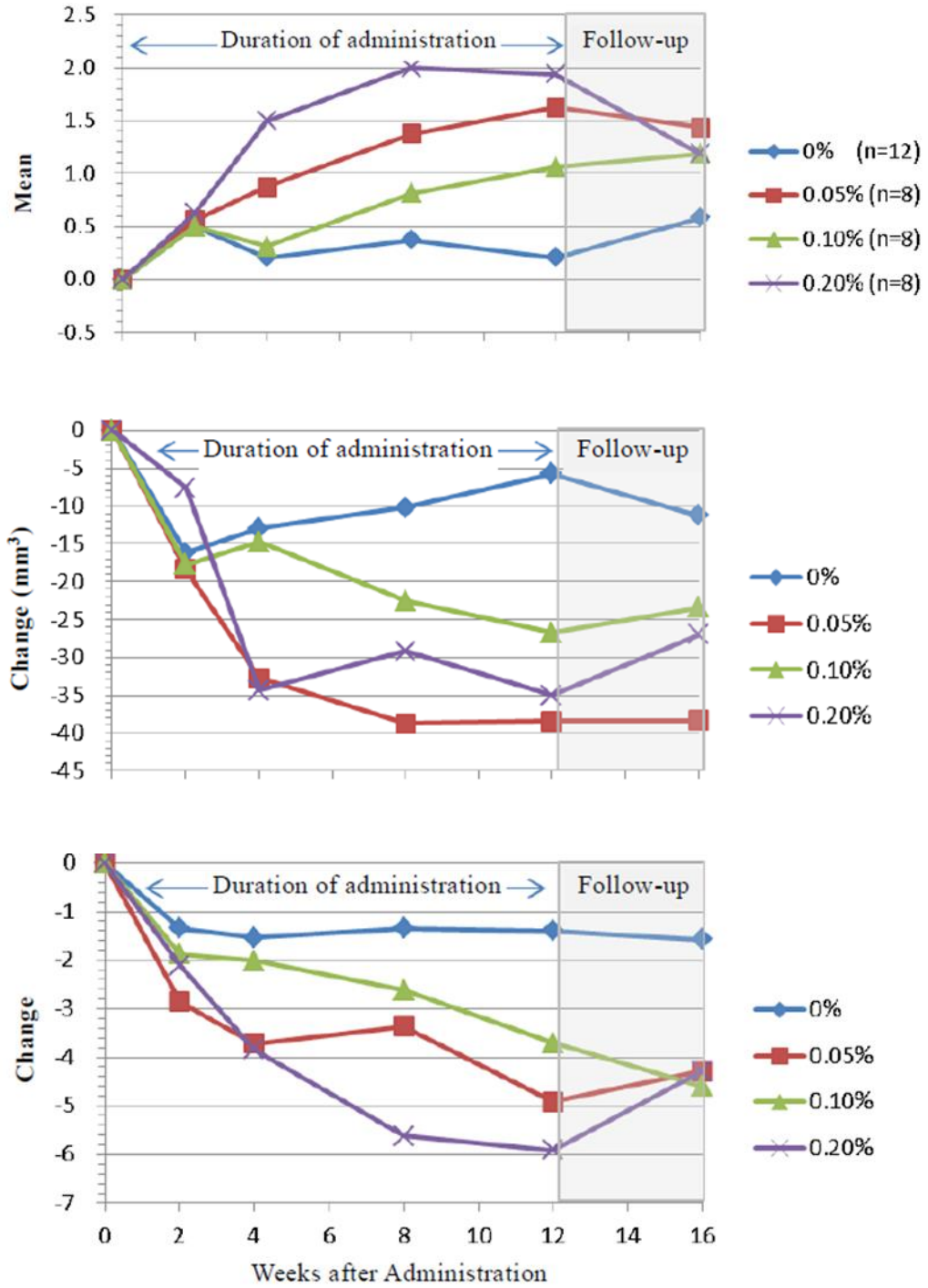
Results

Primary composite endpoint AF improvement at 12 weeks

More patients achieved numerically greater changes in composite AF improvement form baseline in the sirolimus than in the placebo groups. Differences vs.placebo were statistically significant in the sirolimus 0.05%, 0.2% and any dose group. Shirely-Williams' multiple comparison test indicated significant differences between placebo and sirolimus 0.2% ($p<0.001$), 0.1% ($p=0.028$) and 0.05% ($p=0.011$).

AF improvement at 16 weeks

Figure 6. Composite endpoint of AF improvement (top), change in AF lesion volume (middle), and change in AF redness score (bottom) over time; study OSD-001-001, efficacy population



Subgroup analysis–age

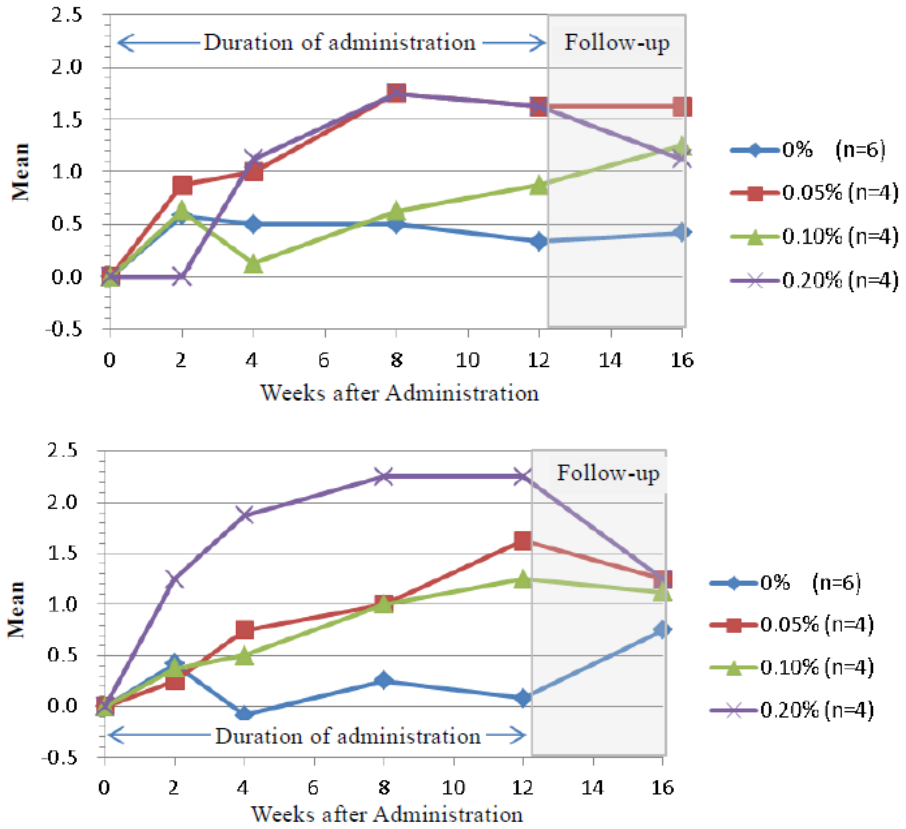
Composite AF improvement at 12 weeks

In adult patients, the distribution in composite AF improvement between sirolimus and placebo were statistically significant in the highest dose group (0.2%) and for sirolimus any dose, but not for sirolimus 0.05% or 0.1% (Wilcoxon test; p-value: 0.05% group, 0.090; 0.1% group, 0.310; 0.2% group, 0.048).

In paediatric patients, differences to placebo were statistically significant for all sirolimus dose groups and for sirolimus any dose. Shirley-Williams' multiple comparison test indicated significant differences between placebo and sirolimus 0.2% (p=0.003), 0.1% (p=0.036), and 0.05% (p=0.027).

Composite AF improvement at 16 weeks

Figure 7: Composite endpoint of AF improvement over time in adults (top) and paediatric patients (bottom); study OSD-001-001, efficacy population



The highest sirolimus dose (0.2%) tended to have the highest treatment effect on the endpoints of composite AF improvement, AF size improvement, and AF redness improvement, but the lowest dose (0.05%) did not systematically have the least effect. However, analyses were based on small patient numbers in each dose group, the study was not powered for these comparisons, and no multiplicity correction was implemented. Hence, results need to be interpreted with caution. Safety data suggested a dose relationship for events in the MedDRA system organ class of skin and subcutaneous tissue disorders as well as for the preferred term of dry skin and the incidence of drug-related AEs overall also increased with the dose. AEs were mild or moderate in intensity and were nonserious.

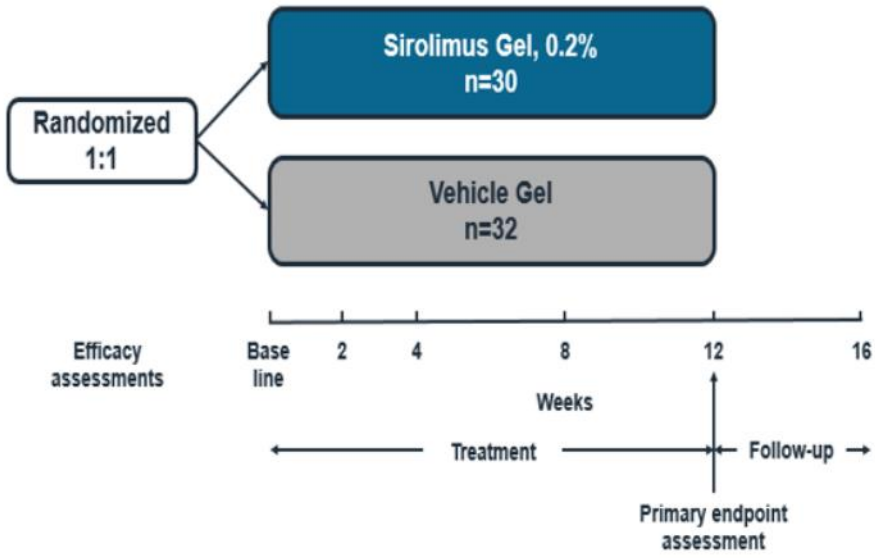
Based on the result of this phase I/II trial, the concentration of 0.2% sirolimus was chosen to be further investigated in phase III trials.

2.4.5.2. Main study

Study NPC-12G-1 (pivotal study): A Phase 3 study of NPC-12G gel in patients with skin lesions associated with tuberous sclerosis complex

Methods

This was a multicentre, randomised, double-blind, placebo-controlled study.



- **Study Participants**

Inclusion criteria	Exclusion Criteria
1) Male or female patients 3 years old or greater at the time of informed consent 2) Patients corresponding to "definite diagnosis" according to the diagnostic criteria for tuberous sclerosis complex (International Tuberous Sclerosis Complex Consensus Conference 2012, Appendix 1). 3) Patients with three or more reddish papules of angiofibroma (≥ 2 mm in diameter) on the face at screening tests 4) Patients who are not suitable for therapy with laser or surgery (including liquid nitrogen therapy and phototherapy) for angiofibroma, or who do not want therapy with laser or surgery 5) Patients who (or whose guardian) give a written informed consent in understanding and willingness after having received enough explanation regarding the study participation	1) Patients who (or whose guardian) are hard to apply the test drug topically with keeping compliance 2) Patients with clinical findings such as erosion, ulcer and eruption on or around the lesion of angiofibroma, which may affect assessment of safety or efficacy 3) Patients who are hard to be taken pictures of their lesions adequately in such cases that they may not follow instruction of stillness 4) Patients with a history of hypersensitivity to alcohol or allergy to sirolimus 5) Patients who have complications such as malignant tumor, infection, serious heart disease, hepatic function disorder, renal function disorder or blood disorders (selected by the investigator or subinvestigator [hereinafter referred to collectively as "investigator"] with reference to grade 2 or more serious disease defined in "Standards for Classification of Seriousness of Adverse Drug Reactions by Drugs etc. (Appendix 2)." 6) Patients who have complications such as diseases unsuitable for the trial participation, for examples, uncontrolled diabetes (fasting blood glucose level >140 mg/dL or postprandial blood glucose level > 200 mg/dL), dyslipidemia (cholesterol level > 300 mg/dL or > 7.75 mmol/L, triglycerides level > 300

	mg/dL or > 3.42 mmol/L), etc. 7) Patients who have taken drugs with mTOR inhibitory action (including sirolimus, everolimus or temsirolimus) within 12 months before the initial registration 8) Patients who have applied topical tacrolimus on the lesion of angiofibroma within 3 months before the initial registration 9) Patients who have received therapy with laser or surgery (including liquid nitrogen therapy and phototherapy) to the lesion of angiofibroma within 6 months before the initial registration 10) Female patients who are pregnant, may be pregnant, or are lactating 11) Patients who cannot agree to take appropriate measures of contraception until completion of the follow-up period or the follow up after withdrawal from informed consent 12) Patients who have participated in other clinical trial and have taken a trial drug within 6 months before the initial registration 13) Other patients who are considered by the investigator as unsuitable for participation in the trial

- **Treatments**

Aqueous gel containing 2 mg of sirolimus in 1 g (0.2% w/w) or a placebo gel that does not contain sirolimus and is indistinguishable from the test medicinal product in appearance, was evenly applied to lesions twice daily (in the morning and at bedtime). The study medication was first applied on angiofibroma lesions, followed by the application to lesions of hypomelanotic macule and plaque on the head.

The dose was 125 mg (approximately 0.5 to 1 cm as the length of gel extruded from the tube) per a lesion of 50 cm2, as a rough standard. Maximum acceptable daily dose was specified for each age range as shown in Table 9.

Table 9: Maximum Daily Dose and Maximum Number of Tubes to Dispense until Next Visit for Each Age Group

Age group	Standard body surface area (m^2)	Maximum daily dose (mg)	Maximum number of tubes to be dispensed for the interval until next visit (number of 10-mg tubes)
5 years and younger	< 0.8	400 (corresponds to approximately to 2 to 3 cm)	2
6 to 11 years	≥ 0.8 , < 1.3	600 (corresponds to approximately to 3 to 4 cm)	3
12 years and older	≥ 1.3	800 (corresponds to approximately to 4 to 5 cm)	4

For patients who strongly deviated from the BSA expected for their age group, the upper limit of dose was to be defined based on BSA instead of age.

Efficacy and safety assessments were performed at site visits which were performed **at baseline; at 4, 8, and 12 weeks** (on-treatment) **and 16 weeks** (i.e. after a 4-week treatment free period), as well as at premature discontinuation if applicable and feasible.

The duration of treatment (double-blind period) was 12 weeks (allowable duration: 11 to 13 weeks). Follow-up observation was performed 4 weeks after the end of the study medication (allowable duration: 3 to 5 weeks).

Protocol-defined discontinuation criteria were in place and included discontinuation in case of need for surgical treatment of AF and failure to apply study drug for ≥8 consecutive days. The protocol did not define allowed dose reductions or treatment interruptions.

- **Objectives**

Objective: To confirm the efficacy of NPC-12G gel for angiofibromas and evaluate its efficacy and safety for other types of skin lesions in patients with tuberous sclerosis complex.

Hypothesis: Superiority

- **Outcomes/endpoints**

Primary Efficacy Endpoint

The primary efficacy endpoint was the composite improvement in angiofibromas assessed using photographs by the IRC (Independent Review Committee on photograph assessment) at 12 weeks after the start of the study medication.

Secondary Endpoints

The following 7 items were the secondary efficacy endpoints.

The timing of the assessment was at baseline plus the following: 4 and 8 weeks after the start of the study medication and 4 weeks after the end of the study medication for item 1; and 4, 8, and 12 weeks after the start of the study medication and 4 weeks after the end of the study medication for items 2 to 7.

1. Composite improvement in angiofibromas assessed using photographs by the IRC

2. Composite improvement in angiofibromas assessed by the investigator

3. Improvement in the size of angiofibromas assessed by the IRC and the investigator

4. Improvement in the redness of angiofibromas assessed by the IRC and the investigator

5. Improvement in hypomelanotic macules and plaques on the head assessed by the IRC and the investigator

6. Proportion of patients assessed as "improved" or a better category in the primary endpoint and in secondary endpoints 1 to 5 (proportion of patients with improvement)

7. Change in total score from baseline for DLQI and CDLQI

The assessments were performed by reference to the Instructions for Completing Assessments of Efficacy Outcomes in Accordance with the Protocol Specified Assessment Criteria.

AF scoring criteria

The primary efficacy assessment was the composite AF improvement, based on criteria in Table 3.4.3.4-1, taking into account **changes in AF size and extension** (shrinkage, flattening, disappearance) and **changes in AF redness**. Exacerbation could be concluded based on changes in AF size/extension in conjunction with changes in AF redness. Consequently, the endpoint was considered as a **composite endpoint**.

The assessment of improvements in angiofibroma shall be performed as a global assessment taking the significance of the size of angiofibroma and that of redness into consideration depending on the symptoms of individual patients.

Table 10. Protocol-defined scoring criteria for primary endpoint of change in AF lesions from baseline, studies NPC-12G-1 and NPC-12G-2

Score	Degree of improvement	Criteria
3	Markedly improved	Shrinkage, flattening, or disappearance of tumours 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 tumours and a decrease in the intensity of redness are observed nearly overall. Or, disappearance of tumours and a large decrease in the intensity of redness is partially observed.
1	Slightly improved	Shrinkage or flattening of tumours and a 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 tumours.
-1	Slightly exacerbated	Enlargement or new formation of tumours and an 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 tumours is observed nearly overall, or a huge enlargement of tumours and an increase in the intensity of redness are partially observed. Or, more severe exacerbation is observed.

Overall: about ≥75% of the extent of the lesion at baseline

Nearly overall: about 50-75% of the extent of the lesion at baseline

Partially: about 25-50% of the extent of the lesion at baseline

Large decrease in intensity of redness: Change of ≥3 levels in redness in accordance with the Pantone® colour sample provided in the protocol

Decrease/increase in intensity of redness: Change of ≥2 levels redness in accordance with the Pantone® colour sample provided in the protocol

Slight decrease/increase in intensity of redness: Changes of 1 level in redness in accordance with the Pantone® colour sample provided in the protocol

For the assessment of redness, the Pantone colour scheme was used (Table 3.4.3.4-2). This was developed by Pantone LLC (New Jersey, US) as a proprietary colour space and standardised colour reproduction system, where colours are described by an allocated number. AF redness was assessed based on the Pantone colour scheme with a score from 1 (least intense redness) to 6 (most intense redness), where scores were 1 for Pantone 489C; 2 for Pantone 486C; 3 for Pantone 7416C; 4 for Pantone 485C; 5 for Pantone 704C; and 6 for tones darker than Pantone 704C.

Table 11. Appearance of redness in terms of the Pantone® color sample

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.

IFA assessment

During Scientific Advice meetings with European health authorities in 2019, it was pointed out that the assessment scale used for the primary efficacy endpoint in study NPC-12G-1 might not allow to quantify the magnitude of the treatment effect, notably because of a lack of baseline assessment. Thus, the relevance of the primary endpoint results was put into question.

Therefore, the original photographs of the AF lesions collected for each patient in study NPC-12G-1 were independently re-assessed, using the alternative Index for Facial Angiofibroma (IFA) scoring system, and the resultant data were analysed as a post-hoc analysis. No new photographs were taken. An Independent Evaluation Committee (IEC), which was different from the IRC previously mentioned re-evaluated all photographs. The IFA was not applied in studies NPC-12G-2 and OSD-001-001.

The IFA is an 8-item score to assess the size and redness of AF lesions. It was developed for a sponsor by a clinical expert from the Department of Paediatric Neurology and Developmental Medicine, University Children's Hospital Basel, Switzerland. The items and their scoring are shown in Table 13. The IFA total score is the sum of the item scores (or subscores); it can range between 0 and 20, with higher scores denoting more pronounced AF lesions (i.e. larger affected facial area, larger lesions, and darker/more visible lesions).

Table 12 IFA scoring system, study NPC-12G-1

Item	Score 0	Score 1	Score 2	Score 3	Maximum score
Erythema	None	Light red	Marked red	-	2
Redness of AF	None	Light red	Marked red	-	2
Extent of red AF of all affected areas	None	Sporadic	<50%	>50%	3
Diameter of largest AF	None	<3 mm	3-10 mm	>10 mm	3
Alarfacial groove affected	No	Yes	-	-	1
Nose	None	<50%	>50%	Cluster	3
Cheeks	None	<50%	>50%	Cluster	3
Chin	None	<50%	>50%	Cluster	3
Overall					20

- **Sample size**

The principal investigator of the study performed a mock assessment of the photographs to evaluate improvement as a post-hoc analysis, using the photographs of the lesions from 36 patients who participated in the 1/2 study (NPC-12G group, 24 patients; placebo group, 12 patients) at baseline and at 12 weeks after the start of the study medication. Using the result of the evaluation as reference, a distribution of patients for each degree of improvement was prepared. On the basis of this distribution, the numbers of child and adult patients were calculated by assuming randomized 1:1 ratio to active and placebo group, tested at two-sided significance level of 0.05, and improvement score as ordinal scale. As a result, the numbers of patients that would simultaneously fulfil a power $(1 - \beta) = 0.8$ by subgroup analysis were 17 patients in child and 21 patients in adult, respectively. Considering withdrawals or dropouts,20 patients in child and 25 patients in adult, total 45 patients were required.

