DSLP-01

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Clinical Study Protocol

Version Number: 8

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AMENDMENT POLICY

Protocol Amendments are to be written if any procedure in the Protocol needs to be changed. It must be signed by the principal investigator and the Sponsor. Only if all signatures are available, the Protocol Amendment can be considered approved.

Signatures may - where necessary - be submitted by Fax or e-mail. All substantial amendments are to be sent to the IEC/IRB.

All ethically relevant changes to the Study Protocol are to be reviewed and approved by the IEC/IRB. Ethically relevant changes could be the amount of blood taken, dosing alternatives and/or number of subjects in the study.

The study must not begin or continue before the IEC/IRB gives its written approval.

CONFIDENTIAL – PROPRIETARY INFORMATION

STUDY TITLE	A Phase 2/3, multi-center, double-blind, placebo-controlled, randomized, parallel-group, dose-response comparison of the efficacy and safety of a topical rapamycin cream for the treatment of facial angiofibromas (FA) associated with Tuberous Sclerosis Complex (TSC) in patients 6 years of age and over.
STUDY SHORT TITLE	Dose-ranging efficacy and safety study of topical rapamycin cream
PROTOCOL NUMBER	DSLP-01
CLINICALTRIALS.GOV ID	NCT03826628
INVESTIGATIONAL PRODUCT	*Rapamycin cream, topical*
DEVELOPMENT PHASE	Phase 2/3
INDICATION	Facial Angiofibromas Associated with Tuberous Sclerosis Complex
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PROTOCOL SYNOPSIS

Name of Sponsor	**DSLP**
Name of Active Ingredients	Rapamycin
Title of Study	Dose-ranging efficacy and safety study of topical rapamycin cream: A Phase 2/3, multi-center, double-blind, placebo-controlled, randomized, parallel-group, dose-response comparison of the efficacy and safety of a topical rapamycin cream for the treatment of facial angiofibromas (FA) associated with Tuberous Sclerosis Complex (TSC) in patients 6 years of age and over.
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Background and Rationale	DSLP have developed a topical cream containing rapamycin 0.5% and 1.0% referred to as *Rapamycin cream, topical.* Tuberous Sclerosis Complex (TSC) is a disorder characterized by the development of multiorgan benign tumor-like growths in any part of the body. TSC is caused by mutations in the *TSC1* and *TSC2* genes which encode a growth suppressor complex that inhibits the mTOR (mammalian Target Of Rapamycin) protein. Loss of regulation of mTOR leads to abnormal differentiation and development, and to the generation of enlarged cells. Facial angiofibromas (FA) are present in 70-80% of patients with TSC and are commonly developed after the first two years of life. FA are distinguished as fibrous and/or highly vascular papules. Facial angiofibromas in patients with TSC are thought to develop due to the mutational activation of the mTOR pathway. These growths tend to spontaneously bleed or can be affected by slight traumas that can also cause uncontrolled bleeding. When present around the eyes, nose and mouth infections become common. Due to their progressive nature, FA can impair vision and breathing. Rapamycin, a macrocyclic antibiotic produced by *Streptomyces hygroscopicus*, is a potent inhibitor of mTOR. Although the mechanism of action of rapamycin is not completely understood, research has shown that when rapamycin binds to mTOR, the activity produced by the mTOR cascade pathway is inhibited, thus restraining uncontrolled cellular proliferation. A number of clinical studies have used different concentrations (0.003-1%) of topical rapamycin for the treatment of FA associated with TSC. Taken as a whole, these studies demonstrate the potent efficacy and great tolerability of topical rapamycin for FA. All cases reported reduction of erythema, papule size and lesion flattening, and improved skin texture. The efficacy and safety of two rapamycin strengths (0.5% and 1.0%) will be assessed during a 26 week double-blind treatment phase with assessments made at clinical visits at baseline, 2, 8, 14, 20 and 26 weeks, and at follow-up (4 weeks after the last dose of study drug).
Study Hypothesis	It is hypothesized that the two strengths of *Rapamycin cream, topical* will improve the appearance of FA associated with TSC compared to placebo. It is also expected that both strengths will be well tolerated.
Study Design	A Phase 2/3, multi-center, double-blind, placebo-controlled, randomized, parallel-group, dose-response study
Duration of Treatment	26 weeks
Test Product, Dose, Mode of Administration	Rapamycin formulated as a topical cream (*Rapamycin cream, topical*) of different dose strengths: 0.5% and 1.0%. *Rapamycin cream, topical* will be applied once daily for 26 weeks on the surface of the facial angiofibroma lesions. The amount of cream required to produce a thin confluent layer on the skin is 6 mg/cm^2. The amount to be applied will be based on the size of the affected area.
Reference Product, Dose, Mode of Administration	A placebo cream will be applied daily for 26 weeks on the surface of the facial angiofibroma lesions.
Number of Participants	40 per treatment group It is anticipated that no more than 10% of the placebo group will achieve the primary endpoint, a successful treatment according to IGA scale after 26 weeks treatment and that each dose of *Rapamycin cream, topical* will achieve at least 40% successful treatment. Including the Holm-Bonferroni adjustment of the type I error rate for multiple comparisons ($\alpha = 0.025$) a sample size of 40 participants per group is required in each randomized group to achieve >80% power for these comparisons.

<table>
<tr><td>Criteria for Inclusion</td><td>
Inclusion Criteria
1. Male and female patients aged ⩾ 6 years and ⩽ 65 years on the day informed consent is obtained
2. Patients diagnosed with TSC based on the clinical diagnostic criteria of International Tuberous Sclerosis Complex Consensus Conference 2012 and presenting visible facial angiofibroma
3. An FA severity score of 2 or 3 on the IGA scale
4. Patients or their legal representatives capable of understanding the explanation of the clinical trial and who give written informed consent for participation
5. Patients or their legal representatives able to maintain patient diaries following the instructions of the investigator or sub-investigator
Exclusion Criteria
1. Patients who cannot carry out the treatment plan or follow-up assessment
2. Patients with serious skin lesions such as erosions or ulcers
3. Patients with known hypersensitivity to any component of the study product
4. Patients who have received rapamycin/sirolimus, everolimus, or temsirolimus within 3 months of enrolment
5. Patients who received laser therapy or surgical therapy within 6 months prior to trial enrolment
6. Patients who participated in any other clinical trial within 3 months prior to the day of enrolment
7. Patients judged unsuitable for this clinical trial by the investigator or sub-investigator
8. Pregnant or lactating females
9. Sexually active females of childbearing potential not using adequate contraception and sexually active males not using adequate contraception
10. Patients with immune dysfunction or receiving any form of immunosuppression
11. Patients with severe FA, with a score of 4 on the IGA scale
12. Patients with an FA severity score of less than 2 on the IGA scale
</td></tr>
<tr><td>Brief Description</td><td>
The study can be divided into a Screening Phase, a Treatment Phase and Follow-up.

The Screening Phase includes collection of Informed Consent and the assessment of the subjects' suitability for the study. Eligible subjects will be assigned a unique randomization number before the first application of the study drug. Subjects will be randomized to receive treatment with one of two strengths of Rapamycin cream, topical (0.5% and 1.0% rapamycin, respectively) or placebo.

The Treatment Phase of the study comprises one clinical visit at baseline (V0) and 5 subsequent clinical visits after 2, 8, 14, 20 and 26 weeks treatment (V1-5) with Rapamycin cream, topical or placebo. The amount of cream will be based on the total area of the facial lesion(s) and patients will be instructed to apply the formulation every evening, about half an hour before retiring for bed, for 26 weeks.

Follow-up will be performed 28 days after the V5 visit, or the last visit where early withdrawal from treatment was confirmed.

Assessment of the extent and severity of facial angiofibroma will be performed at randomization, at each clinical visit (V1-5) and at follow-up using a variety of measures including an Investigator's Global Assessment (IGA) scale, the facial angiofibroma severity index (FASI), as well as subjective and objective improvement ratings.