Moreover, target sample size was set as 60 patients in total, to accumulate experiences in child subgroup as much as possible. For the primary endpoint of this study, the power in the whole study population (sum of adult and child subgroup) was not less than 0.99.

- **Randomisation and blinding (masking)**

Patients were randomised (1:1) to sirolimus gel, 0.2% or placebo.

Randomisation was performed by an allocation manager using the permuted block method, stratified by age (adults ≥19 years vs paediatric patients <19 years).

Blinding was achieved by using in combination with the placebo gel and the test drug that were indistinguishable in appearance (color, form, size, smell, surface texture of a material) and packaging (size, color, descriptions, print density, method of sticking labels, position of the seal).

- **Statistical methods**

Efficacy population: Patients with definitive registration, except those who had not received the study drug and those for whom no information had been obtained on efficacy after the start of administration, were treated as the full analysis set (FAS). In this trial, both the primary endpoint and the secondary endpoints were analysed in the FAS.

Safety population: All patients who had received the study drug were treated as the safety population (SP).

Primary efficacy endpoint: With respect to the composite improvement in angiofibroma assessed using photographs by the IRC at 12 weeks after the start of the study medication (or at the time of withdrawal), the NPC-12G and placebo groups were compared by Wilcoxon rank sum test.

Secondary endpoints:

Improvements in angiofibroma assessed using photographs by the central photo-judgment Committee: with respect to this parameter at the following assessment time points, the present drug and placebo were compared by the Wilcoxon rank sum test for the adults/children subgroups: 4 weeks after the start of administration (or at the time of withdrawal), 8 weeks after the start of administration (or at the time of withdrawal), 12 weeks after the start of administration (or at the time of withdrawal), and 4 weeks after the completion of administration.

Composite improvement in angiofibromas assessed by the investigator, Improvement in the size of angiofibromas assessed by the IRC and the investigator, Improvement in the redness of angiofibromas assessed by the IRC and the investigator, Improvement in hypomelanotic macules and plaques on the head assessed by the IRC and the investigator were compared by the same methods.

Verification of the correlation and consistency between the assessment by the IRC and the assessment by the investigator: With respect to the composite improvement of lesions of angiofibroma (including size and redness) and improvement in hypomelanotic macules and plaques of the upper neck, were performed by preparing a cross table for the IRC's result of assessment and the assessment by the investigator. The Kendall's coefficient of concordance and rank correlation coefficient were evaluated at each time point for the agreement.

"Proportion of Patients with Improvement" was defined as the proportion of patients assessed as "improved" or a better category ("improved" or "markedly improved"), and was calculated based on the improvement rated by the IRC and the investigator. With respect to the composite improvement of lesions as a whole and in the adults/children subgroups, the NPC-12G and placebo groups were compared by Fisher's exact test in the FAS. Data that "cannot be assessed" for improvement were treated as "no improvement" and were included in the data to be used for Fisher's exact test.

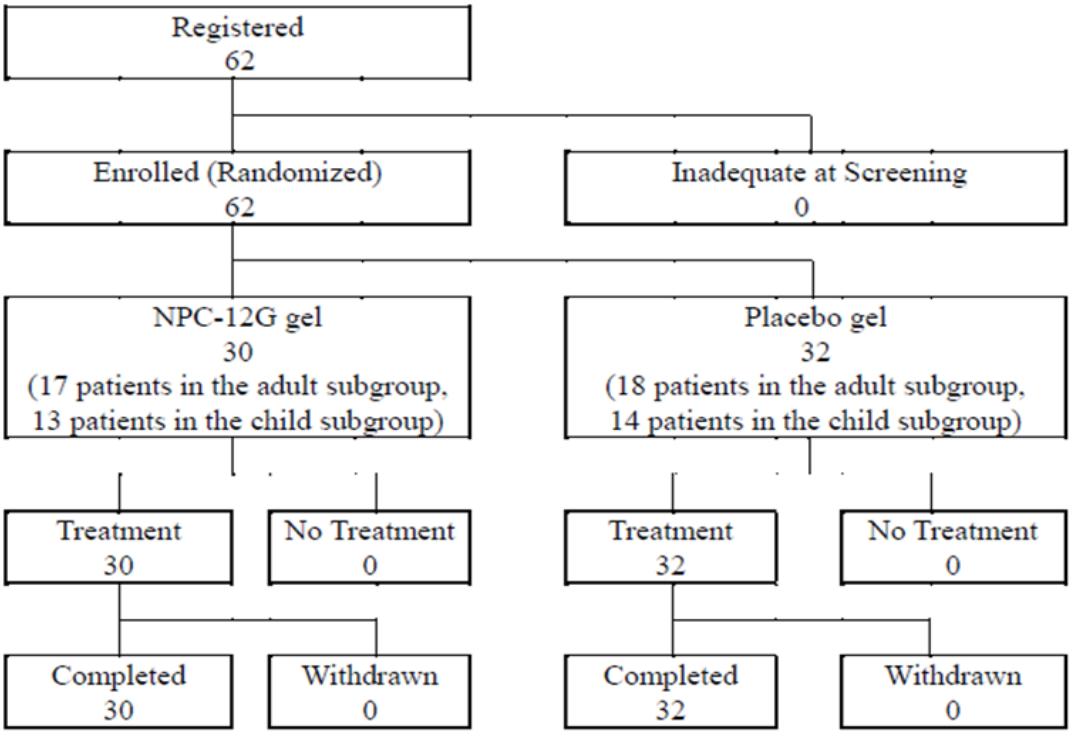
With respect to change from baseline in the total score of DLQI/CDLQI at the following assessment time points, the NPC-12G and placebo groups were compared by the Wilcoxon rank sum test in the FAS and for each of the subgroups of adults, children, those not younger than 16 years (assessed with DLQI), and those younger than 16 years (assessed with CDLQI).

With respect to change from baseline in each subscale score of DLQI at the following time assessment points, the NPC-12G and placebo groups were compared by the Wilcoxon rank sum test in the FAS as a whole and in each of the subgroups of adults and children (those not younger than 16 years and not older than 18 years).

The significance level α for the test of the endpoints of the efficacy and safety were two-sided 5%. No adjustment for multiplicity was performed. The confidence coefficient (1-α) for interval estimation was two-sided 95%.

Results

- **Participant flow**



- **Recruitment**
- **Conduct of the study**

Protocol V1.06 was provided together with the tables of Protocol Revisions. The major amendments in the clinical study protocol are shown in Table 13

Table 13. Major protocol amendments

Version	Points of Change	Before the change	After the change
1.03	Prohibited Concomitant Drugs/Prohibited Concomitant Therapies	· All study drugs other than those used in this trial · Drugs that inhibit mTOR (such as sirolimus, everolimus, and temsirolimus) · Use of tacrolimus ointment, topical steroids, topical antibacterial agents, topical vitamin D3 preparations on the site of application of the study drugs · Surgical treatment, laser treatment, phototherapy on the site of application of the study drugs	· All study drugs other than those used in this trial · Drugs that inhibit mTOR (such as sirolimus, everolimus, and temsirolimus) · Use of tacrolimus ointment, topical steroids, topical antibacterial agents, topical vitamin D3 preparations on the site of application of the study drugs · Use of adapalene, benzoyl peroxide, ibuprofen piconol, resorcin, zinc oxide/salicylic acid ointment on the site of application of the study drugs · Surgical treatment, laser treatment, phototherapy, and liquid nitrogen therapy on the site of application of the study drugs
1.04	Inclusion Criteria	4)Patients who are not suitable for therapy with laser or surgery for angiofibroma, or who do not want therapy with laser or surgery	4)Patients who are not suitable for therapy with laser or surgery (including liquid nitrogen therapy and phototherapy) for angiofibroma, or who do not want therapy with laser or surgery
	Exclusion Criteria	9) Patients who have received therapy with laser or surgery to the lesion of angiofibroma within 6 months before the initial registration	9) Patients who have received therapy with laser or surgery (including liquid nitrogen therapy and phototherapy) to the lesion of angiofibroma within 6 months before the initial registration

There were 35 protocol deviations reported, none of which led to an exclusion of patients from the per protocol analysis. GCP inspections were not reported.

- **Baseline data**

Table 14. Demographic and baseline characteristics:

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%)	

Data Source: Statistical Analysis Report; Table 14.1.3.

a) Fisher's exact test or t-test (α=0.15). b) Complication [Intellectual disabilities]: PT [Intellectual disabilities] [Severe mental retardation] [Autism]. c) Complication [epilepsy]: PT [Epilepsy] [Febrile convulsion] [Infantile spasms] [Seizure] [Status epilepticus]. Abbreviations: NA = Not applicable.

Table 15. Concomitant medications by ATC code reported in >10% of patients in any treatment group; study NPC-12G-1, FAS

ATC2 ATC4	Sirolimus gel, 0.2%	Placebo
Patients, n	30 (100.0)	32 (100.0)
Patients with at least 1 concomitant medication	28 (93.3)	27 (84.4)
Antiepileptics	21 (70.0)	15 (46.9)
Other antiepileptics	15 (50.0)	9 (28.1)
Carboxamide derivatives	10 (33.3)	10 (31.3)
Fatty acid derivatives	9 (30.0)	6 (18.8)
Benzodiazepine derivatives	9 (30.0)	7 (21.9)
Hydantoin derivatives	5 (16.7)	2 (6.3)

Barbiturates and derivatives	4 (13.3)	1 (3.1)
Emollients and protectives	16 (53.3)	8 (25.0)
Soft paraffin and fat products	12 (40.0)	3 (9.4)
Other emollients and protectives	5 (16.7)	5 (15.6)
Antihistamines for systemic use	6 (20.0)	5 (15.6)
Other antihistamines for systemic use	5 (16.7)	5 (15.6)
Analgesics	5 (16.7)	3 (9.4)
Anilides	4 (13.3)	3 (9.4)
Drugs for constipation	4 (13.3)	2 (6.3)
Corticosteroids, dermatological preparations	4 (13.3)	4 (12.5)
Ophthalmologicals	4 (13.3)	3 (9.4)
Antibacterials for systemic use	3 (10.0)	5 (15.6)
Third-generation cephalosporins	0	4 (12.5)
Antiinflammatory and antirheumatic products	1 (3.3)	4 (12.5)
Propionic acid derivatives	1 (3.3)	4 (12.5)
Cough and cold preparations	0	7 (21.9)
Mucolytics	0	6 (18.8)

Sorted by incidence in the sirolimus arm

Source data NPC-12G-1_TableConcMedication

Table 16. Prior medications by ATC2, ATC4 and Preferred Name - Safety Population

Table : Prior medications by ATC2, ATC4 and Preferred Name - Safety Population

ATC2 ATC4	NPC-12G (N=30) n (%)	Placebo (N=32) n (%)	Total (N=62) n (%)
Patients with at least 1 Prior medications	9 (30.0)	11 (34.4)	20 (32.3)
CARDIAC THERAPY	1 (3.3)		1 (1.6)
ANTIARRHYTHMICS, CLASS III	1 (3.3)		1 (1.6)
OTHER DERMATOLOGICAL PREPARATIONS	6 (20.0)	8 (25.0)	14 (22.6)
OTHER DERMATOLOGICALS	6 (20.0)	8 (25.0)	14 (22.6)
ANTINEOPLASTIC AGENTS	1 (3.3)	3 (9.4)	4 (6.5)
MAMMALIAN TARGET OF RAPAMYCIN (MTOR) KINASE INHIBITORS	1 (3.3)	3 (9.4)	4 (6.5)
ANTIEPILEPTICS	1 (3.3)		1 (1.6)
BENZODIAZEPINE DERIVATIVES	1 (3.3)		1 (1.6)
CONTRAST MEDIA	1 (3.3)		1 (1.6)
WATERSOLUBLE, NEPHROTROPIC, LOW OSMOLAR X-RAY CONTRAST MEDIA	1 (3.3)		1 (1.6)

In study NPC-12G-1, the treatment compliance rate (calculated on a weekly basis, as the number of doses during each period as confirmed by the patient diary, divided by the number of days in each period x 2 x 100%) for the overall study period was high and comparable between treatment groups (sirolimus gel, 0.2%: 96%; placebo: 98%).

- **Numbers analysed**

A total of 62 patients were enrolled and treated, including 30 patients receiving sirolimus gel, 0.2% and 32 patients receiving placebo. All patients were also included in the FAS. All patients were considered for the assessment of AF lesions.

Table 17. Number of Patients in Analysis Sets and Other Efficacy Populations for Analysis of Each Efficacy Measure

Analytical population	Group	Whole	Adult subgroup	Child subgroup
Safety population	NPC-12G	30	17	13
	Placebo	32	18	14
FAS	NPC-12G	30	17	13
	Placebo	32	18	14
Angiofibromas	NPC-12G	30	17	13
	Placebo	32	18	14
Hypomelanotic macules on the head	NPC-12G	4	1	3
	Placebo	5	0	5
Plaques on the head	NPC-12G	13	5	8
	Placebo	16	7	9
DLQI and CDLQI	NPC-12G	26	15	11
	Placebo	28	15	13

Data Source: Statistical Analysis Report; Table 14.1.3, Table 14.1.4, Table 14.2.1.1, Table 14.2.5.1, Table 14.2.5.2 and Table 14.2.15.1.

As a result of the case conference between Sponsor and clinical research organisation responsible for monitoring (intellim Corporation), the number of patients included in the analysis for hypomelanotic macules and the plaques on the head were 9 patients (4 patients in the NPC-12G group: 1 adult patient; 3 child patients, 5 patients in the placebo group: 0 adult patient; 5 child patients) and 29 patients (13 patients in the NPC-12G group: 5 adult patients; 8 child patients, 16 patients in the placebo group: 7 adult patients; 9 child patients), respectively. The number of patients included in evaluations of DLQI/CDLQI was 26 (15 adult patients; 11 child patients) for sirolimus gel, 0.2% and 28 for placebo (15 adult patients; 13 child patients).

- **Outcomes and estimation**

Primary endpoint: composite AF improvement at 12 weeks (IRC)

Table 18. Distribution of Patients for Each Degree of Composite Improvement in Angiofibromas at 12 Weeks After the Start of the Study Medication (assessed by IRC)

Categories	Groups	No. of Pts.	Markedly Improved	Improved	Slightly Improved	Unchanged	Slightly Exacerbated	Exacerbated	Not Evaluated	P-value [a)]
Whole	Sirolimus gel 0,2%	30	5(16.7)	13(43.3)	11(36.7)	1(3.3)	0(0.0)	0(0.0)	0(0.0)	P<0.001
	Placebo	32	0(0.0)	0(0.0)	5(15.6)	26(81.3)	0(0.0)	0(0.0)	1(3.1)	

Secondary Efficacy Results

Composite AF improvement over time (IRC)

Table 19. Composite endpoint score for AF improvement over time (IRC); study NPC-12G-1, FAS

	4 weeks		8 weeks		4 weeks after EOT	
	Sirolimus gel, 0.2%	**Placebo**	**Sirolimus gel, 0.2%**	**Placebo**	**Sirolimus gel, 0.2%**	**Placebo**
Patients, n (%)	30 (100.0)	32 (100.0)	30 (100.0)	32 (100.0)	30 (100.0)	32 (100.0)
Markedly improved	0 (0.0)	0 (0.0)	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Improved	6 (20.0)	0 (0.0)	10 (33.3)	0 (0.0)	3 (10.0)	0 (0.0)
Slightly improved	19 (63.3)	5 (15.6)	15 (50.0)	7 (21.9)	17 (56.7)	4 (12.5)
Unchanged	5 (16.7)	27 (84.4)	2 (6.7)	25 (78.1)	10 (33.3)	28 (87.5)
Slightly exacerbated	0 (0.0)	0 (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 (0.0)	0 (0.0)
Not evaluated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
p-value[1]	<0.001		<0.001		<0.001	

Abbreviation: EOT= end of treatment

[1] Wilcoxon rank sum test

Table 20. Rate of improvement in angiofibroma by treatment and visit (IRC); FAS

Popula -tion	Period	Group	No. of Pts.	Improvement rate*		Fisher's exact test
				No. of Pts. (%)	95%CI	
Whole	Week 4 or discontinuation	NPC-12G	30	6 (20.0%)	7.7 - 38.6	P=0.010
		Placebo	32	0 (0.0%)	0.0 - 10.9	
	Week 8 or discontinuation	NPC-12G	30	13 (43.3%)	25.5 - 62.6	P<0.001
		Placebo	32	0 (0.0%)	0.0 - 10.9	
	Week 12 or discontinuation	NPC-12G	30	18 (60.0%)	40.6 - 77.3	P<0.001
		Placebo	32	0 (0.0%)	0.0 - 10.9	
	Follow-up / End of Study	NPC-12G	30	3 (10.0%)	2.1 - 26.5	P=0.107
		Placebo	32	0 (0.0%)	0.0 - 10.9	
Adult	Week 4 or discontinuation	NPC-12G	17	4 (23.5%)	6.8 - 49.9	P=0.045
		Placebo	18	0 (0.0%)	0.0 - 18.5	
	Week 8 or discontinuation	NPC-12G	17	5 (29.4%)	10.3 - 56.0	P=0.019
		Placebo	18	0 (0.0%)	0.0 - 18.5	
	Week 12 or discontinuation	NPC-12G	17	7 (41.2%)	18.4 - 67.1	P=0.003
		Placebo	18	0 (0.0%)	0.0 - 18.5	
	Follow-up / End of Study	NPC-12G	17	2 (11.8%)	1.5 - 36.4	P=0.229
		Placebo	18	0 (0.0%)	0.0 - 18.5	
Child	Week 4 or discontinuation	NPC-12G	13	2 (15.4%)	1.9 - 45.5	P=0.222
		Placebo	14	0 (0.0%)	0.0 - 23.2	
	Week 8 or discontinuation	NPC-12G	13	8 (61.5%)	31.6 - 86.1	P<0.001
		Placebo	14	0 (0.0%)	0.0 - 23.2	
	Week 12 or discontinuation	NPC-12G	13	11 (84.6%)	54.6 - 98.1	P<0.001
		Placebo	14	0 (0.0%)	0.0 - 23.2	
	Follow-up / End of Study	NPC-12G	13	1 (7.7%)	0.2 - 36.0	P=0.481
		Placebo	14	0 (0.0%)	0.0 - 23.2	

*Improvement : Markedly Improved, improvement

Composite AF improvement over time (investigator)

Table 21. Distribution of improvement in angiofibroma by treatment and visit (Investigator) FAS

Population	period	Group	No. of Pts.	Markedly Improved (3)	Improvement (2)	Slightly improvement (1)	Unchanged (0)	Slightly Exacerbated (-1)	Exacerbated (-2)	Wilcoxon two-sample test
Whole	Week 4 or discontinuation	NPC-12G	30	1(3.3%)	3(10.0%)	13(43.3%)	13(43.3%)	0(0.0%)	0(0.0%)	P=0.012
		Placebo	32	1(3.1%)	2(6.3%)	4(12.5%)	25(78.1%)	0(0.0%)	0(0.0%)	
	Week 8 or discontinuation	NPC-12G	30	2(6.7%)	4(13.3%)	12(40.0%)	11(36.7%)	1(3.3%)	0(0.0%)	P=0.008
		Placebo	32	0(0.0%)	2(6.3%)	6(18.8%)	23(71.9%)	1(3.1%)	0(0.0%)	
	Week 12 or discontinuation	NPC-12G	30	3(10.0%)	4(13.3%)	14(46.7%)	9(30.0%)	0(0.0%)	0(0.0%)	P=0.002
		Placebo	32	1(3.1%)	1(3.1%)	8(25.0%)	22(68.8%)	0(0.0%)	0(0.0%)	
	Follow-up / End of Study	NPC-12G	30	2(6.7%)	2(6.7%)	12(40.0%)	14(46.7%)	0(0.0%)	0(0.0%)	P=0.014
		Placebo	32	1(3.1%)	1(3.1%)	5(15.6%)	25(78.1%)	0(0.0%)	0(0.0%)	
Adult	Week 4 or discontinuation	NPC-12G	17	1(5.9%)	1(5.9%)	6(35.3%)	9(52.9%)	0(0.0%)	0(0.0%)	P=0.572
		Placebo	18	1(5.6%)	2(11.1%)	3(16.7%)	12(66.7%)	0(0.0%)	0(0.0%)	
	Week 8 or discontinuation	NPC-12G	17	2(11.8%)	1(5.9%)	7(41.2%)	6(35.3%)	1(5.9%)	0(0.0%)	P=0.226
		Placebo	18	0(0.0%)	2(11.1%)	4(22.2%)	12(66.7%)	0(0.0%)	0(0.0%)	
	Week 12 or discontinuation	NPC-12G	17	2(11.8%)	2(11.8%)	9(52.9%)	4(23.5%)	0(0.0%)	0(0.0%)	P=0.039
		Placebo	18	1(5.6%)	1(5.6%)	5(27.8%)	11(61.1%)	0(0.0%)	0(0.0%)	
	Follow-up / End of Study	NPC-12G	17	2(11.8%)	1(5.9%)	5(29.4%)	9(52.9%)	0(0.0%)	0(0.0%)	P=0.266
		Placebo	18	1(5.6%)	1(5.6%)	3(16.7%)	13(72.2%)	0(0.0%)	0(0.0%)	
Child	Week 4 or discontinuation	NPC-12G	13	0(0.0%)	2(15.4%)	7(53.8%)	4(30.8%)	0(0.0%)	0(0.0%)	P=0.001
		Placebo	14	0(0.0%)	0(0.0%)	1(7.1%)	13(92.9%)	0(0.0%)	0(0.0%)	
	Week 8 or discontinuation	NPC-12G	13	0(0.0%)	3(23.1%)	5(38.5%)	5(38.5%)	0(0.0%)	0(0.0%)	P=0.008
		Placebo	14	0(0.0%)	0(0.0%)	2(14.3%)	11(78.6%)	1(7.1%)	0(0.0%)	
	Week 12 or discontinuation	NPC-12G	13	1(7.7%)	2(15.4%)	5(38.5%)	5(38.5%)	0(0.0%)	0(0.0%)	P=0.025
		Placebo	14	0(0.0%)	0(0.0%)	3(21.4%)	11(78.6%)	0(0.0%)	0(0.0%)	
	Follow-up / End of Study	NPC-12G	13	0(0.0%)	1(7.7%)	7(53.8%)	5(38.5%)	0(0.0%)	0(0.0%)	P=0.013
		Placebo	14	0(0.0%)	0(0.0%)	2(14.3%)	12(85.7%)	0(0.0%)	0(0.0%)	

Improvement in AF size

At Week 12, marked improvement or improvement was seen in 60% of patients receiving sirolimus gel, 0.2% vs 3% with placebo.