The primary efficacy endpoint is based on the IGA scale, described below:
<table>
<tr><th>Grade</th><th>Short Description</th><th>Detailed Description</th></tr>
<tr><td>0</td><td>Clear</td><td>No signs of facial angiofibroma</td></tr>
</table>
</td></tr>
</table>

	1	Almost Clear	Few small angiofibromas (< 2 mm); normal to pink coloration in affected area*
	2	Mild	Predominantly small angiofibromas (< 2 mm) with few intermediate tumors (2-4 mm); pink to red coloration in affected area
	3	Moderate	Predominantly intermediate angiofibromas (2-4 mm) with few large tumors (> 4 mm); red coloration in affected area
	4	Severe	Mix of intermediate (2-4 mm) and large angiofibromas (>4 mm) present diffusely on face; intense and generalized redness on the whole face

* Note: coloration refers to both the FA lesions and the background facial skin tone
Where lesion size and coloration are discrepant within the grade, emphasis should be placed on lesion size.

The following medications are prohibited after enrolment in this trial due to the risk of interference in the evaluation of efficacy/safety:

- Laser and surgical treatment of the target treatment area
- Administration of mTOR inhibitors (rapamycin/sirolimus, everolimus, temsirolimus etc.)
- Application of steroidal or antibacterial agents to the target area
- Administration of cyclosporine or macrolide antibiotics
- Strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin)

Evaluation of Efficacy	**Primary Endpoint:** The percentage of patients obtaining successful treatment based on a blind assessment using the IGA scale after 26 weeks treatment or at last visit if early withdrawal/discontinuation **Secondary Endpoints:** • Time to treatment success • Change from baseline in IGA after 26 weeks treatment or at last visit if early withdrawal/discontinuation • Change from baseline in FASI after 26 weeks treatment or at last visit if early withdrawal/discontinuation • Subjective (patient or parent/caregiver) improvement rating from first visit (V0) after 26 weeks treatment or at last visit if early withdrawal/discontinuation • Objective (clinician) improvement rating from first visit (V0) after 26 weeks treatment or at last visit if early withdrawal/discontinuation • Categorical Improvement of Facial Angiofibroma from first visit (V0) after 26 weeks treatment **Exploratory Endpoints:** • The percentage of patients with successful treatment according to IGA scale after 2, 8, 14 and 20 weeks treatment • Change from baseline in IGA after 2, 8, 14 and 20 weeks treatment • Change from baseline in FASI after 2, 8, 14 and 20 weeks treatment • Change from baseline in each FASI component (erythema, size, extension) after 2, 8, 14, 20 and 26 weeks treatment • Subjective (patient or parent/caregiver) improvement rating from first visit (V0) after 2, 8, 14 and 20 weeks treatment • Objective (clinician) improvement rating from first visit (V0) after 2, 8, 14 and 20 weeks treatment • Change in IGA from week 26 to Follow up (4 weeks after final dose) • Change in FASI from week 26 to Follow up (4 weeks after final dose)
Evaluation of Safety	Safety will be assessed at each of the visits and will include: • the local and systemic tolerability of different doses of topical rapamycin (i.e. reporting of adverse events), including, known topical and known oral rapamycin adverse events. • A physical examination, measurement of vital signs, and tests of hematology, biochemistry, blood lipids and urinalysis at baseline, at each visit (V1-5), and at follow-up • Rapamycin blood concentration, performed at baseline, at each visit (V1-5), and at follow-up
Statistical Methods	The Intent-To-Treat (ITT) population will consist of all subjects who receive at least one dose of study drug. Subjects will be included in the group to which they were randomized irrespective of the treatment actually taken. The ITT population is the primary population for the efficacy analysis. The safety population will include all subjects who are treated with study drug, with group determined by the actual dose of study drug taken. **Primary Endpoint:** The data for the primary endpoint, the percentage of patients obtaining successful treatment after 26 weeks, or at last visit if early withdrawal/discontinuation, based on

	the blind assessment using the IGA scale, will be summarized by treatment group. Success is defined as clear or almost clear with an improvement of at least two grades from baseline, i.e. 2 to 0; 3 to 1. Statistical analysis of the primary endpoint will be performed using a logistic regression model which will include treatment effect and stratum as fixed factors and baseline IGA score as a covariate. This model will be used to generate the odds ratios and 95% confidence intervals of the individual dose treatments compared with placebo, with the p-values for these comparisons adjusted using the Holm-Bonferroni adjustment. **Secondary Endpoints:** The time-to-treatment success will be summarized using Kaplan-Meier analyses and compared between each dose group and placebo using the stratified log-rank test. The secondary endpoints change in IGA and FASI from baseline to 26 weeks/last assessment, and objective and subject improvement from baseline to 26 weeks/last assessment, will be summarized by treatment group using means, medians, standard deviations, interquartile ranges and minima and maxima. These changes will be analyzed using ANOVA including treatment and stratum as main effect fixed factors, with planned pairwise comparisons between each dose group and placebo. If the data is not adequately normally distributed the Kruskal-Wallis non-parametric ANOVA, and Mann-Whitney U tests comparing changes between treatment groups will be used for the analysis. Baseline for the IGA and FASI scores is defined as the last pre-treatment assessment, whether obtained at screening, randomization or V0. Categorical Improvement scores will be compared amongst study groups using the Kruskal-Wallis non-parametric ANOVA, and Mann-Whitney U tests comparing changes between each dose group and placebo. The type I error rate associated with the testing of the six secondary endpoints will be strictly controlled using the Hochberg procedure. This will involve ranking the 6 p-values derived from the testing of each dose group with placebo from highest to lowest. If the highest p-value is <0.05, then all six comparisons are considered statistically significant. If not significant then the next highest is tested at p=0.025. The p-value continues to reduce at each non-significant step based on the Bonferroni adjustment. **Exploratory Endpoints:** The exploratory endpoints, including the change in IGA and FASI from week 26 to follow-up, will be analyzed in the same manner as the appropriate secondary endpoints. The p-values for these comparisons will not be reported but the differences between each dose group and placebo will be summarized as odds ratios or mean differences as appropriate with 95% confidence intervals. **Safety Endpoints: Safety Endpoints:** AEs will be collected for all randomized participants and will be listed with type of AE, severity and relationship for each treatment group, using the safety population. Adverse event data will be summarized for each treatment groups using frequencies and percentages (% of participants with each specific AE). If frequencies permit, Chi-square tests or fisher's exact tests may be used to compare the rates of occurrence between treatment groups. Known AEs specific to oral or topical rapamycin will be individually summarized by treatment group. Between-treatment comparisons will be made for changes in vital signs, hematology, biochemistry, blood lipids and urinalysis from baseline at visits V1-5. Baseline is defined as the last pre-treatment assessment, whether obtained at screening, randomization or V0. Changes between V5 and Follow-up will also be examined. Blood rapamycin concentrations will be summarized for each of the treatment groups at all scheduled timepoints using standard descriptive statistics (means, medians, geometric means, ranges, standard deviations and standard errors), as appropriate. Adverse events will be monitored up to 4 weeks after administration of the final dose of study medication.

Schedule of assessments

Assessment	Screening Phase			Treatment Phase						Follow-Up
	Informed consent	**Screening**	**Randomization**	**V0 Baseline**	**V1 2 weeks**	**V2 8 weeks**	**V3 14 weeks**	**V4 20 weeks**	**V5 26 weeks**	**4 weeks after final dose**
Tolerance	**≤3 months before V0**	**≤14 days before V0**		**NA**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±5 days**
Informed consent	X[1]									
Inclusion/exclusion criteria		X								
Demographic data		X								
Medical history		X								
Physical examination		X			X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X
Pregnancy test[2]		X		X	X	X	X	X	X	
Hematology, biochemistry & lipid panel[3]		X			X	X	X	X	X	X
Urinalysis		X			X	X	X	X	X	X
Blood rapamycin concentration[3,4]		X			X	X	X	X	X	X
Drug administration (once daily, evenings)				X						
Photographs of FA			X		X	X	X	X	X	X
IGA		X	X		X	X	X	X	X	X
FASI			X		X	X	X	X	X	X
Percentage improvement (subjective & objective)					X	X	X	X	X	
Categorical improvement									X[5]	
Concomitant medications		X	X	X						X
Adverse events				X						X

[1] if more than a month passes between obtaining informed consent and randomization, then informed consent should be re-obtained
[2] only conducted for women of childbearing potential
[3] if participants are unable to provide blood samples at all timepoints, the minimum to be collected should be samples at screening, V1 or V2 and V5
[4] blood sampling collected prior to the daily evening dose
[5] categorical assessment only to be done at V5, unless early withdrawal/discontinuation, in which case categorical assessment should be completed at last visit

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of covariance
ANOVA	Analysis of Variance
CRF	Case Report Form
DBP	Double Blind Phase
DCF	Data Clarification Form
DLC	Differential Leukocyte Count
ECG	Electrocardiogram
EXP	Extension Phase
FA	Facial Angiofibroma
FASI	Facial Angiofibroma Severity Index
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
LAM	Lymphangioleiomyomatosis
LOCF	Last Observation Carried Forward
PDL	Pulse-Dye Laser
PP	Per-Protocol
RBC	Red Blood Cell
RH	Relative Humidity
SAE	Serious Adverse Event
SAER	Serious Adverse Event Report
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSC	Tuberous Sclerosis Complex
USFDA	United States Food & Drug Administration
WBC	White Blood Cell

1. INTRODUCTION

1.1 Background

Tuberous Sclerosis Complex (TSC) is an autosomal dominant inherited neurocutaneous disorder that is characterized by the development of multiorgan benign tumor-like growths, most usually observed in the skin, brain, kidney, heart and lungs that could potentially lead to organ dysfunction (2,3).