Based on investigator assessment, marked improvement or improvement in AF size at Week 12 was seen in 27% of patients receiving sirolimus gel, 0.2% vs 6% of the placebo patients.

The treatment difference was statistically significant.

Improvement in AF redness

At Week 12, marked improvement or improvement was seen in 40% of patients receiving sirolimus gel, 0.2% vs 0% with placebo.

Based on investigator assessment, marked improvement or improvement in AF redness at Week 12 was present in 23% of patients on sirolimus gel, 0.2% vs 3% on placebo. The treatment difference was statistically significant ($p<0.05$) at Week 8 but not at the other time points.

Proportion of patients with improvement in AF

Table 22. Proportion of Patients with Improvement in Angiofibroma (assessed by IRC)

Categories	Time	Groups	No. of Pts.	Improved [a)]	Non-improved [b)]	P-value [c)]
Whole	4W	NPC-12G	30	6(20.0)	24(80.0)	P=0.010
		Placebo	32	0(0.0)	32(100.0)	
	8W	NPC-12G	30	13(43.3)	17(56.7)	P<0.001
		Placebo	32	0(0.0)	32(100.0)	
	12W	NPC-12G	30	18(60.0)	12(40.0)	P<0.001
		Placebo	32	0(0.0)	32(100.0)	
	+4W	NPC-12G	30	3(10.0)	27(90.0)	P=0.107
		Placebo	32	0(0.0)	32(100.0)	
Adult subgroup	4W	NPC-12G	17	4(23.5)	13(76.5)	P=0.045
		Placebo	18	0(0.0)	18(100.0)	
	8W	NPC-12G	17	5(29.4)	12(70.6)	P=0.019
		Placebo	18	0(0.0)	18(100.0)	

	12W	NPC-12G	17	7(41.2)	10(58.8)	P=0.003
		Placebo	18	0(0.0)	18(100.0)	
	+4W	NPC-12G	17	2(11.8)	15(88.2)	P=0.229
		Placebo	18	0(0.0)	18(100.0)	
Child subgroup	4W	NPC-12G	13	2(15.4)	11(84.6)	P=0.222
		Placebo	14	0(0.0)	14(100.0)	
	8W	NPC-12G	13	8(61.5)	5(38.5)	P<0.001
		Placebo	14	0(0.0)	14(100.0)	
	12W	NPC-12G	13	11(84.6)	2(15.4)	P<0.001
		Placebo	14	0(0.0)	14(100.0)	
	+4W	NPC-12G	13	1(7.7)	12(92.3)	P=0.481
		Placebo	14	0(0.0)	14(100.0)	

a) Improved = Markedly Improved or Improved.
b) Non- improved = Slightly Improved, Unchanged, Slightly Exacerbated, Exacerbated or Not Evaluated.
c) Fisher's exact test.
Abbreviations: No. of Pts. = Number of Patients, Percentage are given in parentheses.
4W, 8W and 12W = 4, 8 and 12 weeks after the start of the study medication, respectively.
+4W = 4 weeks after the end of the study medication.

Based on investigator assessment, the proportions of patients (whole population) with improvement in angiofibromas in the NPC-12G group were 13.3% (4 of 30 patients), 20.0% (6 of 30 patients), 23.3% (7 of 30 patients) and 13.3% (4 of 30 patients) at 4, 8 and 12 weeks after the start of the study medication and 4 weeks after the end of the study medication, respectively, and the proportion of patients with improvement was the highest at 12 weeks after the start of the study medication. On the other hand, the proportions of patients with improvement in angiofibroma in the placebo group were 9.4% (3 of 32 patients), 6.3% (2 of 32 patients), 6.3% (2 of 32 patients) and 6.3% (2 of 32 patients) at 4, 8 and 12 weeks after the start of the study medication and 4 weeks after the end of the study medication, respectively. There were no significant differences between both groups at any time point.

Quality of life (QOL)

Mean baseline CDLQI total scores (sirolimus gel 0.2%: 1.2; placebo: 0.8) and DLQI total scores (2.1 vs 2.4) were low, leaving virtually no option for further improvement, and comparable between treatment groups. Changes from baseline to post-baseline time points in mean total scores were small (ranging between -1.1 and 0.6 overall). There were no relevant differences between sirolimus and placebo.

- **Ancillary analyses**

Concordance between IRC and investigator assessment of composite AF improvement

Kendall's coefficient of concordance was 0.72 at Week 4 (p<0.001), 0.75 at Week 8 (p<0.001), 0.70 at Week 12 (p<0.001), and 0.71 at 4 weeks after EOT (p<0.001) (Kendall 1955). Kendall's correlation coefficient was 0.42 at Week 4 (p<0.001), 0.46 at Week 8 (p<0.001), 0.37 at Week 12 (p=0.001), and 0.40 at 4 weeks after EOT (p=0.001), indicating moderate similarity of assessments between IRC and investigator (Kendall 1955).

Table 23: Consistency of the Assessments Between IRC and Investigator Regarding Composite Improvement in Angiofibromas

Time	No. of Pts.	The IRC-assessment	The assessment by the investigator						Correlation analysis [a]	Correlation analysis [b]
			Markedly Improved	Improved	Slightly Improved	Unchanged	Slightly Exacerbated	Exacerbated		
4W	62	Markedly Improved	0	0	0	0	0	0	W=0.72 P<0.001	T=0.42 P<0.001
		Improved	0	1	3	2	0	0		
		Slightly Improved	1	3	11	9	0	0		
		Unchanged	1	1	3	27	0	0		
		Slightly Exacerbated	0	0	0	0	0	0		
		Exacerbated	0	0	0	0	0	0		
		Not Evaluated	0	0	0	0	0	0		
8W	62	Markedly Improved	1	0	2	0	0	0	W=0.75 P<0.001	T=0.46 P<0.001
		Improved	1	3	3	3	0	0		
		Slightly Improved	0	2	9	11	0	0		
		Unchanged	0	1	4	20	2	0		
		Slightly Exacerbated	0	0	0	0	0	0		
		Exacerbated	0	0	0	0	0	0		
		Not Evaluated	0	0	0	0	0	0		
12W	62	Markedly Improved	2	0	2	1	0	0	W=0.70 P<0.001	T=0.37 P=0.001
		Improved	1	3	4	5	0	0		
		Slightly Improved	0	2	9	5	0	0		
		Unchanged	1	0	7	19	0	0		
		Slightly Exacerbated	0	0	0	0	0	0		
		Exacerbated	0	0	0	0	0	0		
		Not Evaluated	0	0	0	1	0	0		
+4W	62	Markedly Improved	0	0	0	0	0	0	W=0.71 P<0.001	T=0.40 P=0.001
		Improved	1	0	2	0	0	0		
		Slightly Improved	1	1	10	9	0	0		
		Unchanged	1	2	5	30	0	0		
		Slightly Exacerbated	0	0	0	0	0	0		
		Exacerbated	0	0	0	0	0	0		
		Not Evaluated	0	0	0	0	0	0		

Data Source: Statistical Analysis Report; Table 14.2.14.1.
a) W : the Kendall's coefficient of concordance.
b) T : the Kendall's rank correlation coefficient.
Abbreviations: No. of Pts. = Number of Patients.
4W, 8W and 12W = 4, 8 and 12 weeks after the start of the study medication, respectively.
+4W = 4 weeks after the end of the study medication.

Change in IFA total score from baseline

Table 24: IFA total score change from baseline by Wilcoxon rank sum test; FAS

	NPC-12G		Placebo	
	n	Mean (SD)	n	Mean (SD)
Baseline	30	12.1 (3.69)	32	9.9 (3.43)
Week 12	30	8.6 (4.32)	32	10.4 (3.62)
Change from baseline	30	-3.5 (2.50)	32	0.5 (1.63)
p-value[1]		<0.001		

[1] Wilcoxon rank sum test

There is a baseline imbalance of the IFA score between the treatment groups, with higher (more severe) scores in the NPC-12G group.

The IFA total score change was statistically significantly different between treatment and placebo (Wilcoxon test, without adjustment for baseline).

Subgroup analysis: Composite AF improvement (IRC) over time in patients aged 6-11 years, 12-17 years, and ⩾18 years

Table 25. Distribution of improvement in angiofibroma by treatment and visit (IRC) by age group; study NPC-12G-1

Age group	Time point	Group	n[1]	Markedly improved	Improved	Slightly improved	Unchanged	Slightly exacerbated	Exacerbated	Not evaluated	Wilcoxon p-value[2]	Stratified Wilcoxon p-value[3]
6-11 years	Week 4	Sirolimus	6	0	1 (16.7)	4 (66.7)	1 (16.7)	0	0	0	0.03251	<0.0001
		Placebo	6	0	0	1 (16.7)	5 (83.3)	0	0	0		
	Week 8	Sirolimus	6	0	3 (50.0)	3 (50.0)	0	0	0	0	0.00634	<0.0001
		Placebo	6	0	0	1 (16.7)	5 (83.3)	0	0	0		
	Week 12	Sirolimus	6	2 (33.3)	3 (50.0)	1 (16.7)	0	0	0	0	0.00430	<0.0001
		Placebo	6	0	0	1 (16.7)	5 (83.3)	0	0	0		
	4 weeks after EOT	Sirolimus	6	0	0	5 (83.3)	1 (16.7)	0	0	0	0.03409	<0.0001
		Placebo	6	0	0	1 (16.7)	5 (83.3)	0	0	0		
12-17 years	Week 4	Sirolimus	7	0	1 (14.3)	6 (85.7)	0	0	0	0	0.01617	
		Placebo	6	0	0	2 (33.3)	4 (66.7)	0	0	0		
	Week 8	Sirolimus	7	1 (14.3)	4 (57.1)	2 (28.6)	0	0	0	0	0.00865	
		Placebo	6	0	0	3 (50.0)	3 (50.0)	0	0	0		
	Week 12	Sirolimus	7	0	6 (85.7)	0	1 (14.3)	0	0	0	0.01039	
		Placebo	6	0	0	2 (33.3)	4 (66.7)	0	0	0		
	4 weeks after EOT	Sirolimus	7	0	1 (14.3)	4 (57.1)	2 (28.6)	0	0	0	0.17665	
		Placebo	6	0	0	2 (33.3)	4 (66.7)	0	0	0		
≥18 years	Week 4	Sirolimus	17	0	4 (23.5)	9 (52.9)	4 (23.5)	0	0	0	0.00005	
		Placebo	20	0	0	2 (10.0)	18 (90.0)	0	0	0		
	Week 8	Sirolimus	17	2 (11.8)	3 (17.6)	10 (58.8)	2 (11.8)	0	0	0	0.00001	
		Placebo	20	0	0	3 (15.0)	17 (85.0)	0	0	0		
	Week 12	Sirolimus	17	3 (17.6)	4 (23.5)	10 (58.8)	0	0	0	0	0.00000	
		Placebo	20	0	0	2 (10.0)	17 (85.0)	0	0	1 (5.0)		
	4 weeks after EOT	Sirolimus	17	0	2 (11.8)	8 (47.1)	7 (41.2)	0	0	0	0.00045	
		Placebo	20	0	0	1 (5.0)	19 (95.0)	0	0	0		

[1] Number of patients; [2] Wilcoxon 2-sample test; [3] Stratified Wilcoxon (Van Elteren) test

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Sirolimus gel, 0.2% led to a statistically significant composite AF improvement at 12 weeks compared with placebo, based on IRC assessment. The responder rate, defined as patients with marked improvement or improvement, was 60% vs 0%.

Based on investigator assessment, sirolimus gel, 0.2% led to a statistically significantly greater AF improvement at 12 weeks, compared with placebo (p=0.002 by Wilcoxon rank sum test) .Marked improvement or improvement was noted for 23% of patients receiving sirolimus gel, 0.2% and 6% of patients receiving placebo.

The mean IFA total score at baseline was 12.1 in the sirolimus gel, 0.2% group and 9.9 in the placebo group. Sirolimus treatment caused a mean decrease in IFA total score of -3.5 score points, vs an increase of 0.5 with placebo. The difference was highly statistically significant (p<0.001).

Table 26: Summary of Efficacy for trial NPC-12G-1

Title: A Phase 3 Study of NPC-12G Gel in Patients with Skin Lesions Associated with Tuberous Sclerosis Complex			
Study identifier	NPC-12G-1		
Design	Multicentre, randomised, double-blind, placebo-controlled, parallel-group Phase III study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Sirolimus gel, 0.2%		Sirolimus gel, 0.2% for 12 weeks n=30 patients randomised
	Placebo		Placebo gel for 12 weeks n=32 patients randomised
Endpoints and definitions	Primary: distribution of angiofibroma improvement	Composite AF improvement distribution at 12 weeks (IRC)	Distribution of angiofibroma improvement (defined by change in AF size, extension, and redness) according to the categories "markedly improved", "improved", "slightly improved", "unchanged", "slightly exacerbated", "exacerbated" at 12 weeks, compared with baseline, as assessed by an Independent Review Committee (IRC)
	Secondary: Composite angiofibroma improvement	Composite AF improvement at 12 weeks (IRC)	Proportion of patients reaching a change in angiofibroma (AF) size, extension, and redness of 'markedly improved' or 'improved' at 12 weeks, compared with baseline, as assessed by an Independent Review Committee (IRC)
	Secondary: Improvement in angiofibroma size	Improvement in AF size at 12 weeks (IRC)	Proportion of patients reaching a change in angiofibroma (AF) size or extension of 'markedly improved' or 'improved' at 12 weeks, compared with baseline, as assessed by an Independent Review Committee (IRC)
	Secondary: Improvement in angiofibroma redness	Improvement in AF redness at 12 weeks (IRC)	Proportion of patients reaching a change in angiofibroma (AF) redness of 'markedly improved' or 'improved' at 12 weeks, compared with baseline, as assessed by an Independent Review Committee (IRC)
	Other: Index for Facial Angiofibroma total score	IFA total score change from baseline to 12 weeks (IEC)	Change in IFA total score from baseline to Week 12, as assessed by an Independent Evaluation Committee (IEC)

	change from baseline		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS): all patients with definitive study registration who received study drug and had on-treatment efficacy data From baseline to Week 12		
Descriptive statistics and estimate variability	Treatment group	Sirolimus gel, 0.2%	Placebo
	Number of patients	30	32
	Primary: composite AF improvement distribution at 12 weeks (IRC)	Markedly improved 16.7% Improved 43.3% Slightly improved 36.7% Unchanged 3.3% Slightly exacerbated 0% Exacerbated 0% Not evaluated 0%	Markedly improved 0% Improved 0% Slightly improved 15.6% Unchanged 81.3% Slightly exacerbated 0% Exacerbated 0% Not evaluated 3.1%
	Secondary: Composite AF improvement at 12 weeks (IRC)	60% of patients (18/30)	0% of patients (0/32)
	Secondary: Improvement in AF size at 12 weeks (IRC)	60% of patients (18/30)	3% of patients (1/32)
	Secondary: Improvement in AF redness at 12 weeks (IRC)	40% of patients (12/30)	0% of patients (0/32)
	Other: IFA total score change from baseline to 12 weeks (IEC), mean	-3.5 score points	0.5 score points
	SD	2.50 score points	1.63 score points
Effect estimate per comparison	Primary: composite AF improvement distribution at 12 weeks (IRC)	Comparison groups	Sirolimus gel, 0.2% vs placebo
		p-value (Wilcoxon rank sum test)	<0.001
	Secondary: Composite AF improvement (IRC)	Comparison groups	Sirolimus gel, 0.2% vs placebo
		p-value (Wilcoxon rank sum test)	<0.001
	Secondary: Improvement in AF size (IRC)	Comparison groups	Sirolimus gel, 0.2% vs placebo
		p-value (Wilcoxon rank sum test)	<0.001
		Comparison groups	Sirolimus gel, 0.2% vs placebo

	Secondary: Improvement in AF redness (IRC)	p-value (Wilcoxon rank sum test)	<0.001
	Other: IFA total score change from baseline to 12 weeks (IEC)	Comparison groups	Sirolimus gel, 0.2% vs placebo
		p-value (Wilcoxon rank sum test)	<0.001
Notes	The endpoints were also analysed based on investigator assessment. These analyses are not presented above but generally showed similar results as analyses based on independent assessment. Additional analyses were done for time points other than Week 12, i.e. Weeks 4, 8, and 16 (i.e. 4 weeks after treatment discontinuation). These showed generally the same trends as the analysis at Week 12.		

2.4.5.3. Supportive study

Study NPC-12G-2 (long-term study)

A long-term study of NPC-12G gel in patients with skin lesions associated with tuberous sclerosis complex (NPC-12G-2 CSR)

Methods

This was a multicentre, open-label, single-arm study.

The target sample size was at least 80, which was determined based on feasibility considerations.

The study was intended to allow continued treatment of patients from study NPC-12G-1; accordingly, it allowed the inclusion of patients who wished to use or continue to use sirolimus gel and for whom sirolimus gel was intended or continuous use was considered appropriate as judged by the investigator. Patients missing >25% of the planned doses in study NPC-12G-1 for no valid reason were excluded.

All patients were treated with sirolimus gel, 0.2% BID at the same dose as in NPC-12G-1, with dosing generally defined as in NPC-12G-1.

Visits to the study site occurred at baseline, at 4-weekly intervals through to Week 26, and thereafter at 3-monthly intervals through to Month 12. Additional telephone visits were scheduled in the second half (Weeks 26-52) of the study through Month 12. Beyond 12 months, visits to the study centre occurred at 3-monthly intervals, with a telephone visit between on-site visits to check for AEs, status of study medication, and concomitant medication use.

Study Participants

Male or female patients aged ≥3 years with a definite diagnosis of TSC according to the diagnostic criteria of the International TSC Consensus Conference 2012, with AFs, hypomelanotic macules, or plaques associated with TSC on the head. Patients could roll over from study NPC-12G-1; recruitment of new patients was permitted. Patients who have complications such as diseases unsuitable for the trial participation, for example, uncontrolled diabetes (fasting blood glucose level >140 mg/dL or postprandial blood glucose level >200 mg/dL), dyslipidemia (cholesterol level >300 mg/dL or >7.75 mmol/L, triglycerides level >300 mg/dL or >3.42 mmol/L) were excluded from the study.

Treatments

All patients were treated with sirolimus gel, 0.2%, applied twice daily (at the same dose as in the Phase III study in roll over patients) to facial angiofibroma lesions, and hypomelanotic macules and plaques on the head (above the neck) twice daily (in the morning and at bedtime).