TSC is caused by defects, or mutations, in two genes, *TSC1* and *TSC2*. Only one of the genes needs to be affected for TSC to be present. The *TSC1/2* genes encode the proteins hamartin and tuberin, respectively. These two proteins create a complex that regulates the mammalian target of rapamycin (mTOR). mTOR has been discovered to be a key modulator in multiple processes including cell cycle, cellular growth, proliferation and migration. Mutation in the *TSC1* or *TSC2* genes results in dysregulation of mTOR leading to abnormal growth and proliferation via mTOR's downstream effectors (4,5).

Facial angiofibromas (FA) are one of the major features of TSC. FA are present in 70-80% of patients with TSC and are commonly developed after the first two years of life (5–8). FA present as vesicopapular rashes with pink or bright red papules formed across the medial region of the cheeks and nasolabial folds. In some cases, FA may extend to the lateral cheeks, forehead and eyelids. Spontaneous and uncontrolled bleeding is frequent, and infections are common when the lesions are present around the eyes, nose and mouth. Due to progressive growth, over time FA can impair vision and breathing (8,9) and have psychological consequences (emotional, social and self-image disorders).

Samples of FA from patients with TSC have shown that mTOR plays a key role in the development of the condition. Fundamentally, dysregulated activation of mTOR (via mutations in *TSC1* and/or *TSC2*) results in continuous cell proliferation and differentiation, causing the appearance of FA (10–14). The clinical effect of rapamycin was discovered when a 21 year old female patient with TSC and angiofibromas underwent a double kidney transplant and was prescribed oral rapamycin to prevent graft rejection. After three months of daily intake of 3.5 mg of oral rapamycin the patient's FA regressed in size and also the erythema significantly decreased, improving her facial texture (15).

There is need for a simple, non-invasive method to treat FA. Currently, there is no standard treatment for FA. Patients are often subjected to a variety of different methods to clear and control the growths with the aim of reducing bleeding, infections and preventing/relieving disfigurement. Common methods include cryosurgery, curettage, dermabrasion, chemical peeling, excision, laser therapy (CO_2 laser, argon laser, pulsed dye lasers [PDL]) and surgical excision. The painful and invasive nature of these methods means they often require anesthesia. Such methods are better suited for the treatment of large, severe and well-defined FA, which typically require a combination of therapies and/or numerous laser sessions (9,16). Complications such as infections, or adverse events such as hypertrophic scars or pigmentation disorders are common after such treatments as implementing the required "after-care" is

often difficult for the subset of patients with learning disabilities and/or seizures also attributable to TSC.

1.2 Study Drug Rationale

Rapamycin is a macrolide antibiotic compound produced by *Streptomyces hygroscopicus* that was first isolated from a soil sample from Easter Island, also known as Rapa Nui. Rapamycin ligates with the immunophilin FK506 binding protein-12 creating a complex that inhibits the activation of the mTOR. mTOR is a protein kinase that regulates cell growth and cell proliferation (17). Rapamycin is currently commercially available only as an oral solution or as a tablet (e.g. Rapamune®). The currently approved indication for rapamycin is for the prophylaxis of organ rejection in patients aged ≥ 13 years receiving renal transplants (maintenance immunotherapy) and for the treatment of patients with lymphangioleiomyomatosis (LAM), a rare, cystic lung disease (18).

Due to its potent antiproliferative effects, rapamycin has also been investigated as a treatment for a series of cutaneous diseases including FA associated with TSC. Interest in the use of rapamycin for the treatment of FA began after the publication of a case report of a 21 year old TSC patient that underwent kidney transplant. After initial immunosuppression with tacrolimus, the patient was transferred to *oral rapamycin* therapy, during which time her FA improved dramatically (19).

There is an extensive literature which supports the efficacy and safety of various topical rapamycin formulations for the treatment of FA. In the last 7 years, 11 clinical trials and 17 case reports/observational studies have been published in the literature. Overall, the outcomes obtained by the vast majority of patients in these studies demonstrate that topical rapamycin has potent efficacy for FA associated with TSC (19–43). It is difficult to determine the impact of different treatment frequencies in terms of efficacy (i.e. twice daily or 3 times per week) but one study noted that a twice daily treatment regimen could be replaced by a once daily regimen without loss of efficacy (37). In line with the progressive nature of the disease, there is some data that demonstrates that the positive effect diminishes after treatment is stopped (1,45).

Although a range of concentrations appear to be effective, adults tended to have a poorer response to treatment than children for a given strength, suggesting the need for higher concentrations in this age group where FA are typically more severe (33,45,46). There is some data to suggest that higher concentrations have greater efficacy, particularly in adult patients (37,45). Moreover, most authors suggested the use of topical rapamycin at early stages (in younger patients) so optimal results can be achieved.

Table 1: Published Clinical Trials for Topical Rapamycin for Facial Angiofibroma

Study	Study Design	Strength	N	Frequency and Duration of therapy	Efficacy
Wataya-Kaneda et al., 2018	Multicenter, double-blind, randomized, placebo-controlled, parallel group	0.2%	62	2x daily for 12 weeks	Primary endpoint: composite improvement in angiofibromas (size and color at 12 weeks). Response rate of angiofibromas at weeks 4, 8, and 12 of treatment was 0 in the placebo group in contrast to 20%, 43% and 60% in the rapamycin group. None of the 31 assessable patients in placebo group were rated improved or better and 26 of them were rated unchanged. In contrast 17% and 43% patients in the rapamycin group were rated "markedly improved" and "improved", respectively. In the rapamycin group the response rates were significantly higher in the pediatric patients (85%) than in adult patients (41%) at week 12 (p=0.03) Rapamycin gel, 0.2% demonstrated a significant clinical benefit for patients with TSC involving angiofibromas, thus providing a promising therapeutic modality.
Koenig et al., 2018	Multicenter, double-blind, randomized, vehicle-controlled, parallel group	0.1% 1%	179	1x daily at bed time for 6 months	Clinically meaningful and statistically significant improvement in facial angiofibroma was observed for both 1% and 0.1%. At 6 months, Angiofibroma Grading Scale (AGS) mean improvement for 1% was 16.7 points compared with 11.0 for 0.1% and 2.1 points for vehicle only (P<0.001 for 1% and 0.1% vs vehicle only). End-of-treatment photos were rated "better" for 81.8% of patients in the 1% rapamycin group, compared with 65.5% for those in the 0.1% rapamycin group and 25.5% for those in the vehicle-only group (P<0.001, all 3 pairwise comparisons). Topical rapamycin was generally well-tolerated with no measurable systemic absorption.
Wataya-Kaneda et al., 2017	Double-blind, randomized, placebo-controlled, parallel-group	0.05% 0.1% 0.2%	36	2x daily for 12 weeks	0.05%, 0.1% and 0.2% strengths resulted in a significant 'improvement factor' (author defined composite variable comprised of tumor volume a redness measures) at 12 weeks relative to baseline for children (aged 3-18). Only the 0.2% strength provided a statistically significant 'improvement factor in adults (aged 19 – 65).
Koenig et al., 2012	Double-blind, randomized, placebo-controlled, parallel-group	0.003% 0.015%	23	1x daily for 6 months	73% reported improvement regardless of treatment provided