In non-roll over patients, and placebo treated roll-over patients, the dose to be administered is 125 mg (approximately 0.5 to 1 cm as the length of gel extruded from the tube) per affected skin area of 50 cm2, as a rough standard, and should not exceed the predefined maximum daily dose for each age group.

Study medication was to be continued until the completion of the study or approval, while it was prespecified that efficacy data would be collected through Week 52 only.

Objectives

To investigate the long-term safety and efficacy of NPC-12G gel for AF and other skin lesions associated with TSC and to continuously provide treatment for patients with no alternative treatments.

Outcomes/endpoints

Primary endpoints (safety)

1) Rate of treatment discontinuation due to adverse events (Kaplan-Meier curve)

2) Descriptions and incidences of adverse events leading to treatment discontinuation

Secondary efficacy endpoints

The following at 4, 8, 12, 26, 39, and 52 weeks after the start of administration:

1) Composite improvement in angiofibromas assessed by the Independent Review Committee on Photograph Assessment (IRC) and the investigator

2) Improvement in size of angiofibromas assessed by the IRC and the investigator

3) Improvement in redness of angiofibromas assessed by the IRC and the investigator

4) Improvement in hypomelanotic macules and plaques on the head (above the neck) assessed by the IRC and the investigator

5) Proportion of patients assessed as "improved" or a better category in the secondary efficacy endpoints 1 to 4 (improvement rate)

6) Change from baseline in total score of DLQI and CDLQI

The following at 12, 26, 39, and 52 weeks after the start of administration:

7) Patient satisfaction

Secondary safety endpoints

1) Adverse events and adverse drug reactions

2) Adverse events and adverse drug reactions leading to treatment interruption

3) Adverse drug reactions leading to treatment discontinuation

4) Serious adverse events and serious adverse drug reactions

5) Adverse events and adverse drug reactions leading to modification of dose or regimen

6) Significant adverse events and adverse drug reactions

7) Laboratory findings and vital signs

8) Sirolimus blood concentration (PK samples were taken at baseline, at Weeks 12, 26, 39, and 52, and at premature discontinuation).

Sample size

The targeted sample size for this study was at least 80 based on feasibility considerations.

Randomisation and blinding (masking)

This was an open-label, single-arm study.

Statistical methods

Efficacy Analysis Set: Patients with definitive registration, except those who did not receive the investigational product and those for whom no information was obtained on efficacy after the start of administration, were treated as the full analysis set (FAS). All efficacy endpoints in this study were analysed in the FAS.

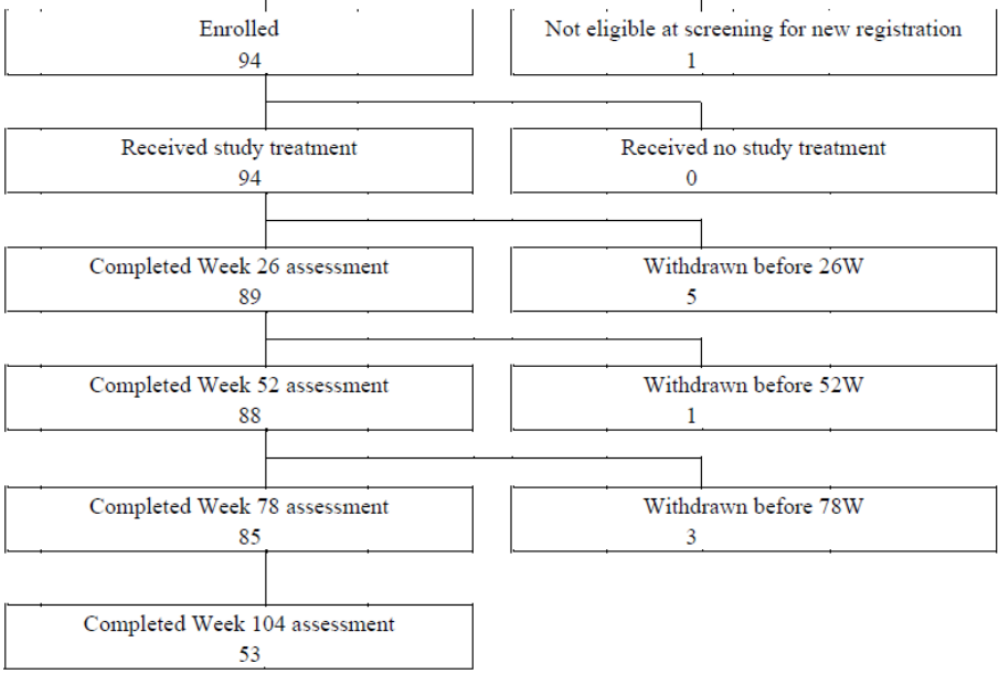
Safety Analysis Set: All patients who received the investigational product were treated as the safety population.

This uncontrolled study was descriptively evaluated.

Results

Participant flow

Registered	
Total	95
Patients from study NPC-12G-1	62
NPC-12G	30
Placebo	32
New registered patients	33



(Statistical Analysis Report, Figure 14.1.1)

Conduct of the study

Three versions of protocol have been submitted (Version number: 1.10 from June 2018 was the last version) together with comprehensible tables on Summary of changes in the protocol. The protocol amendments are acceptable. There were no significant protocol deviations that might have impacted the efficacy and safety of NPC-12G gel.

No information regarding GCP inspections was provided.

Baseline data

Table 27 Demographic and baseline characteristics; study NPC-12G-2, FAS

	Overall
Patients, n (%)	93 (100.0)
Sex	
Male	41 (44.1)
Female	52 (55.9)
Age, categorical	
3 to 5 years	4 (4.3)
6 to 11 years	22 (23.7)
12 to 18 years	24 (25.8)
≥19 years	43 (46.2)
Age [years], mean (SD)	20.9 (12.5)
Body weight [kg], mean (SD)	47.5 (17.0)
Genetic diagnosis of TSC, n (%)	4 (4.3)
Intellectual disability[1], n (%)	43 (46.2)
Epilepsy[2], n (%)	59 (63.4)

- [1] Including MedDRA preferred terms intellectual disability; severe mental retardation; trisomy 21; autism spectrum disorder
- [2] Including MedDRA preferred terms of epilepsy; febrile convulsion; infantile spasms; seizure; status epilepticus; and epileptic encephalopathy

Prior use of topical tacrolimus preparations was reported for 3 patients (3%), and prior use of systemic mTOR inhibitors was reported for 20% of patients.

Numbers analysed

Treated with the investigational product: 94

Included in the efficacy analysis set (full analysis set): 93 (adults: 43; children: 50)

Included in the safety population: 94 (adults: 44; children: 50)

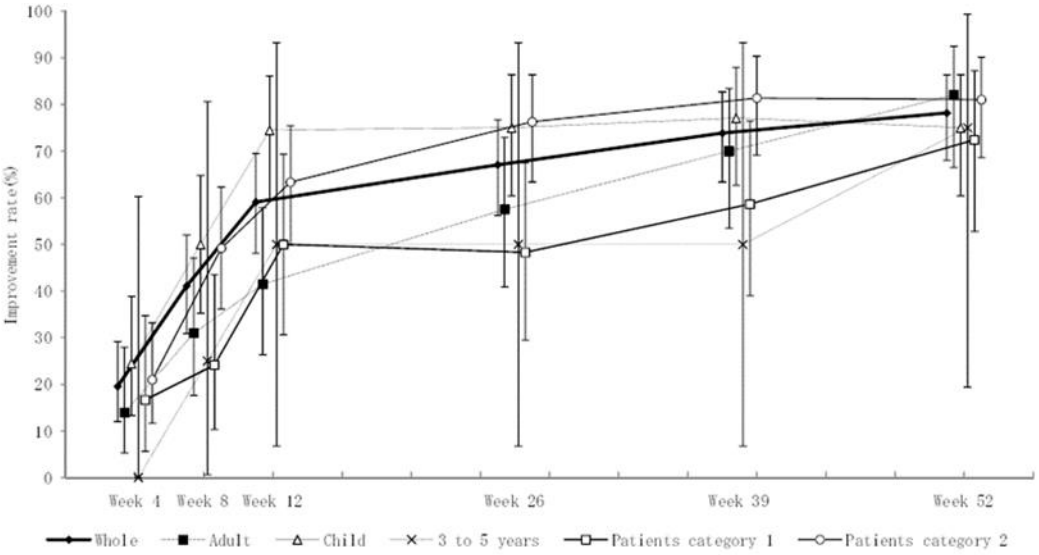
Outcomes and estimation

Efficacy Results

Composite AF improvement (IRC)

At Week 12, the assessment time point used in the Phase III study, the improvement rate (i.e. marked improvement or improvement) was 59.1%. Improvement continued over the assessment period, reaching 78.2% at 52 weeks. No exacerbations of AF were reported for any patient or time point.

Figure 8: Composite AF improvement rate (IRC) over time; study NPC-12G-2, FAS



Composite AF improvement (investigator)

At 12 weeks, the composite AF improvement rate (i.e. marked improvement or improvement) by investigator was 46.1%; at 52 weeks, it was 61%. This was lower than the IRC results of 59% and 78% at the same time points.

Improvement rate in AF (IRC) in the overall efficacy population at 4, 8, 12, 26, 39, and 52 weeks after the start of administration was 19.6% (18/92), 41.1% (37/90), 59.1% (52/88), 67.0% (59/88), 73.9% (65/88), and 78.2% (68/87), respectively.

In adults, the improvement rate was 14.0% (6/43), 31.0% (13/42), 41.5% (17/41), 57.5% (23/40), 70.0% (28/40), and 82.1% (32/39), respectively, and in children, the improvement rate was 24.5% (12/49), 50.0% (24/48), 74.5% (35/47), 75.0% (36/48), 77.1% (37/48), and 75.0% (36/48), respectively.

Improvement rate in AF as assessed by the investigator in overall efficacy population at 4, 8, 12, 26, 39, and 52 weeks after the start of administration was 22.0% (20/91), 28.9% (26/90), 46.1% (41/89), 48.9% (43/88), 54.5% (48/88), and 60.9% (53/87), respectively.

In adults, the improvement rate was 16.3% (7/43), 26.2% (11/42), 45.2% (19/42), 42.5% (17/40), 45.0% (18/40), and 53.8% (21/39), respectively, and in children, the improvement rate was 27.1% (13/48), 31.3% (15/48), 46.8% (22/47), 54.2% (26/48), 62.5% (30/48), and 66.7% (32/48), respectively.

Concordance between IRC and investigator assessment

Concordance of IRC and investigator assessments, as expressed by Kendall's coefficient of concordance, was moderate, with values of 0.68 at Week 4, 0.72 at Week 8, 0.68 at Week 12, 0.61 at Week 26, 0.64 at Week 39, and 0.68 at Week 52.

The mean total scores of DLQI and CDLQI were low at baseline (1.4 and 0.7, respectively), and the total scores at 4, 8, 12, 26, 39, and 52 weeks after the start of administration remained almost unchanged from the baseline.

2.4.5.4. Clinical studies in special populations

The age of the patients in the overall study population ranged from 3 to 61 years and according to the population PK model is considered that the results of the covariate analysis may give an indication that the volume in which the drug is distributed may be greater in children compared to adults.

Because of the low systemic exposure of sirolimus after topical administration, studies in renally or hepatically impaired patients have not been conducted for sirolimus gel (see discussion in section PK).

2.4.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

All efficacy evaluations supporting this MAA are presented on a per-study basis.

No pooling of data across studies was performed due to the different design of the AF studies, notably the differences in duration (12 weeks in NPC-12G-1 and OSD-001-001 vs long-term in NPC-12G-2) and dosing (sirolimus gel, 0.2% in NPC-12G-1 and NPC-12G-2 vs 3 dose levels [0.05%, 0.1%, 0.2%] in OSD-001-001).

2.4.6. Discussion on clinical efficacy

The applicant has submitted a marketing authorisation application (MAA) for sirolimus gel, 0.2% (Hyftor) as a hybrid application according to Article 10(3) of Directive 2001/83/EC intended for the treatment of angiofibroma associated with tuberous sclerosis complex. Of note, a paediatric investigation plan is not required for an MAA submitted as hybrid application.

The proposed reference medicinal product is Rapamune oral solution/oral tablet (EU/1/01/171). Although both products contain the same active substance, there is not actual demonstration of essential similarity. Rapamune is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant and for the treatment of patients with sporadic lymphangioleiomyomatosis (LAM) with moderate lung disease or declining lung function.

Hyftor does not fall within the strict definition of a generic medicinal product considering the fact that the pharmaceutical form and route of administration of Hyftor differ from the reference medicinal product. Therefore, (*in vivo*) bioequivalence with the reference product cannot be reasonably demonstrated. The very low systemic absorption of sirolimus from Hyftor has been confirmed in 3 studies measuring PK.

Since efficacy data for oral Rapamune are not relevant for the present application, an own clinical development programme has been presented for Hyftor.

Scientific bridge to the reference product

For MAAs under Article 10(3), an appropriate scientific bridge to the reference medicinal product needs to be established. The type and strength of the scientific bridge needed depends on the type and amount of data of the reference product referred to and is a matter of scientific assessment. If a PK bridge is considered necessary, the comparative PK study must use an EU-sourced reference product.

In the present MAA, the applicant makes reference to data of Rapamune regarding distribution, metabolism and excretion, as well as drug-drug-interactions, PK in special populations and safety of systemically absorbed sirolimus. Considering that the systemic exposure to sirolimus from the applied gel is much lower than that obtained from orally administered sirolimus and the comprehensive own clinical programme provided to support the different pharmaceutical form, route of administration and new indication, the comparative bioavailability study NPC-12G-4/US is not considered pivotal to establish a scientific bridge to the reference product.

The proposed indication has been restricted to patients aged 6 years and older in line with the CHMP recommendation and now reads as follows:

"Treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and children aged 6 years and older".

The applicant has conducted three clinical studies as part of a clinical development programme to support the Marketing Authorisation Application for 0.2% sirolimus gel for the topical treatment of AF associated with TSC; including phase I/II dose escalation study OSD-001-001 and two Phase III studies (NPC-12G-1 and NPC-12G-2). All three clinical studies were performed in Japan, in a Japanese population with TSC.

Ethnic effects might be mediated by differences in drug absorption and systemic distribution, metabolism, or excretion (ADME). However, sirolimus gel, 0.2% is administered topically and exerts its effect after dermal absorption directly in the AF lesions. There is no indication, however, that AF associated with TSC would differ in a relevant manner between European and Japanese patients. Further, the management of AF associated with TSC is based on the recommendations of the 2012 International TSC Consensus Conference which is globally accepted and generally the same across regions. Therefore, it is not expected that topical sirolimus would act differently in European than in Japanese patients. (See also "Reflection Paper on the Extrapolation of Results from Clinical Studies conducted outside the EU to the EU-population", EMEA/CHMP/EWP/692702/2008. This reflection paper indicates that in particular extrinsic factors, such as medical practice, disease definition and study population, may influence the applicability of foreign data to an EU setting. These factors are also identified in the ICH E5, which highlights the importance of this guideline in the planning of worldwide clinical studies). Also, ethnic differences are not expected to impact the AF scoring and evaluation.

In order to generate data in Caucasian population, the applicant has also conducted a phase I study in Caucasian healthy volunteers (NPC-12G-4/US) (n=12).

Dose response study (OSD-001-001)

Study OSD-001-001 was a single-centre, randomised, double-blind, placebo-controlled phase II study in patients aged 3 to 65 years with a definite diagnosis of TSC. Three sirolimus concentrations were tested (0.05%, 0.1%, and 0.2%).

For the assessment of efficacy, a slightly different composite score was used in this phase II study to that used in pivotal study and long-term safety study and all efficacy assessments were made by the investigator; central assessment was not in place.

Overall, 36 patients were included (18 adults, 18 paediatric patients). Demographics and baseline characteristics in the study OSD-001-001 were assessed separately for adult and paediatric patients.

However, the groups were not further investigated for numerical differences in the distribution of demographics or baseline characteristics given the small sample size overall and by dose group, which is acknowledged. However, total volume of the AF target lesions at baseline is presented (separately for adult and children population). Data suggest a trend towards greater AF target lesion volume in adults, but also a high variability in AF lesion volume between dose groups.

Dosing in study OSD-001-001 was defined based on previous clinical studies in AF using ointment or gel formulations prepared from sirolimus tablets.

According to results, sirolimus gel, 0.2% showed the best outcome regarding the composite AF improvement at Week 12. However, for improvement in AF lesion size, greatest improvement at 12 weeks was seen with the lowest dose of sirolimus 0.05%, although, with no clear separation between sirolimus 0.05% and 0.2% while both doses seemed to perform better than the 0.1% dose level. Improvement in AF redness over time appeared to be most pronounced with the 0.2% dose

concentration, although differences between sirolimus 0.2% and 0.05% at the 12-week readout time point were moderate. The applicant has clarified the reported findings and argued that the results of treatment with sirolimus 0.05% gel on lesion size were mainly driven by a single adult patient (P-006), who must be considered as an outlier in this study. The same evaluation omitting the outlier provides rather comparable results for the 0.05% dose group and the 0.1% dose group, and a higher effect for the 0.2% dose group, which appears to be more reasonable.

In a subgroup analysis according to age, treatment benefit of sirolimus gel over placebo was shown in adults as well as in paediatric patients.

In general, sirolimus led to a greater composite AF improvement than placebo, for the pooled sirolimus doses as well as for the individual dose levels, although statistical significance could not always be demonstrated. However, it should be noted the study was not powered for these comparisons, and multiplicity corrections were not performed. Therefore, results from statistical testing for dose comparison should be considered with caution.

The dose-finding program supporting the dose of 0.2% twice weekly in the pivotal study seems very limited however sufficient enough to support the selection of sirolimus 0.2% gel as the dose to be used for further evaluation in the Phase 2/3 study.

Main Study NPC-12G-1 (pivotal study)

This study was a multicenter, stratified, randomized (1:1), double-blind, placebo-controlled, comparative study, including patients aged ≥3 years with a definite diagnosis of TSC according to the diagnostic criteria of the International TSC Consensus Conference 2012, who had ≥3 facial, red AF lesions ≥2 mm in diameter, and who had not received prior laser therapy or surgery (including liquid nitrogen therapy and phototherapy); n= 62 (30 patients in the NPC-12G group and 32 patients in the placebo group). Patient eligibility in this study was generally determined based on the clinical TSC diagnostic criteria. The placebo-controlled design is considered adequate. Inclusion/exclusion criteria are considered overall acceptable.

As per protocol, only patients older than 3 years could have been included in the Study NPC-12G-1. However, no patients less than 6 years old were enrolled in this pivotal study. Paediatric patients accounted for 44% of the total trial population and were to similar proportions from age cohorts 6-11 years and 12-18 years. The condition of facial AF due to TSC increases with increasing age and is rarely present in very young children Therefore, it was obviously not possible to recruit patients < 6 years into study NPC-12G-1.

Since many patients enrolled in the pivotal study already had more advanced disease stages (including epilepsy), it is not clear why patients had to be off the systemic therapy with mTOR inhibitors for at least 12 months (see exclusion criterion 7). The reasons why this type of therapy was not allowed during the participation in this study was unclear. Concerning exclusion criteria No.7, it was not discussed whether the patient population proposed in the indication need a limitation in relation to concomitant use of systemic mTOR inhibitors particularly since many patients use oral mTOR inhibitors for the systemic treatment of the underlining disease (i.e. TSC).

The applicant clarified that concomitant use of systemic mTOR inhibitors was not permitted in the pivotal study NPC-12G-1 because the influence of oral mTOR inhibitor on the efficacy and safety evaluation of Hyftor should be excluded, but data on such concomitant use is available from the long-term study NPC-12G-2 and from post marketing surveillance. Overall, the impact of the concomitant administration of oral mTOR inhibitors (to a certain level) on both efficacy and safety in patients with facial angiofibroma who were treated with sirolimus gel cannot be completely ruled out. Nevertheless, this impact is not

considered clinically relevant to the extent to influence the overall benefit/risk ratio of the product. The applicant does not plan to make any claims regarding concomitant use in the labelling.

Application on the lesions of hypomelanotic macule and plaque on the head, in addition to AF lesion, was permitted. However, as noted by the applicant, the improvement of hypomelanotic macules on the head was unable to be adequately assessed because the number of patients evaluated was very small (n=9).

The dose of 125 mg (approximately 0.5 to 1 cm as the length of gel extruded from the tube; corresponding to approx. 0.25 mg sirolimus) per a lesion of 50 cm^2, as a rough standard, was applied to skin lesions associated with TSC (including AF). The maximum applied dose in the phase 3 trial was defined by age in conjunction with the assumed BSA, which is less in children compared to adults. The SmPC has been updated during the procedure to more clearly describe the maximum recommended daily dose, and the PIL revised to reflect the agreed recommendations in a more patient-friendly way than originally proposed.