Cinar et al., 2017	Single-blind, left-right, vehicle-controlled, cross-over	0.1%	12	2x daily for 3 months, followed by 6-9 months treatment cessation, and a further 3 months treatment	Significant reduction on FASI seen with initial 3 month treatment. Treatment discontinuation resulted in significantly increased in FASI score. Final 3 month treatment resulted in significant decrease in FASI score.
Tanaka et al., 2013	Open-label, left-right, vehicle-controlled	0.2%	11	2x daily for 12 weeks	General score (total of each measure) was higher on the rapamycin treated cheek that on the vehicle-treated cheek in all patients
Wataya-Kaneda et al., 2011	Open-label, left-right, vehicle-controlled	0.2%	9	2x daily for 3 months	General score (total of each measure) significantly better on combination side than tacrolimus monotherapy side)
Tu et al., 2014	Open-label, uncontrolled case series	0.1% 0.5% 1.0%	19	2x daily for 8-30 months	All demonstrated a significant and sustained improvement
Amin et al., 2016	Open-label, uncontrolled case series	0.1%	14	1x daily for 6 months	FASI scores were improved in 71% of patients (100% of children and 33% of adults)
Salido et al., 2012	Open-label, uncontrolled case series	0.4%	10	3x week for 9 months	Median time to response was 4 weeks Average reduction in FASI: 60.2%
Foster et al., 2012	Open-label, uncontrolled case series	0.1%	4	2x daily for 6 months	Rapid improvement within 1 week maintained for 6 months, younger patients completely resolved FA

Despite promising literature reports of the efficacy and tolerability of topical rapamycin for the treatment of FA, there is only one approved topical rapamycin product, in Japan. This is in part due to the difficulties in producing a stable rapamycin topical formulation. A new topical cream (*Rapamycin cream, topical*) is currently under development by DSLP. The advantage of the base is that it protects molecules that are readily oxidized, such as rapamycin, and it also has excellent cosmetic properties, natural antimicrobial properties and releases the active ingredient into the skin by melting at skin temperature (33-34°C).

DSLP has sponsored a series of non-clinical studies which have demonstrated that *Rapamycin cream, topical* at 0.5% and 1.0% has a good absorption and penetration profile when applied to the skin. At 0.1%, the cream showed a variable absorption profile, so was not selected for further examination. *Rapamycin cream, topical* is not considered to be a contact sensitizer and is classified as a non-irritant to the eye and will not cause eye damage. A 9 month toxicity study found that mean rapamycin blood concentrations following daily dermal application generally increased with increasing cream concentration, but increases were not consistently dose proportional. Rapamycin creams were well tolerated and did not adversely affect any measured parameters.

1.3 Study Rationale

The planned Phase 2/3 dose-response study described in this protocol will investigate the dose-dependent efficacy of *Rapamycin cream, topical* (rapamycin 0.5% and 1.0% w/w) in the treatment of FA associated with TSC and compare with placebo.

1.4 Known and Potential Risks and Benefits

All clinical studies have risks. However, these are likely to be minimal in this study. The systemic absorption of rapamycin from *Rapamycin cream, topical* has been shown to be minimal and very few adverse events have been reported in the literature.

The potential benefit of this study lies in its potential to improve the appearance of FA associated with TSC without the use of surgery.

2 TRIAL OBJECTIVES

2.1 Hypothesis

It is hypothesized that the two strengths of *Rapamycin cream, topical* will improve the appearance of FA associated with TSC compared to placebo. It is also expected that both strengths will be well tolerated.

2.2 Efficacy Objectives

The Efficacy Objectives of the study are to determine and compare the efficacy of two different strengths of *Rapamycin cream, topical* and placebo over 26 weeks of once-daily treatment.

The primary efficacy endpoint is the percentage of patients obtaining successful treatment after 26 weeks or at discontinuation/withdrawal, based on the blind assessment using the IGA scale. Success is defined as clear or almost clear with an improvement of at least two grades from baseline, i.e. 2 to 0; 3 to 1.

The secondary efficacy endpoints are:

1. Time to treatment success
2. Change from baseline in IGA after 26 weeks treatment or at last visit if early withdrawal/discontinuation
3. Change from baseline in FASI after 26 weeks treatment or at last visit if early withdrawal/discontinuation
4. Subjective (patient or parent/caregiver) improvement rating from first visit (V0) after 26 weeks treatment or at last visit if early withdrawal/discontinuation
5. Objective (clinician) improvement rating from first visit (V0) after 26 weeks treatment or at last visit if early withdrawal/discontinuation
6. Categorical Improvement of Facial Angiofibroma from first visit (V0) after 26 weeks treatment

In addition, exploratory efficacy endpoints are:

1. The percentage of patients with successful treatment according to IGA scale after 2, 8, 14 and 20 weeks treatment
2. Change from baseline in IGA after 2, 8, 14 and 20 weeks treatment
3. Change from baseline in FASI after 2, 8, 14 and 20 weeks treatment
4. Change from baseline in each FASI component (erythema, size, extension) after 2, 8, 14, 20 and 26 weeks treatment
5. Subjective (patient or parent/caregiver) improvement rating from first visit (V0) after 2, 8, 14 and 20 weeks treatment
6. Objective (clinician) improvement rating from first visit (V0) after 2, 8, 14 and 20 weeks treatment
7. Change in IGA from week 26 to Follow up (4 weeks after final dose)

8. Change in FASI from week 26 to Follow up (4 weeks after final dose)

2.3 Safety Objective

The Safety Objective of the study is to determine and compare the incidence of treatment-emergent adverse events (TEAEs) over the course of the study among the three treatment groups.

The incidence of known topical rapamycin side effects (e.g. treatment area irritation, dryness, and redness) and oral rapamycin side effects (e.g. hypersensitivity reaction, angioedema, fluid retention, wound healing disturbance, hyperlipidemia and renal function aggravation (etc.) and will be individually summarized by treatment group.

Planned hospital admissions and/or surgical operations for an illness or disease which existed before the drug was given or the participant was randomized in a clinical study will not be considered adverse events.

In addition, a physical examination, vital signs, hematology, biochemistry, blood lipids and urinalysis will be assessed at screening, at each visit (V1-5), and at follow-up to determine if there are any clinically significant changes. Blood rapamycin concentration will also be determined at screening and at each visit (V1-5) and at follow-up to investigate systemic absorption of the drug product.

3 INVESTIGATIONAL PLAN

This is a multi-center, double-blind, randomized, placebo-controlled, dose-response clinical study investigating the efficacy and safety of *Rapamycin cream, topical* in the treatment of facial angiofibroma in patients with a diagnosis of TSC according to the clinical diagnostic criteria of International Tuberous Sclerosis Complex Consensus Conference 2012.

The study can be divided into a Screening Phase, a Treatment Phase, and Follow-Up (Figure 1).

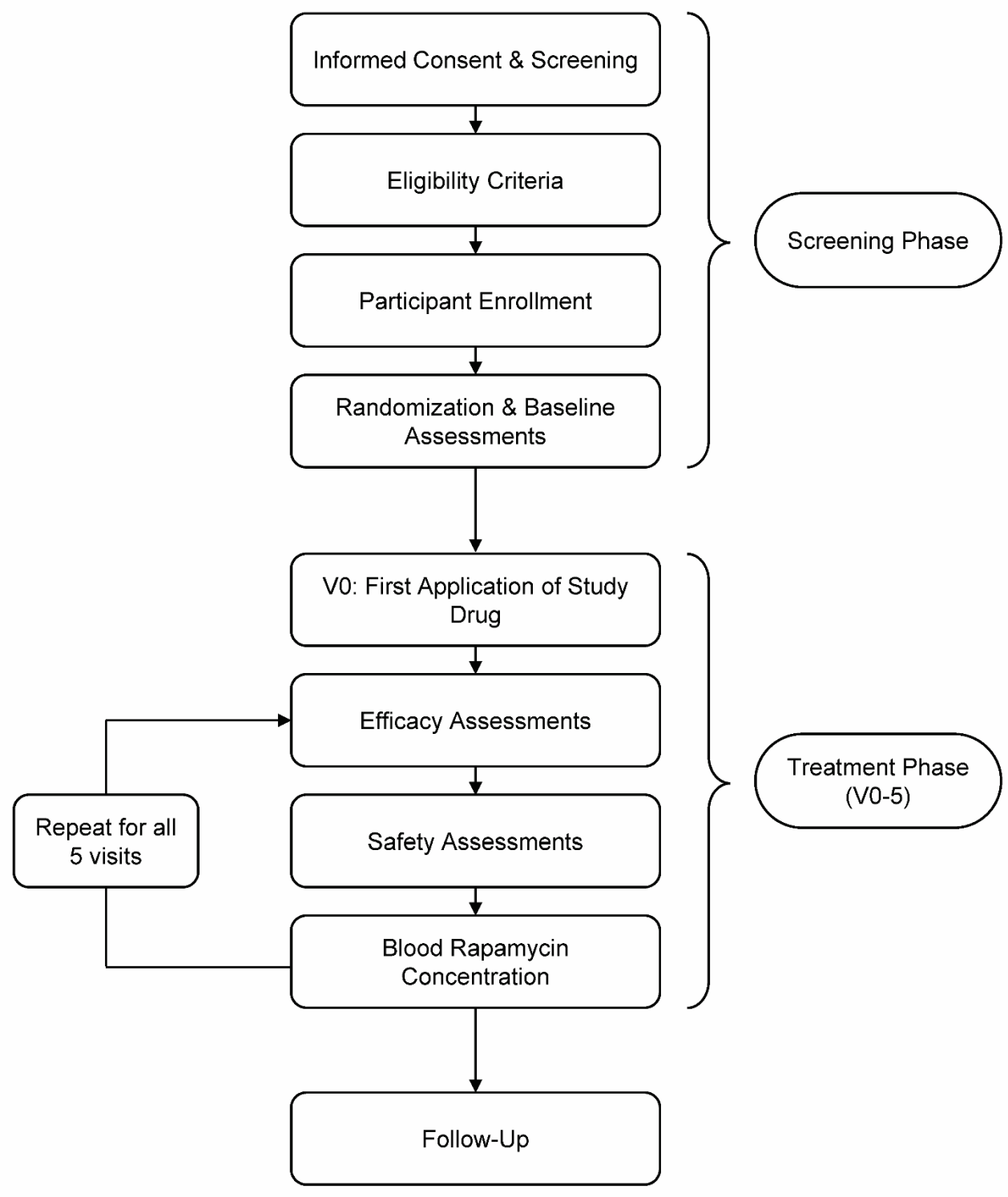
During the Screening Phase, Informed Consent will be obtained for participants prior to the initiation of any study-specific procedures including eligibility confirmation. Following enrolment, up to two weeks prior to the first application of the study drug, participants will be randomly assigned to one of three possible treatments in a 1:1:1 ratio:

- *Rapamycin cream, topical* (0.5% rapamycin)
- *Rapamycin cream, topical* (1.0% rapamycin)
- Placebo cream

The Treatment Phase is divided into baseline visit (V0) and 5 subsequent clinical visits (V1-5).

Follow-up will be performed 28 days after V5 or the last visit where early withdrawal from treatment was confirmed.

Figure 1: Schematic of Trial Design



4 PARTICIPANT POPULATION

4.1 Number of Participants

120 participants who meet all inclusion criteria and none of the exclusion criteria listed below in sections 4.2 and 4.3, respectively, will be enrolled at sites across the United States of America, Europe and Australasia.

4.2 Inclusion Criteria

1. Male and female patients aged ⩾ 6 years and ⩽ 65 years on the day informed consent is obtained
2. Patients diagnosed with TSC based on the clinical diagnostic criteria of International Tuberous Sclerosis Complex Consensus Conference 2012 and presenting visible facial angiofibroma
3. An FA severity score of 2 or 3 on the IGA scale
4. Patients or their legal representatives capable of understanding the explanation of the clinical trial and who give written informed consent for participation
5. Patients or their legal representatives able to maintain patient diaries following the instructions of the investigator or sub-investigator

4.3 Exclusion Criteria

1. Patients who cannot carry out the treatment plan or follow-up assessment
2. Patients with serious skin lesions such as erosions or ulcers
3. Patients with known hypersensitivity to any component of the study product
4. Patients who have received rapamycin/sirolimus, everolimus, or temsirolimus within 3 months of enrolment
5. Patients who received laser therapy or surgical therapy within 6 months prior to trial enrolment
6. Patients who participated in any other clinical trial within 3 months prior to the day of enrolment
7. Patients judged unsuitable for this clinical trial by the investigator or sub-investigator
8. Pregnant or lactating females
9. Sexually active females of childbearing potential not using adequate contraception and sexually active males not using adequate contraception*
10. Patients with immune dysfunction or receiving any form of immunosuppression
11. Patients with severe FA, with a score of 4 on the IGA scale
12. Patients with an FA severity score of less than 2 on the IGA scale

*Methods of contraception that are deemed adequate have failure rates of < 1%, including: established use of oral contraceptives in conjunction with a barrier method of contraception, injected or implanted hormonal methods of contraception; placement of intrauterine device (IUD) or intrauterine system (IUS); barrier methods of contraception including condom and/or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; sexual abstinence; hysterectomy; post-menopausal; sterilized; vasectomy.

4.4 Withdrawal Criteria

All participants have the right to withdraw at any point during the study without prejudice. Investigators can discontinue any participant at any time if it is in the opinion of the Investigator that it would not be in the participant's best interest to participate in the study. Whether participant withdrawal is the decision of the participant, or an investigator, the following situations may occur:

- The participant is withdrawn from the study and the participant withdraws consent to release follow-up information.
- The participant is withdrawn from the study but all follow-up information can still be collected.

4.5 Study or Study Site Termination and Subject Discontinuation

4.5.1 Study or Study Site Discontinuation

If the Sponsor, Investigator, Study Monitor, Drug Safety Officer, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study center should be terminated this action may be taken after appropriate consultation among the Sponsor, Investigator, Study Monitor and Drug Safety Officer.

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation or development of the product

A study conducted at a single study site may also warrant termination under the following conditions:

- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or appropriate regulatory authority
- Insufficient adherence to protocol requirements

4.5.2 Subject Discontinuation

Participants will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The Investigator will provide a written report on the appropriate case report from (CRF) page describing the reasons for discontinuation. If a participant withdraws before completion this will be managed as described in Section 4.4. A participant may be removed from the study for the following medical or alternative reasons:

- Adverse event
    - If a participant suffers an adverse event assessed as ⩾ Grade 3 (⩾ Grade 2 for the system-organ class of Cardiac Disorders; see Appendix 5: Grading of adverse events)

or, that, in the judgement of the Investigator or the Sponsor, presents an unacceptable consequence or risk to the subject, the subject should not receive additional doses. The participant should remain in the study and be followed until the adverse event resolves or stabilizes.

- Intercurrent illness
    - A subject may be discontinued from the study if, in the judgement of the Investigator, he or she develops an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies his or her withdrawal from the study

5 TREATMENTS

5.1 Treatments to be administered

Active Drug: *Rapamycin cream, topical* (cream preparation containing 0.5% or 1.0% rapamycin). Control: Placebo (cream preparation indistinguishable from the active drug and not containing any rapamycin).

Details of administration are as follows:

- The initial application of the study drug will be performed under medical supervision at the baseline clinical visit (V0). Subsequent applications will be made by the patient every evening, about half an hour before retiring for bed.
- The participating clinician will determine the size of facial area affected and instruct the patient the amount of product to be applied. This will be recorded in source documents.
- Prior to application, subjects should wash their face with a mild cleanser and pat dry.
- The study drug is to be applied using the fingertips to the entire area of the face affected by facial angiofibroma. The amount of cream required to produce a thin confluent layer on the skin is 6 mg/cm^2. The amount to be applied will be based on the size of the affected area.

  For example: for an affected area of 150 cm^2, dose = 900 mg (150 cm^2 x 6 mg/cm^2)
- Squeezing the tube slowly and consistently between the thumb and index finger until the product emerges and falls from the tube produces a globule weighing approximately 600 mg, measuring 16.5 mm in diameter.
- Once the study treatment has been applied to the face, subjects should not wash their face or apply anything else to the face until morning.
- After the study cream is applied, subjects should wash their hands thoroughly with soap and water.
- Patients will be advised to avoid direct sunlight and ultraviolet (UV) light during the clinical trial. Protective clothing and a sunscreen with a high protection factor should be worn to reduce exposure.