The protocol-defined primary efficacy endpoint of the study is a composite endpoint of improvement in AF (improvement in AF size and AF redness), assessed by an IRC using photographs taken at 12 weeks after the start of treatment compared to baseline. Assessments were performed by investigators during site visits (at baseline; at 4, 8, and 12 weeks (on-treatment) and 16 weeks (i.e. after a 4-week treatment free period)), and additionally by an IRC based on patient photographs taken at the time of investigator assessments (the IRC assessments supported the primary endpoint analysis). Composite AF improvement (improvement in AF size and AF redness) as well as improvement in AF size and AF redness separately were assessed.

Both AF size and AF redness are considered clinically relevant signs of AF. Improvement was determined using a 6-point scale ranging from 'markedly improved' to 'exacerbated', compared to the patient's AF lesions at baseline. However, since this scale has not been validated and there is no prior experience of using this scale, there were some doubts as to the primary endpoint being adequately assessed and its relevance altogether.

Therefore, the photographs of the AF lesions collected for each patient were independently re-assessed, using the alternative Index for Facial Angiofibroma (IFA) scoring system, and the resulting data were analysed as a post-hoc analysis.

Of note, the scale used for efficacy assessment in studies NPC-12G-1 and NPC-12G-2 is different from the one used in the Phase I/II OSD-001-001 (which measured the volume of 3 target AFs quantitatively).

In the pivotal study, the assessment of the AF size was not done by measuring target AFs but was done by global assessment. Since the scale does not provide information on the "extent" of the lesions at baseline and post-treatment, there is a lack of information on the absolute change in the severity of AF. Furthermore, 3 target AF lesions may not necessarily represent the whole picture. Assessment of the AF redness in both the phase I/II and phase III study was done by the same method.

In published literature, the scales are reported, which try to characterise the AF lesion more quantitatively, e.g. the FASI (Facial Angiofibroma Severity Index), which has been validated. Nevertheless, there is still no gold standard of a scale for assessing AF.

For the primary endpoint, it was clarified that the scoring of efficacy assessment criteria is always based on the totality of facial angiofibromas, which were treated with the investigational product, not based on any single specific lesion. This holds true for the assessment of size and redness of angiofibromas as well as for the composite change in angiofibromas.

The information on intra-rater and inter-rater reliability were requested. For inter-rater reliability, the Applicant provided Kendall's coefficient of concordance, which shows reasonable agreement between the raters. Demonstration of W being significantly different from 0 does not add much, only showing that

there is any trend of agreement between raters which is a minimal requirement. Additional descriptive data on pairwise agreement between raters would have been more helpful. Intra-rater reliability could not be evaluated as the required data were not collected.

Altogether, the applicant's discussion on rationale for setting primary endpoint is acknowledged, both the size and the redness of a tumour are considered clinically important therapeutic indicators for AF, with the shrinkage of the size of AF representing an important therapeutic goal.

The primary endpoint is assessed at 12 Weeks after the start of therapy (the 12 Weeks is also the duration of the pivotal study). When reviewing the duration of studies from the published literature that reported efficacy /safety of topical mTOR inhibitors (including sirolimus), longer treatment duration such as 24 weeks have been reported. Furthermore, it is to be expected that a greater treatment response could be seen beyond week 12. This is evident from published literature, but also from the long-term safety study where AF improvement rate further increased until Week 52.

The QOL was assessed by version 9 of DLQI 7 or CDLQI 8. Considering a patient population with a high proportion of intellectual disability, it is possible that not all patients were fully able to comprehend the questionnaires and/or to express their perceived QOL. Furthermore, questions targeting on work or schooling activities, sports, or social activities were not fully applicable to some patients who were limited in their activities of daily living by e.g. epilepsy or paraplegy/tetraplegia. Angiofibromas are typically asymptomatic, but they can bleed, cause pruritus or pain. Therefore, e.g. the question "Over the last week, how itchy, sore, painful or stinging has your skin been?" might have not been relevant to many patients. It is considered that the DLQI/CDLQI questionnaire may not be an appropriate QOL instrument for TSC-related facial angiofibroma. It may not adequately capture the effect of the disease on QoL at baseline or a change from baseline in this patient population.

The safety assessment principally is acceptable. The Applicant additionally clarified that in study NPG-12G-1 no structured interview was performed to assess skin symptoms and local tolerability.

Sample size and statistical analysis

Target sample size was set as 60 patients in total, to accumulate experiences in child subgroup as much as possible. For the primary endpoint of this study, the power in the whole study population (sum of adult and child subgroup) was not less than 0.99.

The sample size calculation cannot be completely reconstructed from the applicant's description, however, the sample size proved to be sufficient. Overpowering to have sufficient data in important subgroups is also acceptable.

Restricting the FAS for primary analysis to patients with post-baseline data is generally not acceptable; however, this is no issue as no treated patients was excluded.

The Wilcoxon rank sum test is a valid non-parametric test for the null hypothesis that distributions of degrees in composite improvement in angiofibromas are equal in experimental and placebo group. However, it is not associated with an effect measure for the treatment effect, which hampers the assessment of the clinical relevance of the effect and the evaluation of uncertainty of estimation.

For secondary endpoints, also only non-parametric analyses not allowing a quantification of the treatment effect were provided.

No strategy to adjust for multiple testing was pre-specified such that only the primary analysis can be interpreted in a confirmatory way while all secondary analyses need to be considered as exploratory.

The randomisation was stratified by age (≤19 years, ≥ 19 years).

Replacing missing values by LOCF is generally not appropriate, however, all patients completed treatment and only one patient was not evaluable such that handling of missing/non-evaluable data has no influence on the conclusions (whereby it seems that missing data was not replaced by LOCF for this patient but a new degree 'not evaluable' was introduced).

The assessment of consistency across subgroups is also hampered by the lack of an effect measure to describe the size of the treatment effect.

Results

In terms of age, height, body weight, presence or absence of gene diagnosis, presence or absence of complication (intellectual capacity disorder), presence or absence of use of pretreatment drugs (mTOR inhibitors, topical tacrolimus), there were no relevant differences.

The treatment compliance rate (calculated on a weekly basis, as the number of doses during each period as confirmed by the patient diary, divided by the number of days in each period x 2 x 100%) for the overall study period was high and comparable between treatment groups (sirolimus gel, 0.2%: 96%; placebo: 98%).

The composite improvement in angiofibromas in the NPC-12G group at 12 Weeks were 16.7% (5 of 30 patients) in "markedly improved", 43.3% (13 of 30 patients) in "improved", 36.7% (11 of 30 patients) in "slightly improved", 3.3% (1 of 30 patients) in "unchanged", whereas the composite improvement in angiofibromas in the placebo group were 0% in both "markedly improved" and "improved", 15.6% (5 of 32 patients) in "slightly improved", 81.3% (26 of 32 patients) in "unchanged", 3.1% (1 of 32 patients) in "no evaluation".

The primary composite endpoint score for AF improvement at 12 weeks for sirolimus group was higher than for the placebo group (Wilcoxon rank sum test: P<0.001), which indicates superiority of sirolimus gel to placebo.. In addition, for assessment of clinical relevance, a responder analysis including the difference in response rates and corresponding exact 95% CI was provided (although without the requested 95% confidence interval CI for the difference in improvement rates between treatment groups but with the 95% CI for improvement rate by treatment group). However, the response rate by treatment arm is also sufficient for informing B/R and inclusion in SmPC. At week 12 compared to baseline in the treatment group 60% and in the placebo group 0% of the patients "markedly improved" or "improved" in regard to angiofibroma (p< 0.001). The response rate in children at week 12 was higher (84.6% vs. 0% [p<0.001]) than in adults (41.2% vs. 0% [p=0.003]), treatment group vs. placebo group each.

The protocol-defined composite endpoint score for AF improvement by IRC was reassessed for the age categories 6-11 years, 12-17 years, and ≥18 years, including an analysis using the Stratified Wilcoxon (Van Elteren) Test, as requested. There is a trend for greater response in the young children (6-11 years); 83.3% of them "markedly improved" or "improved" with sirolimus gel at week 12. In the age group 12-17 years the response rate was 71.4% and in adults the response rate was 41.1% with sirolimus gel. In the placebo group, the response rate was 0% each in the different age groups. The evaluation of consistency across subgroups is hampered by the small size of subgroups. Although no final conclusion is possible on this basis, results in subgroups are generally in line with the overall results.

Based on investigator assessment, sirolimus gel, 0.2% led to a statistically significantly greater AF improvement at 12 weeks, compared with placebo (p=0.002 by Wilcoxon rank sum test). At 12 weeks, marked improvement or improvement was noted for 23% of patients receiving sirolimus gel, 0.2% and 6% of patients receiving placebo. At least slight improvement was found in 70% and 31% of patients, respectively.

At 4 weeks, marked improvement or improvement was noted for 13% of sirolimus patients and 9% of placebo patients. At least slight improvement was found in 56% and 22%, respectively. At 16 weeks,

marked improvement or improvement was noted for 13% of sirolimus patients and 6% of placebo patients. At least slight improvement was found in 53% and 22%, respectively. The treatment difference was statistically significant at all assessment timepoints.

Of note, the investigators concluded lower improvement rates with sirolimus gel, 0.2% than the IRC. Marked improvement or improvement with sirolimus gel, 0.2% was recorded by the IRC in 20%, 43%, 60%, and 10% of patients at Weeks 4, 8, 12, and 16, compared with 13%, 20%, 23%, and 13% of patients according to investigator judgement. At least slight improvement at these time points was determined for 83%, 93%, 97%, and 67% of patients by the IRC and for 57%, 60%, 70%, and 53% of patients, respectively, by investigator judgement.

Furthermore, there is a more pronounced placebo effect based on investigator assessment: Based on IRC review, placebo response rates (marked improvement or improvement) were 0% each at 4, 8, 12, and 16 weeks. This compared with 9%, 6%, 6%, and 6%, respectively, based on investigator assessment.

The Applicant was requested to summarize the outcomes from the three independent assessments (investigator, IRC and IEC) and present information assessing the consistency between the evaluations of the three independent teams, Tables summarising the three different assessments (investigator, IRC and IEC) and comparing the consistency of all assessments teams using the FASI and IFA scoring systems evaluated by the Kendall's coefficient of concordance and the Kendall's rank correlation coefficient were provided and the results further discussed. According to the Applicant the weaker results for Kendall' s correlation coefficient T, indicating weak or moderate association between assessments, are impacted by the outliers (defined as a discrepancy in the assessment by $\geqslant$2 ranks) that appeared in the comparison between investigators and the IRC. The similarity between the improvement rates of AF at Week 12 between Investigator and IRC have been evaluated and, while the IRC assessment is statistically significant, a non-statistically significant result is shown in the evaluations made by the Investigator.

Kendall's coefficient of concordance and Kendall's correlation coefficient do not show high agreement between IRC and investigators. The reported discrepancy between IRC and investigator assessment was explained by a different method of assessment between IRC and investigator. Since investigators evaluated AF lesions while assessing the patient at the clinical site in comparison with baseline photos (while IRC was entirely based on photos), the investigators' assessment may have been impacted by light and/or weather conditions or also the failure of paediatric patients or patients with intellectual disability to remain still during the assessments, leading to discrepancies between IRC and investigator assessments.

Comparisons of in situ assessment with previously taken pictures (Investigator assessment) may be more unreliable than comparison of pictures taken under standardized conditions (IRC assessment).

Overall, even if the differences in the assessment by different teams as explained by the applicant are acknowledged, it is somehow striking that assessment by the investigator are generally less favourable. Nevertheless, the effect size is still considered meaningful.

Mean baseline CDLQI total scores (sirolimus gel 0.2%: 1.2; placebo: 0.8) and DLQI total scores (2.1 vs 2.4) were already low. Changes from baseline to post-baseline time points in mean total scores were also small (ranging between -1.1 and 0.6 overall). Therefore, no improvement in QoL could be seen. As discussed previously, the choice of questionnaire used was most likely not appropriate for this condition and patient population studied.

Based on efficacy results by age at 12 week in study NPC-12G-1, paediatric patients receiving sirolimus gel, 0.2% had a greater improvement rate than adults at Week 12 for composite AF improvement and

improvement in AF size. No relevant difference between adult and paediatric patients was seen for improvement in AF redness.

In addition, the composite, or global, AF improvement at week 12 is primarily in correlation with AF size but not with AF redness.

Based on efficacy results by sex at 12 week, a slight trend for males receiving sirolimus to benefit more from treatment than females could be seen for composite AF improvement and improvement in AF size.

Post-Hoc Efficacy Assessments

Since critical issues have been identified regarding the instrument for assessing the primary efficacy endpoint in the pivotal study (that was neither validated nor there was any prior experience of using this scale in earlier studies, and is only based on the relative change from baseline rather the absolute change), the applicant decided to conduct a post-hoc efficacy analysis in addition using the Index for Facial Angiofibroma (IFA) scoring system. Despite the fact that for the assessment of AF lesions, the FASI has been proposed and validated, the applicant decided to use IFA justifying this with the argument that smaller changes are difficult to detect with the FASI. The IFA uses a scaling of 20 points, therefore smaller changes can be objectified, the focus is based on the angiogenic component of the facial angiofibromas, which causes redness and hypervascularisation of the angiofibromas as well as the skin (erythema). Red cheeks and "red dots" on facial skin are typically the first visible signs of AF in patients, and the patients complain about these symptoms, while the fibrotic component of AF generally grows more slowly. Further, the angiogenic component of AF typically responds better and faster to treatment than the fibrotic component of AF.

However, this IFA scoring system is also not validated, nor used in any clinical studies, it is actually developed for the sponsor itself. In addition, it was not a pre-specified endpoint but developed and used post-hoc such that the analysis needs to be considered as highly exploratory.

Overall, the results of this additional analysis of the photographs of AF lesions using the alternative IFA score showed consistency with the results of the protocol-defined primary composite endpoint score. Patients treated with sirolimus gel achieved a significantly greater change from baseline to Week 12 in mean total IFA score than patients receiving placebo. Furthermore, the results were consistent across subgroups, including adult patients and paediatric patients. Despite an imbalance in baseline IFA score between the treatment groups, indicating more severe disease in the NPC-12G group in comparison to placebo, the treatment effect of NPC-12G is clear as is the treatment benefit when compared to placebo.

Study NPC-12G-2 (long-term study)

This was a multicentre, open-label, single-arm study, including patients aged ≥3 years with a definite diagnosis of TSC according to the diagnostic criteria of the International TSC Consensus Conference 2012 with AFs, hypomelanotic macules, or plaques associated with TSC on the head. Patients could roll over from study NPC-12G-1 and recruitment of new patients was permitted.

Per protocol, the patients with uncontrolled diabetes (fasting blood glucose level >140 mg/dL or postprandial blood glucose level >200 mg/dL) or dyslipidemia (cholesterol level >300 mg/dL or >7.75 mmol/L, triglycerides level >300 mg/dL or >3.42 mmol/L), were excluded from the long–term study (NPC-12G-2). Furthermore, the use of the reference medicinal product Rapamune has been associated with increased serum cholesterol and triglycerides that may require treatment and monitoring for hyperlipidaemia using laboratory tests is required. Regardless of the low systemic exposure after the local application of sirolimus gel, given that the systemic effect cannot be excluded, the applicant was asked to include specific wording on the use of Hyftor in patients with hyperlipidaemia.

The primary objective of the study NPC-12G-2 was to investigate the long-term safety.

Actually, the same efficacy endpoints as in the phase 3 pivotal study were selected for this study. AF improvement was assessed in studies NPC-12G-1 and NPC-12G-2 in the same manner.

The long-term efficacy of NPC-12G (sirolimus) gel was also investigated.

Results

In contrast to the placebo-controlled trial (12G-1), 4 patients (4.3%) enrolled in 12G-2 were 3-5 years of age. The concomitant use of mTOR inhibitors was not prohibited, the concomitant use of topical tacrolimus preparations was reported for 3 patients (3%) and use of systemic mTOR inhibitors was reported for 20% of patients. Evidence to support concomitant use of oral mTOR inhibitors is very limited.

The mean treatment compliance rate in patients overall was 99%. Although due to adverse events there had been missed some applications, the treatment compliance can be considered as high.

Improvement rate in AF (as assessed by the IRC) in the overall efficacy population at 4, 8, 12, 26, 39, and 52 weeks after the start of administration was 19.6% (18/92), 41.1% (37/90), 59.1% (52/88), 67.0% (59/88), 73.9% (65/88), and 78.2% (68/87), respectively. Thus, a continuous increase over time is observed.

The improvement rate increased until week 52 for adults, but not for children, where it stayed relatively the same from the week 12 onwards. The results suggest that it takes longer to reverse larger long-standing lesions but that even those lesions are responsive to topical treatment with sirolimus.

Improvement rate in AF as assessed by the investigator in overall efficacy population at 4, 8, 12, 26, 39, and 52 weeks after the start of administration was 22.0% (20/91), 28.9% (26/90), 46.1% (41/89), 48.9% (43/88), 54.5% (48/88), and 60.9% (53/87), respectively, with an increase over time.

A discrepancy between IRC and investigator assessment is also seen here as in the pivotal study; the investigators concluded lower improvement rates with sirolimus gel, 0.2% than the IRC at every measured time point. Nevertheless, the improvements are considered clinically relevant with both assessments.

The mean total scores of DLQI and CDLQI were low at baseline (1.4 and 0.7, respectively), and the total scores at 4, 8, 12, 26, 39, and 52 weeks after the start of administration remained almost unchanged from the baseline. Thus, topic sirolimus treatment for at least 52 weeks did not affect QoL.

Of note, AF clinical studies did not include patients above 65 years of age to determine whether they will respond differently to sirolimus gel than younger patients. However, current published clinical experience does not suggest any specific problems that would limit the usefulness of sirolimus topical gel in the elderly.

Wording of the indication

During the Protocol Assistance with EMA in 2018, the applicant proposed an indication excluding children under the age of 3. In the present MAA, however, the applicant initially proposed the use of the sirolimus 0.2% gel without age limit. Currently, there are insufficient data available that would justify inclusion of patients below the age of 6 years. Therefore, the applicant has included an age limit for paediatric population and added "facial" to "angiofibroma" in the revised indication.

The new revised indication reads:

Hyftor is indicated for the treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older.

2.4.7. Conclusions on clinical efficacy

The application is based on pivotal evidence from a single randomized, placebo-controlled trial supported by a long-term (safety) study (plus a Phase 1/2 dose escalation study).

The pivotal study NPC-12G-1 and the long-term study NPC-12G-2 both investigated a single dose of sirolimus gel, 0.2%. Sirolimus gel, 0.2% achieved a statistically significant and clinically relevant improvement of AF lesions compared to placebo in terms of composite AF improvement, improvement in AF size, and improvement in AF redness. The primary composite endpoint score for AF improvement at 12 weeks for sirolimus group was higher than for the placebo group (Wilcoxon rank sum test: $P<0.001$), which indicates superiority of sirolimus gel to placebo. Furthermore, a responder analysis, defined as the percentage of patients who "markedly improved" and "improved" additionally reported, shows that at week 12 compared to baseline in the treatment group 60% and in the placebo group 0% of the patients "markedly improved" or "improved" in regard to angiofibroma ($p< 0.001$). The response rate in children at week 12 was even higher (84.6% vs. 0% [$p<0.001$]) than in adults (41.2% vs. 0% [$p=0.003$]), treatment group vs. placebo group each.

In study NPC-12G-2, overall AF improvement over baseline could be shown to a degree that was comparable to that in study NPC-12G-1, with continued improvement for up to 52 weeks.

The investigators' assessment, however, led to lower improvement rates with sirolimus gel, 0.2% than the primary IRC's assessment, the potential reasons of which have been outlined by the applicant but cannot be verified. Nevertheless, even the results obtained with the investigators' assessment are still considered clinically relevant.

2.4.8. Clinical safety

Four clinical studies have been performed with sirolimus gel, 0.2% in the AF development programme. Study NPC-12G-1, a randomised, placebo-controlled Phase III study, provides main safety data for sirolimus gel, 0.2%. Study NPC-12G-2 was an uncontrolled, open-label long-term study in patients who had completed study NPC-12G-1 (both sirolimus and placebo group) and 32 newly recruited patients. Study OSD-001-001 was a dose escalation study in AF patients and provides information on possible dose effects of sirolimus gel. All studies in AF patients were performed in Japanese patients. All 3 AF studies included adult and paediatric patients. Safety information is also available from a Phase I study NPC-12G-4/US in Caucasian healthy volunteers.