5.1.1 Treatment Phase

After informed consent has been provided, screening has been performed and participant eligibility confirmed, subjects will be admitted to the study site and randomized to one of three following treatments in a 1:1:1 ratio:

- *Rapamycin cream, topical* (0.5% rapamycin)
- *Rapamycin cream, topical* (1.0% rapamycin)
- Placebo cream

Patients will be instructed to apply the randomized treatment to the affected area once a day in the evenings (i.e. before retiring) for 26 weeks.

5.2 Investigational Products

The investigational products have been manufactured by Sterling Pharmaceuticals Services, LLC in its GMP approved manufacturing facility. Sterling Pharmaceutical Services holds a valid GMP issued by the USDFDA (Establishment Identifier No. 3009705561).

Lab scale batches of both strengths of *Rapamycin cream, topical* have been shown to be stable under room temperature conditions (25°C/60%RH) for at least 12 months. It is expected that the study drug will be stable long term under these conditions and stability studies are ongoing. Re-testing of the samples of the remaining study drugs will be conducted at the end of the study to confirm that the product is compliant with stability specifications.

The study drugs are contained in aluminum tubes with screw caps. Each 35 g tube contains 30 g of the study drug.

The study drug supplied for use in this study is to be prescribed only by the principal investigator or named co/sub-investigators and may not be used for any purpose other than that outlined in this protocol. Neither the investigators nor any designees may provide study drug to any patient not participating in the study.

The investigator or pharmacy designee will maintain an inventory record of study drug dispensed to assure regulatory authorities and the Sponsor that it has not been dispensed to any person who is not a participant under the terms and conditions set forth in this protocol.

At the termination of the study, all unused study drug (once it has been inventoried and accountability documents have been reviewed by the assigned study monitor) will be destroyed, and a destruction certificate will be issued by a licensed destruction company.

5.3 Randomization

Randomization will occur at the study site once participant eligibility is confirmed, up to two weeks before the first clinical visit (V0), which includes the first application of the study drug. Participants

will be randomly assigned to one of three possible treatments in a balanced fashion (i.e. 1:1:1 ratio). Each successive subject will receive a unique study randomization number which includes both a two-digit site prefix (e.g. 01), a single-digit age stratum identifier (e.g. 0) and two-digit subject identifier (e.g. 01). For example, the first patient in the first stratum (age group: 6 – 11 years) at site #1 will be assigned the randomization number 01-001. Randomization will be balanced by using permuted blocks and stratified by site and age group (6 – 11 years; 12 – 17 years; 18 – 65 years). Participants will be enrolled into the study until a minimum of 120 participants are randomized and have started using study drug.

The randomization sequence will be computer-generated by the study statistician prior to any enrolment. The statistician will maintain a confidential schedule of participant IDs and treatment allocations. The dispensing pharmacist at each site will not be blinded, and will maintain a confidential schedule of participant IDs and treatment allocations for participants at their site. The pharmacist will be responsible for over-labelling the study medication. The randomization sequences will be maintained by the site pharmacist in a secure location which cannot be accessed by other staff members involved in the conduct of the trial.

The sites will receive a set of sealed blinding envelopes for emergency un-blinding, with a separate envelope for each participant number. The principal investigator will be the first point of contact should the randomization code need to be broken for an individual participant during the study. The emergency unblinding envelopes for each participant should only be opened in an emergency when knowledge of the study drug may affect the management of the patient.

5.4 Blinding

Double-blinding will be achieved by the use of a vehicle placebo cream that has the same composition as *Rapamycin cream, topical*, but does not contain any active ingredient (rapamycin). The placebo cream and *Rapamycin cream, topical* are visually indistinguishable and are packaged into identical aluminum 30 g (net) tubes. Patients and treating and assessing dermatologists will all be blind to randomized treatment.

5.5 Prohibited concomitant medications

The following medications are prohibited after enrolment in this trial due to the risk of interference in the evaluation of efficacy/safety:

- Laser and surgical treatment of the target treatment area
- Administration of mTOR inhibitors (rapamycin/sirolimus, everolimus, temsirolimus etc.)
- Application of steroidal or antibacterial agents to the target area
- Administration of cyclosporine or macrolide antibiotics

- Strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin)

While not prohibited, concomitant use of rapamycin with some medications may increase the risk of certain adverse events. The following precautions will be taken:

- Patients taking drugs known to cause angioedema, such as angiotensin-converting enzyme (ACE) inhibitors, will be closely monitored as concomitant use of rapamycin may increase the risk of developing angioedema.
- Patients taking statins and/or fibrates will be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labelling for these agents.

5.6 Treatment compliance

The nightly administration of study medication will be documented by the patient or caregiver in the patient diary. A clinical trial monitor will review patient source documents, drug accountability records and patient diaries on an ongoing basis to assess treatment compliance. Additionally, returned tubes will be weighed to determine the amount of study medication used by the participant.

Acceptable compliance is no more than an average of one missed dose per week (26 missed doses over the course of the study) and no more than seven missed consecutive doses.

6 STUDY DATA AND ENDPOINTS

6.1 Efficacy data

6.1.1 Primary Efficacy Endpoint

At screening, each visit (V1-V5) and at follow-up a blinded dermatologist will grade each patient's lesion using the Investigator's Global Assessment (IGA) of facial angiofibroma severity developed by the sponsor and created solely to identify the response of a treatment in FA associated with TSC.

Table 2: IGA scoring of Facial Angiofibroma Lesions

Grade	Short Description	Detailed Description
0	Clear	No signs of facial angiofibroma
1	Almost Clear	Few small angiofibromas (< 2 mm); normal to pink coloration in affected area*
2	Mild	Predominantly small angiofibromas (< 2 mm) with few intermediate tumors (2-4 mm); pink to red coloration in affected area
3	Moderate	Predominantly intermediate angiofibromas (2-4 mm) with few large tumors (> 4 mm); red coloration in affected area
4	Severe	Mix of intermediate (2-4 mm) and large angiofibromas (>4 mm) present diffusely on face; intense and generalized redness on the whole face

* Note: coloration refers to both the FA lesions and the background facial skin tone
Where lesion size and coloration are discrepant within the grade, emphasis should be placed on lesion size.

The primary efficacy endpoint is the percentage of patients obtaining successful treatment, based on the blind assessment using the IGA scale after 26 weeks or at discontinuation/withdrawal. Success is defined as clear or almost clear with an improvement of at least two grades from baseline, i.e. 2 to 0; 3 to 1.

To the extent possible, the same Investigator should conduct all IGA assessments per patient at each site throughout the study.

6.1.2 Secondary and Exploratory Efficacy Endpoints

The following *secondary* efficacy endpoints will be derived from IGA scores:

1. Time to treatment success
2. Change from baseline in IGA after 26 weeks treatment or at last visit if early withdrawal/discontinuation

In addition, the following *exploratory* efficacy endpoint will be derived from IGA scores:

1. The percentage of patients with successful treatment according to IGA scale after 2, 8, 14 and 20 weeks treatment
2. Change from baseline in IGA after 2, 8, 14 and 20 weeks treatment
7. Change in IGA from week 26 to Follow-up (4 weeks after final dose)

Lesion severity will also be graded using the Facial Angiofibroma Severity Index (FASI) [Appendix 2: Facial Angiofibroma severity index (FASI)]. Using the FASI, lesions are graded according to their erythema, size and extent. Erythema is scored from 0 to 3 and lesion size are scored from 0 to 3, while extent carries greater specific weight (scored from 2 to 3), as the scale's developers consider the lesion's extent to be a fundamental factor in estimating the degree of severity.

The FASI is obtained by summing the partial scores assigned to each of three relevant features of FA for a maximum score of 9. FASI was first described in a clinical trial of 9 months duration (33) and the reliability and validity was subsequently reported (16). This will provide data for the following *secondary* efficacy endpoint:

3. The change in FASI from baseline after 26 weeks treatment or at last visit if early withdrawal/discontinuation

In addition, the following *exploratory* efficacy endpoints will be derived from FASI scores:

3. Change from baseline in FASI after 2, 8, 14 and 20 weeks treatment
4. Change from baseline in each FASI component (erythema, size, extension) after 2, 8, 14, 20 and 26 weeks treatment
8. Change in FASI from week 26 to Follow-up (4 weeks after final dose)

To the extent possible, the same Investigator should conduct all FASI assessments per patient at each site throughout the study.