Across studies, **148 AF patients and 12 healthy** volunteers have been exposed to sirolimus gel. The total number of unique AF patients, however, is lower: all patients from study NPC-12G-1 rolled after study completion over to NPC-12G-2, and furthermore, due to lack of unique identifying information, it was not possible to track the number of patients from study OSD-001-001 through enrolment into other studies (it is assumed that the patients from OSD-001-001 eventually also participated in NPC-12G-1 and NPC-12G-2).

Sirolimus gel is also developed in neurofibromatosis type 1 (NF1). An investigator-initiated, randomised, double-blind, placebo-controlled Phase II study (OSD-001-003) and investigator-initiated, randomised, double-blind, placebo-controlled Phase II/III study (OSD-001-004) have been completed, while a Phase III, long-term safety study (NPC-12G-5) has been terminated.

2.4.8.1. Patient exposure

In studies NPC-12G-1 and NPC-12G-2, exposure was assessed in terms of treatment duration (i.e. from the first to the last application of study medication) as well as total gel amount used.

In study OSD-001-001, exposure was assessed in terms of treatment duration.

	Patients enrolled	*Patients exposed*	*Patients exposed to the proposed dose range*	*Patients with long term safety data*
Placebo-controlled	36 (OSD-001-001) 62 (NPC-12G-1) 82 (Total*)	24 (OSD-001-001) 30 (NPC-12G-1) 49 (Total**)	8 (OSD-001-001) 30 (NPC-12G-1) 37 (Total***)	0
Active - controlled	0	0	0	0
Open studies	94	94	94	89
Post marketing	871	871	871	681
Compassio-nate use	0	0	0	0

* With 16 patients in study NPC-12G1-1 that rolled over from study OSD-001-001
** With 5 patients in study NPC-12G1-1 that rolled over from study OSD-001-001
** With 1 patient in study NPC-12G1-1 that rolled over from study OSD-001-001

Study NPC-12G-1

All 62 patients in the study received at least one application of study drug (Table 3.8-1).

Mean (SD) treatment duration was 87.1 (3.5) days in the sirolimus gel, 0.2% group and 86.1 (4.1) days in the placebo group.

Based on a dose concentration of 0.2%, the mean gel amounts correspond to 0.12 g sirolimus administered in patients overall over a 12-week period, and 0.13 g and 0.11 g, respectively, in adult and paediatric patients.

Study NPC-12G-2

All 94 patients received at least one application of study medication (Table 3.8-2).

Mean treatment duration was 731 days (about 2 years). It was somewhat shorter in adults (682 days, or about 1.9 years) than in paediatric patients (774 days, or about 2.1 years). The longest treatment duration was 933 days in adults (2.6 years) and 951 days in paediatric patients (2.6 years).

The mean total gel amount was 346 g for patients overall; it was highly similar between adult patients (341 g) and paediatric patients (350 g). This corresponds to 0.69 g sirolimus (adults: 0.68 g, paediatric patients: 0.70 g).

Study OSD-001-001

All 36 patients received at least one application of study drug.

Overall mean treatment duration was 85 days, with no relevant differences seen between dose levels or age groups.

2.4.8.2. Adverse events

Table 28. Overall summary of adverse events; studies NPC-12G-1, NPC-12G-2, OSD-001-001, safety population

	NPC-12G-1		NPC-12G-2	OSD-001-001			
	S0.2%	**PBO**	**S0.2%**	**PBO**	**S0.05%**	**S0.1%**	**S0.2%**
Patients, n	30	32	94	12	8	8	8
Patients with…							
Any AE	27 (90.0)	22 (68.8)	92 (97.9)	7 (58.3)	6 (75.0)	7 (87.5)	7 (87.5)
Related AE	22 (73.3)	15 (46.9)	72 (76.6)	3 (25.0)	3 (37.5)	4 (50.0)	7 (87.5)
SAE	1 (3.3)	0	9 (9.6)	1 (8.3)	0	0	1 (12.5)
Related SAEs	1 (3.3)	0	0	0	0	0	0
AE leading to death	0	0	0	0	0	0	0
AE leading to disc.	0	0	2 (2.1)	0	0	0	0
Mild AEs	19 (63.3)	20 (62.5)	40 (42.6)	3 (25.0)	3 (37.5)	4 (50.0)	4 (50.0)
Moderate AEs	8 (26.7)	2 (6.3)	46 (48.9)	4 (33.3)	3 (37.5)	3 (37.5)	2 (25.0)
Severe AEs	0	0	6 (6.4)	0	0	0	1 (12.5)
Skin irritation AEs	24 (80.0)	15 (46.9)	80 (85.1)	NR	NR	NR	NR

Abbreviations: disc.= discontinuation; NR= not reported; PBO= placebo; S= sirolimus

Of note, NPC-12G-2 was a long term study with up to 2 years mean treatment duration, while the other 2 studies had planned durations of 12 weeks each. Therefore, comparison of AE incidences across studies should be done carefully.

Study NPC-12G-1

In the study NPC-12G-1 the incidence of AEs was 90% in patients treated with sirolimus gel, 0.2%, vs 69% in patients treated with placebo. The most frequent (>10%) AEs by preferred term in patients treated with sirolimus gel, 0.2% were dry skin and application site irritation (each 37%), followed by pruritus (23%). Incidences of these events tended to be higher with sirolimus than with placebo, although the high incidence of application site irritation in the placebo group of 28% (vs 37% with sirolimus) was reported.

No severe AEs were reported in study NPC-12G-1; all adverse events were mild (63% for sirolimus 0.2% and placebo each) or moderate (27% for sirolimus 0.2%, vs 6% for placebo). The pattern of AEs of moderate intensity AEs in the sirolimus group was reflective of the overall AE profile. No AE of moderate intensity by preferred term was reported in >1 patient in the sirolimus arm.

Drug-related AEs were reported in 73.3% of patients receiving sirolimus gel, 0.2%, vs 46.9% of patients on placebo. The most frequent (>10%) drug-related AEs in patients receiving sirolimus gel, 0.2% were dry skin and application site irritation (36.7% each), followed by pruritus (16.7%).

Of note, 28.1% of patients in the placebo group had application site irritation judged as being drug-related.

Table 29. Drug-related adverse events; study NPC-12G-1, safety population

	Sirolimus gel, 0.2%	Placebo
Patients, n	30	32
Patients with events, n (%)	22 (73.3)	15 (46.9)
Skin and subcutaneous tissue disorders	16 (53.3)	7 (21.9)
Dry skin	11 (36.7)	4 (12.5)
Pruritus	5 (16.7)	4 (12.5)
Acne	2 (6.7)	0
Dermatitis acneiform	1 (3.3)	0
Skin irritation	1 (3.3)	0
Asteatosis	1 (3.3)	0
Skin haemorrhage	1 (3.3)	0
General disorders and administration site conditions	11 (36.7)	10 (31.3)
Application site irritation	11 (36.7)	9 (28.1)
Feeling abnormal	0	1 (3.1)
Eye disorders	2 (6.7)	2 (6.3)
Eye irritation	1 (3.3)	2 (6.3)
Ocular hyperaemia	1 (3.3)	0
Gastrointestinal disorders	1 (3.3)	0
Pancreatitis acute	1 (3.3)	0
Renal and urinary disorders	1 (3.3)	0
Proteinuria	1 (3.3)	0
Infections and infestations	0	1 (3.1)
Sinusitis	0	1 (3.1)
Nervous system disorders	0	1 (3.1)
Paraesthesia	0	1 (3.1)
Injury, poisoning and procedural complications	0	1 (3.1)
Skin abrasion	0	1 (3.1)

Sorted by incidence in the sirolimus arm

Source data: NPC-12G-1 CSR, Table 14.3.2.3

Study NPC-12G-2

The most frequent (>20%) AE by preferred term was nasopharyngitis (52%), followed by dry skin (37%), acne (35%), application site irritation (31%), and influenza (22%).

Severe AEs were reported in 6% of patients, with preferred terms of pneumonia mycoplasmal, loss of consciousness, brain oedema, pneumothorax, therapeutic embolisation, and corpus callosotomy reported in one patient each.

Moderate intensity AEs were reported in 49% of patients. The most frequent (>10%) moderate AEs were nasopharyngitis (19%), influenza (14%), dry skin (12%), and acne (11%).

The most frequent (>10%) drug related AEs were application site irritation (31%), dry skin (28%), and acne (20%).

Table 30. Drug-related adverse events; study NPC-12G-2, safety population

	Sirolimus gel, 0.2%
Patients, n	94
Patients with events, n (%)	72 (76.6)
Skin and subcutaneous tissue disorders	60 (63.8)
Dry skin	26 (27.7)
Acne	19 (20.2)
Pruritus	8 (8.5)
Erythema	7 (7.4)
Dermatitis acneiform	6 (6.4)
Dermatitis contact	5 (5.3)
Dermatitis	2 (2.1)
Dermal cyst	1 (1.1)
Photosensitivity reaction	1 (1.1)
Skin exfoliation	1 (1.1)
Urticaria	1 (1.1)
Skin haemorrhage	1 (1.1)
Eczema	1 (1.1)
Papule	1 (1.1)
Rash	1 (1.1)
Rash pruritic	1 (1.1)
Seborrhoeic dermatitis	1 (1.1)
Solar dermatitis	1 (1.1)
General disorders and administration site conditions	33 (35.1)
Application site irritation	29 (30.9)
Application site haemorrhage	3 (3.2)
Feeling abnormal	1 (1.1)
Application site paraesthesia	1 (1.1)
Application site swelling	1 (1.1)
Eye disorders	8 (8.5)
Eye irritation	8 (8.5)
Erythema of eyelid	1 (1.1)
Infections and infestations	5 (5.3)

Folliculitis	3 (3.2)
Conjunctivitis	1 (1.1)
Furuncle	1 (1.1)
Tinea versicolour	1 (1.1)
Injury, poisoning and procedural complications	2 (2.1)
Skin abrasion	2 (2.1)
Metabolism and nutrition disorders	1 (1.1)
Hypertriglyceridaemia	1 (1.1)
Vascular disorders	1 (1.1)
Hot flush	1 (1.1)
Respiratory, thoracic and mediastinal disorders	1 (1.1)
Nasal discomfort	1 (1.1)
Investigations	1 (1.1)
Platelet count increased	1 (1.1)
Gastrointestinal disorders	1 (1.1)
Stomatitis	1 (1.1)
Nervous system disorders	1 (1.1)
Paraesthesia	1 (1.1)

Sorted by incidence

Source data: NPC-12G-2 CSR, Table 14.3.2.3

Study OSD-001-001

In the study OSD-001-001 the incidence of AEs was 58.3% in the placebo group, 75% for sirolimus 0.05%, and 87.5% for each sirolimus 0.1% and 0.2%, suggesting a sirolimus concentration effect. In patients receiving sirolimus 0.2%, skin and subcutaneous tissue disorders (87.5%) were the most frequent AEs by SOC, with dry skin (50%) and dermatitis acneiform (37.5%) as most frequent preferred terms. Even though the patient numbers overall and in each group are small, the data suggest a possible concentration relationship, notably for skin and subcutaneous tissue disorders and for the preferred term of dry skin in particular.

A single patient, treated with sirolimus 0.2%, reported a severe AE (preferred term: pneumothorax). AEs of moderate intensity occurred in 38% of patients each receiving sirolimus 0.05% or 0.1% and 25% of patients receiving sirolimus 0.2%, compared with 33% of the placebo patients.

Data presented for the study OSD-001-001 suggest an increase in the incidence of drug-related AEs with the concentration. In patients receiving sirolimus 0.2%, skin and subcutaneous tissue disorders (88%) were the most frequent drug-related AEs, with dry skin (50%) and dermatitis acneiform (25%) as most frequent preferred terms. Despite small numbers, the data suggest a dose relationship for AEs in the SOC of skin and subcutaneous tissue disorders and for dry skin as preferred term.

Table 31. Drug-related adverse events; study OSD-001-001, safety population

	Placebo	Sirolimus 0.05%	Sirolimus 0.1%	Sirolimus 0.2%
Patients, n	12	8	8	8
Patients with events, n (%)	3 (25.0)	3 (37.5)	4 (50.0)	7 (87.5)
Skin and subcutaneous tissue disorders	1 (8.3)	3 (37.5)	3 (37.5)	7 (87.5)
Dry skin	1 (8.3)	3 (37.5)	3 (37.5)	4 (50.0)
Dermatitis acneiform	0	0	0	2 (25.0)
Xeroderma	0	0	0	1 (12.5)
Acne	0	0	1 (12.5)	0
Gastrointestinal disorders	0	0	0	1 (12.5)
Stomatitis	0	0	0	1 (12.5)
Infections and infestations	0	1 (12.5)	0	0
Oral herpes	0	1 (12.5)	0	0
Investigations	1 (8.3)	0	0	0
C-reactive protein increased	1 (8.3)	0	0	0
General disorders and administration site conditions	2 (16.7)	1 (12.5)	1 (12.5)	0
Irritability	2 (16.7)	1 (12.5)	1 (12.5)	0

Sorted by incidence in the sirolimus gel, 0.2% group

Source data: OSD-001-001 CSR, Table 12.2-8

Adverse drug reactions for the Summary of Product Characteristics (SmPC)

For the purpose of the presentation of undesirable effects for the SmPC, drug-related AEs were pooled across the studies NPC-12G-1 (active group only), NPC-12G-2 and OSD-001-001. 4 out of 98 patients who received 0.2% sirolimus gel were treated in study OSD-001-001 only and were not enrolled thereafter in either study NPC-12G-1 or NPC-12G-2. Even though the gel formulation used in study OSD-001-001 differed from the gel formulation used in studies NPC-12G-1 and NPC-12G-2, which chemically is identical to the to-be commercialized formulation, the safety data generated in these 4 patients reflect dermal treatment with 0,2% sirolimus. Therefore, the most comprehensive safety data will be the data from all 98 patients who received 0,2% sirolimus gel formulation throughout the three studies.

Table 32. Adverse Drug Reactions per individual patient (pooled data from patients treated with 0.2% gel in any of the three studies)

		Sirolimus Gel, 0.2%		
SOC				
	PT	**N=98**		
		n	**(%)**	**Events**
Patients with AEs		77	(78.6)	223
Skin and subcutaneous tissue disorders		66	(67.3)	132
	Dry skin	33	(33.7)	47
	Acne	19	(19.4)	23
	Pruritus	11	(11.2)	13
	Dermatitis acneiform	9	(9.2)	9
	Erythema	7	(7.1)	7
	Dermatitis contact	5	(5.1)	14
	Dermatitis	2	(2.0)	2
	Skin haemorrhage	2	(2.0)	3
	Dermal cyst	1	(1.0)	1
	Eczema	1	(1.0)	1
	Papule	1	(1.0)	1
	Photosensitivity reaction	1	(1.0)	1
	Rash	1	(1.0)	1

		Sirolimus Gel, 0.2%		
SOC				
	PT	N=98		
	Rash pruritic	1	(1.0)	1
	Seborrhoeic dermatitis	1	(1.0)	2
	Skin exfoliation	1	(1.0)	1
	Skin irritation	1	(1.0)	1
	Solar dermatitis	1	(1.0)	1
	Urticaria	1	(1.0)	1
	Xeroderma	1	(1.0)	1
	Asteatosis	1	(1.0)	1
General disorders and administration site conditions		38	(38.8)	62
	Application site irritation	34	(34.7)	44
	Application site haemorrhage	3	(3.1)	9
	Feeling abnormal	1	(1.0)	7
	Application site paraesthesia	1	(1.0)	1
	Application site swelling	1	(1.0)	1
Eye disorders		10	(10.2)	11
	Eye irritation	9	(9.2)	9
	Erythema of eyelid	1	(1.0)	1
	Ocular hyperaemia	1	(1.0)	1
Infections and infestations		5	(5.1)	7
	Folliculitis	3	(3.1)	3
	Conjunctivitis	1	(1.0)	1
	Furuncle	1	(1.0)	2
	Tinea versicolour	1	(1.0)	1
Gastrointestinal disorders		3	(3.1)	3
	Stomatitis	2	(2.0)	2
Injury, poisoning and procedural complications		2	(2.0)	2
	Skin abrasion	2	(2.0)	2
Investigations		1	(1.0)	1
	Platelet count increased	1	(1.0)	1
Metabolism and nutrition disorders		1	(1.0)	1
	Hypertriglyceridaemia	1	(1.0)	1
Nervous system disorders		1	(1.0)	1
	Paraesthesia	1	(1.0)	1
Renal and urinary disorders		1	(1.0)	1
	Proteinuria	1	(1.0)	1
Respiratory, thoracic and mediastinal disorders		1	(1.0)	1
	Nasal discomfort	1	(1.0)	1
Vascular disorders		1	(1.0)	1
	Hot flush	1	(1.0)	1

Analysis of Adverse Events by Organ System or Syndrome

Skin irritation symptoms

Study NPC-12G-1

Skin irritation symptoms were identified in 80% of patients receiving sirolimus gel, 0.2% and 47% of patients receiving placebo. Most frequent (>10%) preferred terms in the sirolimus group were dry skin and application site irritation (37% each) followed by pruritus (23%).

When the analysis was limited to drug-related AEs, the incidences were 70% and 47% for the sirolimus and placebo groups, respectively. The most frequent (>10%), drug-related skin irritation events by preferred term were dry skin and application site irritation (37% each) and pruritus (17%).

Study NPC-12G-2

Most frequent (>10%) skin irritation symptoms by preferred terms were dry skin (37%) and application site irritation (31%), followed by eczema (18%), contact dermatitis (14%), pruritus and erythema (12% each), and acneiform dermatitis (11%).

The most frequent (>10%) drug-related skin irritation symptoms were application site irritation (31%) and dry skin (28%).

Seven patients had individual values of sirolimus in blood >1 ng/mL: of the 7 patients, 5 were adult, 3 were female. The group included the 2 patients using oral sirolimus (NPC-06-53, 06-56) and 3 patient (NPC-06-53, 06-56, 08-52) using everolimus. Six of the 7 patients experienced skin irritation events around the time of the high plasma levels, and 5 events were judged as being drug-related.

Study OSD-001-001

In this trial, different from NPC-12G-1 and NPC-12G-2, it was checked only for the 4 predefined events of dermatitis acneiform, dry skin, irritability, and xeroderma. Data suggest a dose relationship between occurrence of skin irritation events and sirolimus dose.

Infections/ infestation

Infections and infestations were reported in 23% of patients treated with sirolimus gel, 0.2% in study NPC-12G-1. The incidence in the placebo arm was similar, 22%. Also at the preferred term level, incidences were comparable between sirolimus and placebo. The only term reported in more than a single sirolimus-treated patient was influenza (3 patients), vs 0 placebo patients. On the other hand, 3 placebo patients had nasopharyngitis, vs 1 sirolimus patient. Overall, these data do not suggest an increase of infection events in patients receiving topical sirolimus treatment. There were no infections or infestations judged as being drug related with sirolimus gel, 0.2%.

In study NPC-12G-2, infections and infestations were reported in 71% of the patients, with nasopharyngitis, influenza, folliculitis, and gastroenteritis as the most frequent preferred terms. In only 5 of the patients (5%), events were regarded as drug-related: folliculitis in 3 patients (3%), and conjunctivitis, furuncle, and tinea versicolour in 1 patient (1%) each.

In study OSD-001-001, infection events occurred in 2 placebo patients (17%), 3 patients each (38%) in the sirolimus 0.05% and 0.1% groups, and 1 patient (13%) in the sirolimus 0.2% group. The most frequent preferred term was nasopharyngitis (2 placebo patients, vs 3, 2, and 1 patient in the sirolimus 0.05%, 0.1%, and 0.2% groups, respectively. Other preferred terms were herpes zoster (sirolimus 0.1%: 1 patient), influenza (placebo: 1 patient), sinusitis (placebo: 1 patient), and oral herpes (sirolimus 0.05%: 1 patient). The event of oral herpes was judged as being drug-related.

Photosensitivity

Overall, 4 patients were identified in the long-term study NPC-12G-2 based on preferred terms : 2 patients with solar dermatitis (unrelated) and 2 patients in whom drug relatedness of the event could not be excluded (drug-related photosensitivity and drug-related solar dermatitis).

No AEs indicative of photosensitivity were identified in studies NPC-12G-1 or OSD-001-001.

Based on the findings from study NPC-12G-2, the Sponsor concluded that the risk of inducing photosensitivity with sirolimus gel, 0.2% cannot be ruled out.

2.4.8.3. Serious adverse event/deaths/other significant events

Deaths

No AEs leading to death were reported in any of the AF studies

Other Serious Adverse Events

Study NPC-12G-1

Two SAEs were reported, both in the same patient treated with sirolimus gel, 0.2%. Preferred terms were gastric haemorrhage (not related) and pancreatitis acute (drug related as per investigator).

> Patient no., a 24-year old Japanese male, started treatment with sirolimus gel, 0.2%, on, he complained of black gastric residuals and abdominal distension. The family physician diagnosed acute pancreatitis and gastric haemorrhage, and the patient was hospitalised and fluid therapy was started. Study medication was continued. the investigator established the cause of acute pancreatitis as compression of the pancreas by marked intestinal gas due to aerophagia and severe constipation, but nevertheless stated that causal relationship with study drug could not be ruled out. Pancreatitis is a known, common ADR of sirolimus. Gastric haemorrhage was considered to be unrelated to the study drug by the investigator based on clinical course, even though the cause of gastric haemorrhage remained unclear. The patient was discharged. The patient had measurements of sirolimus available, i.e. 0.368 ng/mL at 4 weeks and 0.265 ng/mL at 12 weeks. Of these, the concentration value at 4 weeks was closest to the date of onset of the SAEs.

Study NPC-12G-2

A total of 14 SAEs occurred in 9 patients, none of them was judged as drug related.

Study OSD-001-001

One SAE was reported in each the placebo group (epilepsy) and the sirolimus 0.2% group (pneumothorax). Neither judged as study drug related.

2.4.8.4. Laboratory findings

Study NPC-12G-1

There was no pattern of normal baseline values shifting to abnormally high or abnormally low haematology or biochemistry values at Week 4 or Week 12.

Study NPC-12G-2

Haematology

There was no trend of normal baseline values shifting to abnormally high or abnormally low haematology values at Week 12 or 52 or at the other assessment time points.

Biochemistry

There was no trend of normal baseline values shifting to abnormally high or abnormally low biochemistry values at Week 12 or 52 or the other assessment time points. Exceptions were seen for cholesterol, low density lipoprotein (LDL), and triglycerides, which showed shifts from normal to high values in >5% of

patients at most assessment time points. Maximum percentages of patients with shifts to high values were 13.5% for cholesterol (Week 26); 11.3% for LDL (Week 104); and 7.9% for triglycerides (Week 26).

To understand if the use of oral mTOR inhibitors might have contributed to these findings, laboratory shift tables were generated for patients with and without use of mTOR inhibitors. There was no consistent difference seen between these groups notably for cholesterol, LDL, and triglycerides. In any case, this comparison must be regarded with caution as patient numbers were small, notably for patients using oral mTOR inhibitors, and the study was not planned to detect such differences.

'Blood triglycerides increased' was a preferred term in 6% of patients, but none of the events was drug-related. Likewise, LDL increased was a preferred term in 2% of patients (drug-related 0%). There was no reported AE for increased cholesterol values in the SOC of investigations.

Study OSD-001-001

Given the small patient numbers overall and by dose group, there was no indication of a relevant pattern of shifts from normal baseline values to high or low values at Week 12 or at any of the other time points.

Cardiac safety

Cardiac safety based on ECG parameters was not assessed in the AF studies. No AEs were reported in study NPC-12G-1 or OSD-001-001 from the SOC of cardiac disorders. A single cardiac event was reported in NPC-12G-2, i.e. ventricular extrasystole (not study drug related) in a paediatric patient with a medical history of arrythmia which was also noted as complication of the underlying disease.

2.4.8.5. In vitro biomarker test for patient selection for safety

N/A

2.4.8.6. Safety in special populations

Age

The age of the patients in the overall study population ranged from 3 to 61 years. No patients aged > 65 years were treated in AF studies.

Study NPC-12G-1

Treatment duration was not separately analysed for adult vs paediatric patients, but data on gel amount suggest that adults received a higher mean total gel dose (adults: 64-67 g; paediatric patients: 54-55 g).

In patients treated with sirolimus gel, 0.2%, all of the most frequent skin irritation events (dry skin, pruritus, acne, application site irritation) were more frequent (>10% difference) in adult than in paediatric patients. On the other hand, influenza was more frequent in paediatric patients (23% vs 0%). Interestingly, in the placebo group, paediatric patients had nasopharyngitis with comparable frequency to influenza in sirolimus group.

In the placebo group, application site irritation and stomatitis were more frequent in adult than in paediatric patients.

All of the most frequent drug-related AEs were more frequent (>10%) in adults as compared to paediatric patients treated with sirolimus gel, 0.2%. No relevant differences were seen in placebo treated patients,

with the exception of application site irritation, which was again more frequent in adult patients (33% vs 21% in paediatric patients).

Table 33. Adverse events reported in >10% of patients in any group, by age; study NPC-12G-1, safety population

	Sirolimus		Placebo	
	Adult	Paediatric	Adult	Paediatric
Patients, n	17	13	18	14
Patients with events, n (%)	17 (100.0)	10 (76.9)	12 (66.7)	10 (71.4)
Skin and subcutaneous tissue disorders	13 (76.5)	6 (46.2)	4 (22.2)	4 (28.6)
Dry skin	7 (41.2)	4 (30.8)	2 (11.1)	2 (14.3)
Pruritus	6 (35.3)	1 (7.7)	2 (11.1)	2 (14.3)
Acne	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	8 (47.1)	5 (38.5)	8 (44.4)	3 (21.4)
Application site irritation	7 (41.2)	4 (30.8)	6 (33.3)	3 (21.4)
Gastrointestinal disorders	3 (17.6)	1 (7.7)	3 (16.7)	1 (7.1)
Stomatitis	1 (5.9)	0	2 (11.1)	0
Neoplasms benign, malignant and unspecified	2 (11.8)	0	0	0
Infections and infestations	1 (5.9)	6 (46.2)	2 (11.1)	5 (35.7)
Influenza	0	3 (23.1)	0	0
Nasopharyngitis	0	1 (7.7)	0	3 (21.4)
Injury, poisoning and procedural complications	1 (5.9)	1 (7.7)	2 (11.1)	2 (14.3)
Eye disorders	0	2 (15.4)	1 (5.6)	1 (7.1)

Sorted by incidence in the sirolimus arm

Source data: NPC-12G-1 CSR, Table 14.3.2.4

Study NPC-12G-2

Mean treatment duration was shorter in adults (682 days, or about 1.9 years) than in paediatric patients (774 days, or about 2.1 years). Mean total gel amount was similar between adults (341 g) and paediatric patients (350 g).

Preferred terms that were more frequent in adult patients were pruritus (18% vs 6% in paediatric patients) and back pain (11% vs 0%). Different from what was observed in study NPC-12G-1, there was no relevant difference between adult and paediatric patients for any of the skin irritation events (except for pruritus). Preferred terms that were more frequent (>10%) in paediatric patients were nasopharyngitis (62%, vs 41% in adults), influenza (34% vs 9%), and contusion (12% vs 0%).

Incidences of drug related AEs were comparable between adult and paediatric patients.

Table 34. Adverse events reported in >10% of patients in any group, by age; study NPC-12G-2, safety population

	Adults	Paediatric patients
Patients, n	44	50
Patients with events, n (%)	43 (97.7)	49 (98.0)
Skin and subcutaneous tissue disorders	37 (84.1)	44 (88.0)
Dry skin	16 (36.4)	19 (38.0)
Acne	14 (31.8)	19 (38.0)
Eczema	8 (18.2)	10 (20.0)
Pruritus	8 (18.2)	3 (6.0)
Dermatitis contact	7 (15.9)	8 (16.0)
Erythema	6 (13.6)	5 (10.0)
Dermatitis acneiform	5 (11.4)	5 (10.0)
Infections and infestations	26 (59.1)	41 (82.0)
Nasopharyngitis	18 (40.9)	31 (62.0)
Folliculitis	5 (11.4)	5 (10.0)
Gastroenteritis	5 (11.4)	5 (10.0)
Influenza	4 (9.1)	17 (34.0)
Gastrointestinal disorders	21 (47.7)	22 (44.0)
Stomatitis	7 (15.9)	11 (22.0)
General disorders and administration site conditions	20 (45.5)	21 (42.0)
Application site irritation	14 (31.8)	15 (30.0)
Injury, poisoning and procedural complications	10 (22.7)	17 (34.0)
Contusion	0 (0.0)	6 (12.0)
Respiratory, thoracic and mediastinal disorders	10 (22.7)	14 (28.0)
Investigations	10 (22.7)	8 (16.0)
Eye disorders	9 (20.5)	9 (18.0)
Nervous system disorders	8 (18.2)	10 (20.0)
Musculoskeletal and connective tissue disorders	8 (18.2)	3 (6.0)
Back pain	5 (11.4)	0 (0.0)

Sorted by incidence in adults

Source data: NPC-12G-2 CSR, Table 14.3.2.3

Study OSD-001-001

Overall, there appeared to be no systematic trend for adults to have AE incidences different from paediatric patients, within each of the treatment groups, i.e. placebo (67%, vs 50% in paediatric patients), sirolimus 0.05% (75% vs 75%), sirolimus 0.1% (100% vs 75%), and sirolimus 0.2% (75% vs 100%).

Sex

The AE profile for male vs female patients was investigated in study NPC-12G-1.

Among patients treated with sirolimus gel, 0.2%, males had higher incidences of dry skin (47% vs 23% in females) and pruritus (29% vs 15%); however, a similar imbalance was seen for male vs female patients receiving placebo. Female patients receiving sirolimus reported more frequently application site irritation (46%, vs 29% in males), however, with a similar pattern in the placebo group (33% females, 18% males).

In male as well as in female patients, the most frequent drug-related AEs generally occurred with higher incidences in the sirolimus gel, 0.2% group than the placebo group.

Pregnancy

The reproductive effects of sirolimus gel, 0.2% in humans have not been studied.

No pregnancies were reported in the AF studies.

Lactation

Sirolimus gel, 0.2% has not been studied in lactating/breastfeeding women.

Overdose

A topical overdose is not likely to occur after topical administration to AF lesions. If overdose occurs, treatment should be symptomatic and supportive.

Clinical AF programme of sirolimus gel, 0.2%

The highest dose concentration used in planned clinical studies in AF patients has been sirolimus gel, 0.2% twice daily, with a daily gel amount of 800 mg sirolimus gel, corresponding to 1.6 mg sirolimus/day (studies NPC-12G-1, NPC-12G-2).

Other clinical programmes of sirolimus gel

The highest dose concentration used in planned clinical studies of neurofibromatosis type 1 has been sirolimus gel, 0.4% twice daily. The AE profile in these patients was in general not appreciably different from that in AF patients receiving sirolimus gel, 0.2% twice daily.

Drug Abuse

Sirolimus gel, 0.2% is not considered to have abuse potential in the targeted indication based on its mechanism of action and safety profile.

No dependence studies were conducted in humans or animals.

Withdrawal and Rebound

No studies were performed that were specifically designed to evaluate adverse withdrawal and/or rebound effects.

Continued assessment of patients after EOT through Week 16 in studies OSD-001-001 and NPC-12G-1 confirmed that the size and redness of AF lesions worsened after treatment cessation.

2.4.8.7. Immunological events

N/A

2.4.8.8. Safety related to drug-drug interactions and other interactions

Dedicated studies of drug-drug interactions were not performed for sirolimus gel, 0.2% (see also Clinical Pharmacology section).

2.4.8.9. Discontinuation due to adverse events

No patient discontinued the 12-week studies NPC-12G-1 or OSD-001-001 for AEs, while 2 patients (2%) discontinued the long term study NPC-12G-2 because of AEs. The preferred terms in these 2 patients were eye irritation and erythema in one patient and contact dermatitis in another patient. The patients discontinued treatment after 15 and 29 days, respectively. All 3 AEs were mild and judged as being drug-related.

The incidence of adverse events and adverse drug reactions leading to treatment interruption was 27.7% (26/94) and 13.8% (13/94), respectively, in overall safety population of the long term study NPC-12G-2. The incidence of both adverse events and adverse drug reactions leading to dosage modification was 3.2% (3/94) in overall safety population.

2.4.8.10. Post marketing experience

Sirolimus gel, 0.2% was approved in Japan under the brand name Rapalimus Gel 0.2% on 1 Mar 2018. To date, sirolimus gel, 0.2% has not been authorised in another region or country.

A Periodic Safety Update Report (PSUR), covering the period from 15 Mar 2020 to 14 Mar 2021 is available; PSURs of earlier reporting periods are currently not available in English language. A cumulative presentation of all safety data since the approval of Rapalimus Gel 0.2% in Japan is currently not available. The above-mentioned PSUR summarised a general drug-use survey of Rapalimus® Gel.

General drug-use survey

A general drug-use survey of Rapalimus® Gel was started on 6 Jun 2018, i.e. the date of product launch in Japan, and is ongoing as an all-case survey under the conditions for approval. The target number of registered patients was 375 patients. Since the target number of patients enrolled exceeded 375 patients in this survey, the registration of patients requiring collection of case report forms in consultation with the Japanese regulatory authority was set to patients starting treatment on or before 30 Sep 2019, and the survey system was changed to a system in which only patient registration is continued for patients starting treatment on or after 1 Oct 2019.

For patients in the safety analysis set, all events reported during the period of 52 weeks after the start of Rapalimus Gel or within 28 days after discontinuation of this drug were included in the analysis. Adverse events were classified by preferred term and system organ class on the basis of MedDRA/ ver. 23.1. Events for which the causal relationship with Rapalimus Gel could not be ruled out were handled as adverse reactions.

Of the **639 patients** in the **safety analysis set**, 54% were female. Patients aged <15 years accounted for 32% of patients, while 67% were aged between 15 and <65 years, and 1% was aged ≥65 years. Mean (SD) duration of use was 292 (119) days; mean (SD) total dose was 47 (61) g.

Overall, **27% of patients discontinued treatment** before the end of the 52-week observation period; most frequent discontinuation reasons were AEs (n=38), transfer to another hospital (n=37), recovering/resolution (n=27), lack of response (n=23), death (n=2), and other (n=54).

The incidence of adverse reactions was 18%. Adverse reactions with incidence ≥1% are: acne (4%), application site irritation (3%), dry skin (2%), application site erythema (2%), dermatitis acneiform

(1%), and skin irritation (1%). Serious adverse reactions occurred in one patient (<1%), reporting application site haemorrhage. No adverse reactions leading to death were observed in this survey.

Adverse reactions leading to discontinuation occurred in 4% of patients, the most frequent (≥2 patients) being acne (5 patients), application site erythema and application site irritation (4 patients each, pruritus (3 patients), and dry skin and application site pain (2 patients each).

Photosensitivity was assessed in detail, searching for MedDRA preferred terms of: photosensitivity reaction, application site photosensitivity reaction, solar dermatitis, and administration site photosensitivity reaction. Three patients were identified with adverse reactions of photosensitivity (<1%), all being non-serious. All of them were non-serious and the outcome was "resolved."

Two patients were confirmed to be pregnant during the observation period:

a 31-year old Japanese female, discontinued treatment due to pregnancy on Day 77. The last menstruation is unknown. The patient gave birth to a baby approximately 9 months after treatment discontinuation. No abnormality in delivery or in the baby was reported.

a 29-year old Japanese female, had her last menstruation on Day 65 of treatment. On Day 126, treatment was discontinued at her request due to pregnancy. She was diagnosed as having cervical incompetence on Day 49 after discontinuation and aborted due to cervical incompetence and premature rupture of membranes on Day 59. There were no apparent external malformations in the foetus. The abortin was judged as not drug related.

Of note, serious adverse reaction of pancreatitis acute (observed in one patient in study NPC-12G-1) was not observed in this survey.

The adverse reaction which was observed not before approval but only in this survey and occurred in at least 1% of patients was "application site erythema" with the incidence of 1.56% (10/639 patients).

Safety in concomitant use of mTOR inhibitors

Since the number of patients who concomitantly used mTOR inhibitors is limited in the domestic long-term treatment study, and Rapalimus Gel and mTOR inhibitors are expected to be concomitantly used in daily medical practice, the company is still collecting information on the safety and effectiveness of concomitant use of mTOR, This is done as part of the routine Pharmacovigilance and reported in the PSUR.

2.4.9. Discussion on clinical safety

Safety data is available from 4 clinical studies, which have been performed with sirolimus gel, 0.2% in the AF development programme. Study NPC-12G-1, a randomised, placebo-controlled Phase III study, provides main safety data for sirolimus gel, 0.2%. Study NPC-12G-2 was an uncontrolled, open-label long-term study in patients who had completed study NPC-12G-1, where treatment was continued until (individual) study completion or approval of sirolimus gel. Study OSD-001-001 was a dose escalation study in AF patients and provides information on possible dose effects of sirolimus gel. All studies in AF patients were performed in Japanese (adult and paediatric) patients. Safety information is also available from a Phase I study NPC-12G-4/US in Caucasian healthy volunteers.

Sirolimus gel is also developed in neurofibromatosis type 1 (NF1).

The applicant presented the safety data on a by-study basis and argued that pooling safety data across AF studies was not feasible; however, pooled data was displayed for section 4.8 of the SmPC ("*Adverse drug reactions reported from the placebo-controlled phase III and the long-term study are summarized in the table below by system organ class and frequency*.").

Across studies, the Applicant claimed that 148 AF patients (both adult and paediatric) and 12 healthy volunteers have been exposed to sirolimus gel. The safety database is considered limited; however, since the underlying disease TSC is an orphan disease this is acceptable.

The uncertainty of how many individual patient were actually exposed to sirolimus gel in the clinical studies has been clarified. Since patients from OSD-001-001 eventually also participated in NPC-12G-1, and all patients from study NPC-12G-1 rolled over, after study completion, to NPC-12G-2, there were 108 AF patients exposed to sirolimus gel (any concentration), and overall 98 individual patients received 0.2% sirolimus gel in any of the three studies.

Four different formulations of sirolimus gel, 0.2% have been used in clinical studies. The commercial formulation for the EU market (formulation 4) in comparison to formulation 3 (used in LTS study NPC-12G-2 and BE study NPC-12G-4/US) includes a 3% drug substance overage. The applicant however decided not to include a sirolimus overage in the gel formulation. In consequence, the formulation foreseen for the EU market is Formulation 3 rather than Formulation 4.

Comparability of PK-data and comparability of efficacy and safety resulting from the different sirolimus formulations which have been applied in the PK-studies, phase I/II and phase III study and differing from the commercial formulation has been sufficiently justified. Formulation 3 and the preceding Formulation 2 are essentially the same. As the vast majority of clinical datasets has been generated with both Formulations 2 and 3, it is agreed that nearly all pivotal efficacy and safety data were obtained with the gel formulation without overage, as proposed for marketing.

The safety data from clinical studies in NF1 patients is considered to represent a worst-case scenario, i.e. administration of a higher sirolimus dose concentration on a greater skin surface. Furthermore, since the underlying disease is different and the pathogenic processes in the skin are not the same in AF and NF1, safety data presented could be considered of limited relevance to this MAA. However, formulation 4 was used in NF1 studies, therefore, the safety data from these studies has also been assessed.

Treatment duration/gel amount

In pivotal study (NPC 12G-1) the mean treatment duration was comparable between the groups (87.1 days in the sirolimus gel, 0.2% group and 86.1 days in the placebo group).

In long-term study, the mean treatment duration was 731 days (about 2 years), and the longest treatment duration approximately 2.6 years.

There were no differences in mean gel amount used between patients receiving sirolimus gel, 0.2% (59.9 g-corresponding to 0.12 g sirolimus administered overall over a 12-week period) and placebo (61.4g) in study NPC-12G-1.

In NPC-12G-2 study, the mean total gel amount was 346 g for patients overall (corresponding to 0.69 g sirolimus administered overall over a 2-year period).

Adverse events

Study NPC-12G-1

In the study NPC-12G-1 the incidence of AEs was 90% in patients treated with sirolimus gel, 0.2%, vs 69% in patients treated with placebo. The most frequent (>10%) AEs by preferred term in patients treated with sirolimus gel, 0.2% were dry skin and application site irritation (each 37%), followed by pruritus (23%). Incidences of these events tended to be higher with sirolimus than with placebo, although the high incidence of application site irritation in the placebo group of 28% (vs 37% with sirolimus) was reported.

No severe AEs were reported in study NPC-12G-1; all adverse events were mild (63% for sirolimus 0.2% and placebo each) or moderate (27% for sirolimus 0.2%, vs 6% for placebo). The pattern of AEs of moderate intensity AEs in the sirolimus group was reflective of the overall AE profile. No AE of moderate intensity by preferred term was reported in >1 patient in the sirolimus arm.

Drug-related AEs were reported in 73.3% of patients receiving sirolimus gel, 0.2%, vs 46.9% of patients on placebo. The most frequent (>10%) drug-related AEs in patients receiving sirolimus gel, 0.2% were dry skin and application site irritation (36.7% each), followed by pruritus (16.7%).