At Visits 1-5 patients or their parents/caregivers (for patients under the age of 18) will be asked to estimate the percentage improvement in the FA lesion appearance from their perspective since baseline (V0) [Appendix 3: Subjective and Objective Improvement Ratings]. Similarly, the investigators will estimate the percentage improvement from a clinical perspective. Improvement will be defined as: minimal <30%, moderate 30-59%, good 60-89%, excellent >90%. This is similar to the objective and subjective improvement ratings used by Foster et al. (23) and Tu et al. (37). This will provide data for the following *secondary* efficacy endpoints:

4. Subjective improvement rating (minimal, moderate, good or excellent) in facial angiofibroma from first visit (V0) after 26 weeks of treatment or at last visit if early withdrawal/discontinuation
5. Objective improvement rating (minimal, moderate, good or excellent) in facial angiofibroma from first visit (V0) after 26 weeks of treatment or at last visit if early withdrawal/discontinuation

In addition, the following *exploratory* efficacy endpoints will be derived from percentage improvement scores:

5. Subjective (patient or parent/caregiver) improvement rating from first visit (V0) after 2, 8, 14 and 20 weeks treatment
6. Objective (clinician) improvement rating from first visit (V0) after 2, 8, 14 and 20 weeks treatment

To the extent possible, the same clinician should conduct all improvement rating assessments per patient at each site throughout the study. Similarly, the same person (patient of parent/caregiver) should report all improvement rating assessments throughout the study.

Upon completion of the double-blind treatment phase, patients or their parents/caregivers (for patients under the age of 18) will be asked which of the following statements they agree with:

- 3: I got significantly better on the treatment
- 2: I got moderately better on the treatment
- 1: I got slightly better on the treatment
- 0: The treatment made no difference
- -1: I got worse on the treatment

This is similar to the subjective improvement rating used by Koenig et al. (47). See also Appendix 4: Categorical improvement of Facial Angiofibroma. This will provide data for the following *secondary* efficacy endpoint:

6. Categorical Improvement of Facial Angiofibroma from first visit (V0) after 26 weeks treatment

Photographs of the FA lesions will be taken at randomization, and V1-5 and at follow-up to document changes. These will not be used directly for any efficacy endpoints, but will be available for auditing purposes.

6.2 Safety Data

The definitions and requirements in relation to adverse events are described in Section 8. All adverse events (AEs), including serious adverse events will be assessed by the Investigator according to Common Terminology Criteria for Adverse Events (CTCAE v 5.0) (see Appendix 5: Grading of adverse events) and documented up until 4 weeks after the final dose of study medication i.e. Follow-up visit.

Planned hospital admissions and/or surgical operations for an illness or disease which existed before the drug was given or the participant was randomized into the clinical study will not be considered adverse events.

6.2.1 Evaluations of Specific AEs

Known topical rapamycin adverse events will be compared between groups:

- Treatment area irritation (e.g. erythema, papules, vesicles, erosion etc.)
- Treatment area dryness

Known oral rapamycin adverse events will be compared between groups:

- Hypersensitivity reactions
- Angioedema

- Fluid retention
- Wound healing disturbance
- Hyperlipidemia
- Renal function decline
- Proteinuria
- Infections

CRFs will not specifically list these adverse events but they will be separated for analysis.

6.2.2 Overall Evaluation of Safety

The overall evaluation of safety throughout the trial will be based on all adverse events observed during the Treatment Phase and Follow-Up.

A physical exam, vital signs and laboratory tests (hematology, biochemistry, lipid panel and urinalysis) will be conducted during screening (baseline results), at each subsequent visit (V1-V5) and at follow-up. Clinically significant changes to the test results from baseline will be evaluated and compared among the three study groups. If participants are unable to provide blood samples at all timepoints, the minimum to be collected should be samples at screening, V1 or V2 and V5.

6.2.3 Systemic absorption of rapamycin

Blood rapamycin concentrations should be measured at screening and at each subsequent visit (V1-5) and at follow-up. If participants are unable to provide blood samples at all timepoints, the minimum to be collected should be samples at screening, V1 or V2 and V5. Samples will be collected by venipuncture by a qualified member of the study team. A total of approximately 5 mL blood will be collected into a lithium-heparin vacutainer.

As blood rapamycin levels are being measured as a safety parameter (blood rapamycin levels are not anticipated to exceed immunosuppression levels of 8-20 ng/mL), samples should be analyzed at a local accredited laboratory using validated analytical methods. As blood rapamycin concentrations may be measured by various chromatographic and immunoassay methodologies, each site should use the same analytical method throughout the study.

7 EXPERIMENTAL PROCEDURE

The study is intended to be carried out over a total of up to 10 months. The study consists of a Screening Phase (up to 3 months), a Treatment Phase (baseline and 5 clinical visits; 6 months), and Follow-Up (1 month). For early withdrawals, the follow-up visit will be scheduled from the last visit where subject withdrawal was confirmed. The study assessments are summarized in Table 3.

Table 3: Schedule of Assessments

Assessment	Screening Phase			Treatment Phase						Follow-Up
	Informed consent	**Screening**	**Randomization**	**V0 Baseline**	**V1 2 weeks**	**V2 8 weeks**	**V3 14 weeks**	**V4 20 weeks**	**V5 26 weeks**	**4 weeks after final dose**
Tolerance	**≤3 months before V0**	**≤14 days before V0**		**NA**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±5 days**
Informed consent	X[1]									
Inclusion/exclusion criteria		X								
Demographic data		X								
Medical history		X								
Physical examination		X			X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X
Pregnancy test[2]		X		X	X	X	X	X	X	
Hematology, biochemistry & lipid panel[3]		X			X	X	X	X	X	X
Urinalysis		X			X	X	X	X	X	X
Blood rapamycin concentration[3,4]		X			X	X	X	X	X	X
Drug administration (once daily, evenings)				X						
Photographs of FA			X		X	X	X	X	X	X
IGA		X	X		X	X	X	X	X	X
FASI			X		X	X	X	X	X	X
Percentage improvement (subjective & objective)					X	X	X	X	X	
Categorical improvement									X[5]	
Concomitant medications		X	X	X						X
Adverse events				X						X

[1] if more than a month passes between obtaining informed consent and randomization, then informed consent should be re-obtained

[2] only conducted for women of childbearing potential

[3] if participants are unable to provide blood samples at all timepoints, the minimum to be collected should be samples at screening, V1 or V2 and V5

[4] blood sampling collected prior to the daily evening dose

[5] categorical assessment only to be done at V5, unless early withdrawal/discontinuation, in which case categorical assessment should be completed at last visit

7.1 Screening Phase

The screening phase will occur up to 3 months prior to the initial Clinical Visit (V0).

Prior to the initiation of the screening assessments, potential participants will be given a complete explanation of the study.

Informed Consent may be obtained up to 3 months prior to the initial Clinical Visit (V0), however if more than one month passes between obtaining informed consent and randomization, then informed consent should be re-obtained.

Once an individual has agreed to participate and signed a copy of the Informed Consent documents the following assessments will be performed up to 14 days prior to V0 to assess the participant's eligibility for enrolment in the study according to the Inclusion/Exclusion criteria:

- Demographic data (age, sex, height, weight etc.)
- Complete medical history - including past or present history of cardiac, pulmonary, gastrointestinal, hepatic, renal, immunological, hematological, neurological, musculoskeletal or psychiatric conditions (if any), allergy to food or drugs and medication history for the previous three months.
- Physical examination
- Vital signs (temperature, blood pressure [systolic and diastolic], pulse rate)
- Urine pregnancy tests (females of childbearing potential only)
- Hematology
    - Hemoglobin
    - Hematocrit
    - Platelet count
    - Red Blood Cell (RBC) count
    - White Blood Cell (WBC) count
    - Differential Leukocyte Count (DLC)
- Biochemistry
    - Sodium
    - Potassium
    - Urea
    - Creatinine
    - Phosphate
    - Glucose
    - Albumin
    - Total protein
    - Alkaline phosphatase

  - Gamma-glutamyl transferase
  - Aspartate transaminase
  - Alanine transaminase
  - Bilirubin
- Lipid panel
  - Total cholesterol
  - High-density lipid cholesterol
  - Low-density lipid cholesterol
  - Triglycerides
- Blood rapamycin concentration
- Urinalysis
- Clinical examination of FA lesions using the Investigators Global Assessment (IGA)
- Concomitant medications

If subjects meet all eligibility criteria, they will be assigned a unique randomization number up to two weeks before the first application of the study drug, at which time the following baseline assessments will be conducted:

- Vital signs (temperature, blood pressure [systolic and diastolic], pulse rate)
- Photographs of FA lesions
- Clinical examination of FA lesions using the Investigators Global Assessment (IGA) and Facial Angiofibroma Severity Index (FASI)
- Concomitant Medications

Photographs of FA lesions will be taken using standardized methodologies as established at each site. Photographs at each visit will be signed and dated by the Investigator. The randomization number of the patient will be recorded on the photograph along with the IGA and FASI scores determined at that visit. Photographs will not be used directly for any efficacy endpoints, but will be available for auditing purposes and may be used in publications of the study results (deidentified photographs only).