Of note, 28.1% of patients in the placebo group had application site irritation judged as being drug-related.

Study NPC-12G-2

The most frequent (>20%) AE by preferred term was nasopharyngitis (52%), followed by dry skin (37%), acne (35%), application site irritation (31%), and influenza (22%). The most frequent (>10%) drug related AEs were application site irritation (31%), dry skin (28%), and acne (20%).

Severe AEs were reported in 6% of patients, with preferred terms of pneumonia mycoplasmal, loss of consciousness, brain oedema, pneumothorax, therapeutic embolisation, and corpus callosotomy reported in one patient each.

Moderate intensity AEs were reported in 49% of patients. The most frequent (>10%) moderate AEs were nasopharyngitis (19%), influenza (14%), dry skin (12%), and acne (11%).

Study OSD-001-001

In the study OSD-001-001 the incidence of AEs was 58.3% in the placebo group, 75% for sirolimus 0.05%, and 87.5% for each sirolimus 0.1% and 0.2%, suggesting a sirolimus concentration effect. In patients receiving sirolimus 0.2%, skin and subcutaneous tissue disorders (87.5%) were the most frequent AEs by SOC, with dry skin (50%) and dermatitis acneiform (37.5%) as most frequent preferred terms and were all (except for one case of Dermatitis acneiform) considered drug related. Even though the patient numbers overall and in each group are small, the data suggest a possible concentration relationship, notably for skin and subcutaneous tissue disorders and for the preferred term of dry skin in particular.

Only 2 patients discontinued because of AEs (eye irritation/erythema and contact dermatitis), and that being in the long-term study NPC-12G-2.

No AEs leading to death were reported in any of the AF studies.

There were two SAE reported in study NPC-12G-1, both in same patient (gastric haemorrhage and pancreatitis acute) in the NPC-12G group. Pancreatitis acute was considered drug related as per investigator, and pancreatitis is a known, common ADR of oral sirolimus. The investigator stated that the primary cause of the acute pancreatitis was oppression of the pancreas caused by marked intestinal gas with aerophagia and severe constipation. After gaining control on the underlying causes (defecation control) the patient was discharged from hospital. However, relation to the study drug could not be rule out (although this relationship seems highly unlikely). Therefore, the final assessment of the applicant is that the one case of acute pancreatitis in the patient NPC-01-04 should not be considered causally related to the study drug.

None of SAE reported in the study NPC-12G-2 and Study OSD-001-001 were considered as drug related.

Based on the nonclinical findings and as a precaution in the clinical setting, patients in all AF studies were instructed to avoid direct sunlight and to use sunscreen. AE data from the AF studies were scrutinised to identify any possible event potentially indicative of photosensitivity. Overall, 4 patients

were identified in the long-term study NPC-12G-2 based on preferred terms; including 2 patients in whom drug relatedness of the event could not be excluded. Therefore, risk of inducing photosensitivity with sirolimus gel, 0.2% cannot be ruled out.

In addition, for systemic sirolimus, the Rapamune SmPC section 4.4 includes a rather strict wording related to malignancy and protection from UV light ("Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression (see section 4.8). As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor"). The SmPC for Hyftor contains a recommendation to avoid UV light, however, there is no mentioning of the risk of skin malignancies. The Applicant agreed to include a warning in Section 4.4 of the revised SmPC as precautionary measure, which is considered adequate.

Adverse drug reactions for the SmPC

The ADRs of the reference medicinal product Rapamune were not directly taken into account since Rapamune is used systemically and according to the applicant, not representative for safety profile of topical sirolimus administration. Nevertheless, PK data collected in the AF studies shows certain (in most cases low) systemic exposure after topical sirolimus gel, therefore, systemic effects cannot be ruled out.

The Applicant has provided a detailed presentation of the patient flow between studies including the respective treatment received and included the 0.2% population as of study OSD-001-001 in an additional safety analysis. Overall, 4 out of 98 patients who received 0.2% sirolimus gel were treated only in study OSD-001-001 and were not enrolled thereafter in either study NPC-12G-1 or NPC-12G-2.

The most comprehensive safety data now includes all 98 patients who received 0,2% sirolimus gel formulation throughout the three studies.

AEs of hypercholesterolaemia, increased LDL, and hypertriglyceridaemia were initially added to the ADR table of the initially proposed SmPC, in addition to adverse drug reactions identified from studies NPC-12G-1 and NPC-12G-2. However, after further internal evaluations and discussions with experts in the field, the low expected systemic exposure, if any, and the fact that none of the AEs was judged as being drug-related by either the investigators or the sponsor, the Applicant and the CHMP concluded that these AEs should not be included in the ADR table of the SmPC section 4.8.

The ADR table in the section 4.8 of the SmPC has been updated, accordingly.

Drug interaction

Drug-drug interaction profile of the sirolimus is already known from the approved oral sirolimus formulations, therefore applicant conducted no dedicated DDI studies. Since systemic exposure after topical treatment is lower than with oral sirolimus therapy, the risk of any systemic interaction emerging is also considered lower. The section 4.5 of the proposed SmPC already included some general information, based on oral sirolimus interaction potential which is acknowledged. However, as seven patients in long term study had sirolimus blood concentration > 1 ng/ml (with a maximum value of 3.27 ng/ml) at individual assessments time points, it is seen that the absorption of the topical sirolimus could be considerable to that measure where drug interactions could be possible and clinically relevant. This applies in particulary to inhibitors of CYP3A4 (e.g. ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin), which decrease the metabolism of sirolimus and increase sirolimus levels and consequently may lead to worse safety profile from the one seen in AF clinical studies.

Withdrawal and Rebound

No studies were performed that were specifically designed to evaluate adverse withdrawal and/or rebound effects. However, the results from the studies OSD-001-001 and NPC-12G-1 indicate that

stopping topical sirolimus treatment leads to relapse of AF lesions. The same has also been suggested in the literature. Therefore, continued exposure would be required to suppress/control the disease. The Applicant does not propose any recommendations for dose interruptions or dose modifications, although according to the data presented from the long-term safety study NPC-12G-2, in this study, dosing was stopped, interrupted, or modified based investigator's assessment due to the occurrence of adverse events. It is agreed however that due to a limited number of patients the available data do not allow concrete recommendations for dose interruptions or dose modifications to be given in the product information at this time.

Paediatric population

Impaired skin barrier function in very young children exposing them to an even higher risk of systemic absorption of sirolimus should be considered. Since no patients less than 6 years actually enrolled in the pivotal phase III study nor in the phase I/II study, there are currently, very limited data justifying an indication below the age of 6 years. Of note, only 4 paediatric patients age ≥3 <6 were enrolled in the long-term safety study. Furthermore, paediatric study population ≥ 6 years has not been sufficiently characterised yet. The proposed indication now includes an age limit for paediatric population (i.e. 6 years and older).

Post marketing experience

Additional pharmacovigilance activities following approval of Rapalimus Gel in Japan included: post-marketing clinical study, early post-marketing phase vigilance and drug use-results survey. Overall, 639 patients were included in the safety analysis set and 634 patients were included in the effectiveness analysis set.

The incidence of adverse reactions was 18%, which is lower when compared to incidence of adverse reactions observed in AF clinical studies; acne (4%), application site irritation (3%), dry skin (2%), application site erythema (2%) being most common.

The applicant is not planning to update section 4.8 of the SmPC with any new safety information from the post-marketing surveillance Rapalimus Gel 0.2% general drug use survey.

2.4.10. Conclusions on clinical safety

Overall, topical 0.2% sirolimus gel was generally well tolerated; the symptom most frequently reported by patients were mild-to moderate and dermatologic in nature, occurring at or near the site of application (i.e. irritation limited to the site of application).

Systemic exposure after topical treatment is considerably lower compared to oral sirolimus therapy. Consequently, the risk of any systemic adverse reaction of sirolimus gel is expected to be lower, compared to the reference product (Rapamune oral). However, both the risk of systemic interactions or the risk of systemic adverse reactions cannot be completely excluded based on the available PK and safety data.

Considering the number of patients included in clinical studies for sirolimus gel 0.2% was limited, the information on the safety of sirolimus gel should continue to be collected via routine post-marketing surveillance.

2.5. Risk Management Plan

2.5.1. Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 35. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Malignancy
Missing information	None

2.5.2. Pharmacovigilance plan

Not applicable. There are no ongoing or planned additional pharmacovigilance activities for Hyftor.

2.5.3. Risk minimisation measures

Table 36. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Malignancy	Routine risk communication: SmPC Section 4.4 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Physicians should advise patients on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing and/or headgear (SmPC Section 4.4)	None

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

Based on the new pharmaceutical form, route of administration and indication, the PRAC is of the opinion that a separate entry in the EURD list for Hyftor is needed, as it cannot follow the already existing entry for sirolimus. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

Therapeutic Context

Disease or condition

Tuberous sclerosis (TSC) is a rare genetic disease caused by defects in the TSC1 or TSC1 gene leading to the development of non-cancerous (benign) tumors in the brain and several areas of the body, including the spinal cord, nerves, eyes, lung, heart, kidneys, and skin. TSC is a lifelong condition. Currently there is no cure for TSC, but some symptoms can be treated. The prognosis for individuals with TSC is highly variable and depends on the severity of symptoms.

Nearly all individuals with TSC develop skin abnormalities, including angiofibromas (AFs), hypomelanotic macules, shagreen patches, fibrous plaques, and ungual fibromas. In the Tuberous Sclerosis Registry to Increase Disease Awareness (TOSCA) study, facial angiofibromas were observed in 57.3% of the patients and manifested since the early years of life in patients from the TOSCA study.

AF presents as small papules or red spots primarily on the face, often in a butterfly pattern, and may first appear in patients aged 3 to 5 years. Some can start early in life (in the first years) and then affect the skin during puberty and later stages. Untreated, these papules become more numerous and larger over time and through adolescence. In adulthood, the lesions tend to be stable or to grow more slowly.

Available therapies and unmet medical need

Management of AF associated with TSC is today based on the recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference which is globally accepted. With regard to dermal manifestations of TSC, the guidelines recommend that rapidly changing, bleeding, disfiguring, or symptomatic TSC-associated skin lesions should be treated as appropriate for the lesion and clinical context, using physical approaches such as surgical excision, laser, or possibly topical mTOR inhibitors. As topical mTORs are not yet marketed (exception is Japan where sirolimus 0.2% gel is marketed since 2018), the modalities of its use are heterogeneous, with widespread uncontrolled use.

Hyftor, the product applied for, is a sirolimus gel for topical use. The final wording of the indication is:

"Hyftor is indicated for treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older."

Main clinical studies

Main efficacy data come from a randomised, double blind, placebo-controlled Phase III study NPC-12G-1 (n=30 patients receiving sirolimus gel, 0.2% for 12 weeks) and an uncontrolled, open-label long-time (safety) study (NPC-12G-2)(n=94 patients receiving sirolimus gel, 0.2%, with efficacy data through 52 weeks), with supportive evidence from a dose escalation (OSD-001-001) study of sirolimus 0.05, 0.1, and 0.2% in 36 patients, all of them performed in Japanese AF patients.

The primary efficacy endpoint was a composite endpoint measuring changes from baseline to week 12 in AF size and extension (shrinkage, flattening, disappearance) and changes in AF redness. The scoring system included the degrees markedly improved, improved, slightly improved, unchanged, slightly exacerbated and exacerbated based on prespecified criteria. The primary assessment was performed by the IRC (Independent Review Committee) using photographs.

Favourable effects

In the pivotal study NPC-12G-1, sirolimus gel, 0.2% achieved a statistically significant and clinically relevant improvement in AF over placebo, including composite AF improvement, improvement in AF size, and improvement in AF redness. The response rate with sirolimus gel, 0.2% at 12 weeks (based on composite AF improvement and IRC assessment) was 60.0% (18/30) vs. 0% in placebo group.

Change in AF size at Week 12 compared to baseline was markedly improved or improved in 60% (18/30) of patients receiving sirolimus gel 0.2% vs 3% (1/32) of patients receiving placebo.

Change in AF redness at Week 12 compared to baseline (by IRC) was markedly improved or improved in 40% (12/30) of patients receiving sirolimus gel 0.2% vs 0% of patients receiving placebo.

The redness and size of angiofibromas are considered clinically relevant characteristics of facial angiofibroma.

In study NPC-12G-2, the response rate at Week 12 was at 59%, confirming the response rate seen in the pivotal study. Composite AF improvement in the long-term safety study continued beyond 12 weeks and over the entire assessment period, reaching 78% at 52 weeks. Paediatric patients improved faster than adult patients but to a similar extent at week 52.

Systemic exposure after topical treatment is considerably lower compared to oral sirolimus therapy.

Uncertainties and limitations about favourable effects

The scale/scoring system used in the primary analysis is not formally validated, however, appears reasonable and acceptable. The applicant does not plan to make any claims regarding concomitant use of oral mTOR inhibitors in the labelling and it is agreed that currently no treatment recommendation for such patient population can be issued. Nevertheless, the Applicant should further continue to collect information on the safety and effectiveness of concomitant use of mTOR inhibitors via routine pharmacovigilance.

Unfavourable effects

Topical 0.2% sirolimus gel was generally well tolerated; the symptom most frequently reported by patients were mild-to moderate and dermatologic in nature, occurring at or near the site of application (i.e. irritation limited to the site of application).

PK data retrieved from 3 studies show that about 3 quarters of patients had measurable blood concentrations upon treatment with sirolimus gel, 0.2%, with mean and median blood concentrations being <1 ng/mL. This is considerably lower than the targeted concentrations of oral Rapamune treatment for immunosuppression or for the treatment of sLAM.

Systemic AEs considered related to the treatment (including, among other things, stomatitis) have been reported.

Uncertainties and limitations about unfavourable effects

The safety database is considered limited; however, since the underlying disease TSC is an orphan disease this is considered acceptable.

In some of the patients with systemic adverse effects, concomitant use of oral mTOR inhibitors may have been the culprit. Nevertheless, the risk of systemic adverse reactions with the sirolimus gel cannot be completely excluded based on the available PK and safety data. Therefore, certain systemic ADRs and the risk of the specific ADRs of the reference product Rapamune have been included in the SmPC of Hyftor.

3.1. Effects Table

Table 37 Effects Table for Hyftor for treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older.

Effect	Short Description	Unit	Sirolimus gel 0.2%	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Composite AF improvement distribution at 12 weeks (IRC) (primary endpoint)	Distribution of angiofibroma improvement (defined by change in AF size, extension, and redness) according to the categories "markedly improved", "improved", "slightly improved", "unchanged", "slightly exacerbated", "exacerbated" at 12 weeks, compared with baseline, as assessed by an IRC	%	Markedly improved 16.7% Improved 43.3% Slightly improved 36.7% Unchanged 3.3% Slightly exacerbated 0% Exacerbated 0% Not evaluated 0%	Markedly improved 0% Improved 0% Slightly improved 15.6% Unchanged 81.3% Slightly exacerbated 0% Exacerbated 0% Not evaluated 3.1%	The scale/scoring system used in the primary analysis is not formally validated, however, appears reasonable and acceptable.	(1)
Composite AF improvement at 12 weeks (IRC) (secondary endpoint)	Proportion of patients reaching a change in AF size, extension, and redness of 'markedly improved' or 'improved' at 12 weeks, compared with baseline, as assessed by an IRC	%	60% of patients (18/30)	0% of patients (0/32)		(1)
Improvement in AF size at 12 weeks (IRC) (secondary endpoint)	Proportion of patients reaching a change in AF size or extension of 'markedly improved' or 'improved' at 12 weeks, compared with baseline, as assessed by an IRC	%	60% of patients (18/30)	3% of patients (1/32)		(1)

Effect	Short Description	Unit	Sirolimus gel 0.2%	Placebo	Uncertainties/ Strength of evidence	References
Improvement in AF redness at 12 weeks (IRC) (secondary endpoint)	Proportion of patients reaching a change in AF redness of 'markedly improved' or 'improved' at 12 weeks, compared with baseline, as assessed by an IRC	%	40% of patients (12/30)	0% of patients (0/32)		(1)
Composite AF improvement at 52 weeks (IRC)	Proportion of patients reaching a change in AF size, extension, and redness of 'markedly improved' or 'improved' at 52 weeks, compared with baseline, as assessed by an IRC	%	78% of patients			(2)
Unfavourable Effects						
Dry skin	Incidence of dry skin	%	36.7 33.7	12.5		(1) (3)
Application site irritation	Incidence of application site irritation	%	36.7 34.7	28.1		(1) (3)
Acne	Incidence of acne	%	6.7 19.4	0		(1) (3)
Pruritus	Incidence of pruritus	%	16.7 11.2	12.5		(1) (3)
Dermatitis acneiform	Incidence of dermatitis acneiform	%	3.3 9.2	0		(1) (3)
Eye irritation	Incidence of eye irritation	%	3.3 9.2	6.3		(1) (3)
Erythema	Incidence of erythema	%	7.1			(3)
Dermatitis contact	Incidence of dermatitis contact	%	5.1			(3)
Stomatitis	Incidence of stomatitis	%	2.0			(3)

Abbreviations: Independent Review Committee (IRC); angiofibroma (AF)
Notes: (1) Data from the multicentre, randomised, double-blind, placebo-controlled, parallel-group Phase III study NPC-12G-1; (2) Data from the multicentre, open-label, single-arm Phase III study NPC-12G-2; (3) Pooled data from patients treated with 0.2% gel in any of the three studies (OSD-001-001, NPC-12G-1, NPC-12-2)

3.2. Benefit-risk assessment and discussion

3.2.1. Importance of favourable and unfavourable effects

The most important effect observed in the pivotal study NPC-12G-1 is improvement in AFs which includes composite AF improvement, improvement in AF size, and improvement in AF redness. The response rate with sirolimus gel, 0.2% at 12 weeks (based on composite AF improvement and IRC assessment) was 60.0% (18/30) vs. 0% in placebo group. Change in AF size at Week 12 compared to baseline was markedly improved or improved in 60% (18/30) of patients receiving sirolimus gel 0.2% vs 3% (1/32) of patients receiving placebo. Change in AF redness at Week 12 compared to baseline (by IRC) was markedly improved or improved in 40% (12/30) of patients receiving sirolimus gel 0.2% vs 0% of patients receiving placebo. The redness and size of angiofibromas are considered clinically relevant characteristics of facial angiofibroma and statistically significant treatment benefit of sirolimus gel, 0.2% over placebo based on 3 endpoints, i.e. composite AF improvement and its components has been demonstrated.

The treatment benefit of sirolimus gel, 0.2% was generally shown to be consistent across subgroups.

In study NPC-12G-2, the response rate at Week 12 was at 59%, confirming the response rate seen in the pivotal study. Composite AF improvement in the long-term safety study continued beyond 12 weeks and over the entire assessment period, reaching 78% at 52 weeks. Paediatric patients improved faster than adult patients but to a similar extent at week 52.

Systemic exposure after topical treatment is considerably lower compared to oral sirolimus therapy. Nevertheless, both the risk of systemic interactions and the risk of systemic adverse reactions cannot be completely excluded based on the available PK and safety data.

Almost all patients treated with sirolimus gel reported at least one AE, which were generally mild and moderate in intensity. About 70% of patients across the AF studies experienced drug-related skin irritation symptoms. In about a third of the patients dry skin and application site irritation were reported as ADRs. Pruritus (17%) was also frequent in pivotal phase III study, while in the long-term safety study, acne (20%) was frequent but not pruritus.

3.2.2. Balance of benefits and risks

The response rate of 60% observed with sirolimus gel, 0.2% at 12 weeks (based on composite AF improvement and IRC assessment) is considered clinically relevant from the clinical point of view and is considered to outweigh the increased incidence of mild-to moderate AE, dermatologic in nature, occurring mostly at or near the site of application.

Short and long-term efficacy of the sirolimus gel applied for (Hyftor) in the treatment of facial angiofibroma have been sufficiently shown and the safety profile is acceptable.

Taking into account the favourable and unfavourable effects, the benefit-risk balance is considered positive.

3.2.3. Additional considerations on the benefit-risk balance

The applicant makes reference to data generated with the reference product Rapamune with regard to pharmacology and safety of systemically absorbed sirolimus. Considering the substantial own development programme to support efficacy and safety in the new indication applied for and the much lower systemic exposure to sirolimus from topically applied Hyftor compared to oral Rapamune, the

comparative bioavailability study NPC-12G-4/US is not considered pivotal to establish a scientific bridge to the reference product. In this specific case, containing the same active substance is sufficient to establish a "scientific bridge" between Hyftor and the reference product.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Hyftor is not similar to Votubia and Epidyolex within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Hyftor is favourable in the following indication:

Hyftor is indicated for the treatment of facial angiofibroma associated with tuberous sclerosis complex in adults and paediatric patients aged 6 years and older.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.