7.2 Treatment Phase

Once an individual's eligibility for the trial has been confirmed and the participant has been randomized, the Treatment Phase can start. The Treatment Phase is divided into an initial clinical Visit (V0) and 5 subsequent clinical visits (V1-5).

7.2.1 Initial Clinical Visit (V0)

During the Initial Clinical Visit (V0) the initial application of the study drug will be performed under medical supervision. The participating clinician will determine the size of facial area affected and instruct the patient the amount of product to be applied. This will be recorded in source documents.

In addition, the following assessments will be conducted:

- Vital signs (temperature, blood pressure [systolic and diastolic], pulse rate)
- Urine Pregnancy test (females of childbearing potential only)
- Concomitant Medications
- Adverse event monitoring

7.2.2 Clinical Visits 1-5 (V1-5)

During Clinical Visits (V1-5) the following assessments will be performed:

- Physical examination
- Vital signs (temperature, blood pressure [systolic and diastolic], pulse rate)
- Urine Pregnancy test (females of childbearing potential only)
- Hematology, Biochemistry, Lipid panel (as per screening assessments)
- Urinalysis
- Blood rapamycin concentration
- Confirm application of study drug from the patient diary
- Photographs of FA lesions
- Lesion severity with IGA
- Lesion severity with FASI
- Percentage Improvement since V0
    - Subjective assessment
    - Objective assessment
- Categorical Improvement (at V5 or visit when withdrawal is confirmed only)
- Concomitant medications
- Adverse event monitoring

7.3 Follow-Up Period

Patients will be invited back for a follow up visit ~28 days (4 weeks) after their final visit of the Treatment Phase (depending on participation and withdrawal status) and the following assessments will be performed:

- Physical examination
- Vital signs (temperature, blood pressure [systolic and diastolic], pulse rate)
- Hematology, Biochemistry, Lipid panel (as per screening assessments)
- Urinalysis
- Blood rapamycin concentration
- Photographs of FA lesions
- Lesion severity with IGA
- Lesion severity with FASI
- Adverse event monitoring

- Concomitant medications

8 ADVERSE EVENTS

8.1 Definitions

An adverse event (AE) is defined as any unintended, unfavorable clinical sign or symptom, any new illness or disease or deterioration of existing illness or disease, or any clinically relevant deterioration in laboratory variables (e.g., hematological, biochemical, hormonal) or other clinical tests (e.g., ECG, X-ray), whether or not considered treatment related.

Planned hospital admissions and/or surgical operations for an illness or disease which existed before using the treatment or before the participant was randomized in the clinical study will not be considered adverse events.

The severity of an adverse event will be assessed by the Investigator according to Common Terminology Criteria for Adverse Events (CTCAE v 5.0) (see Appendix 5: Grading of adverse events). The relationship of an adverse event to the use of the drug will be assessed by the Investigator as described in Appendix 5: Grading of adverse events.

Participants will be specifically asked about the expected side-effects (such as treatment area irritation, dryness and redness), as well as any other symptoms they may have experienced, at each study visit. Other important aspects include photosensitivity reactions and adverse events reported for the oral formulation of rapamycin (Rapamune) including:

- Hypersensitivity reactions (including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis and hypersensitivity vasculitis)
- Angioedema
- Fluid retention
- Wound healing disturbance
- Hyperlipidemia
- Renal function decline
- Proteinuria
- Increased susceptibility to opportunistic infections (including tuberculosis, progressive multifocal leukoencephalopathy (PML), interstitial lung disease, Pneumocystis carinii pneumonia)

Participants experiencing adverse events will be followed clinically until their health has returned to baseline status or until all abnormal values have returned to normal or have otherwise been explained. The investigators will provide or arrange appropriate supportive care for the participant if necessary.

Participants will be advised to contact their doctor immediately if they develop signs or symptoms of hypersensitivity.

8.1.1 Serious Adverse Event

A serious adverse event is an AE that:

- results in death;
- results in persistent or significant disability/incapacity;
- is life-threatening (i.e. the participant was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred; this does not include an event that, had it occurred in a more severe form, might have caused death);
- requires participant hospitalization or prolongs hospitalization;
- is a congenital anomaly/birth defect; or
- is another medically significant event that, on the basis of appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g. allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

An adverse event fulfilling any one or more of these criteria must be reported as a serious adverse event, irrespective of the interventions given, and even if it is the result of an interaction or drug abuse.

A distinction should be drawn between serious and severe adverse events. Severity is an estimate or measure of the intensity of an adverse event, while the criteria for serious are indications of adverse participant outcomes for regulatory reporting purposes. A severe adverse event need not necessarily be considered serious and a serious adverse event need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not a serious adverse event. On the other hand, a myocardial infarction that may be considered minor could also be a serious adverse event if it prolonged hospitalization, for example. The severity of AEs will be graded according to Common Terminology Criteria for Adverse Events (CTCAE v 5.0).

8.1.2 Suspected Adverse Drug Reactions (ADR)

According to ICH GCP 1.1, *"all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions."*

8.1.3 Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.2 Procedure for Adverse Event Reporting

All adverse events (non-serious and serious) spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded.

All adverse events (non-serious and serious) must be recorded on the source documents and case report forms provided by the Sponsor. The following information shall be included:

- nature of the adverse event
- the onset date of adverse event
- the end date of adverse event (if applicable)
- the outcome of the AE
- the frequency of the AE
- action taken with the investigational product
- relationship to the investigational product
- whether any treatment was received for this adverse event
- whether this adverse event was serious

Any adverse event or abnormal laboratory result evaluated as clinically significant by the study investigator shall be followed until satisfactory resolution: it becomes stable, or it can be attributed to other causes (existing conditions) and in the opinion of investigators that further follow-up is not required.

8.3 Procedure for Serious Adverse Event Reporting

8.3.1 Reporting to the Sponsor

In addition to entering each serious adverse event irrespective of causality on the appropriate page of the case report form (CRF), the Investigator must complete a Serious Adverse Event Report (SAER) for each serious adverse event regardless of causality to the investigational drug. A sample of the SAE form for reporting is presented in Appendix 6: SAE Reporting Form. The SAER must be faxed to the Drug Safety Officer at the CRO and then to AFT Pharmaceuticals Ltd (+64 9 488 0234) within 24 hours of the event being notified to/realized by study site staff. The Drug Safety Officer will contact the Investigator should it be necessary to clarify any of the event information. The Investigator should provide any additional follow-up information for the event to AFT Pharmaceuticals Ltd as soon as it becomes available and up to the point the event has been resolved. This reporting requirement is applicable to serious adverse events that occur during the designated study period. If the Investigator is notified of a serious event post study that he or she determines to be causally related to study medication, the event should also be reported through this process.

8.3.2 Reporting to Local IEC and Regulatory Authorities

Serious adverse events will be reported to the local ethics committee and the relevant health authority as per the requirements.

8.3.2.1 Local Ethics Committee

There is no general requirement for applicants to submit individual or expedited reports of SAEs or suspected unexpected serious adverse reactions (SUSARs) to local ethics committees who do not have

the expertise or resources to review them. In the case of intervention studies involving a new medicine, the researcher is required to submit an annual summary of safety information.

8.3.2.2 Regulatory Authorities

Fatal or Life-Threatening Unexpected ADRs

An ADR is considered "fatal or life-threatening" if, in the review of either the investigator or sponsor, its occurrence places the participants at immediate risk of death. It does not include an adverse events of adverse drug reaction that, had it occurred in a more severe form, might have caused death.

Fatal of life-threatening ADRs occurring in clinical investigations is subject to expedited reporting. Regulatory agencies should be notified (e.g., by telephone, facsimile, transmission, or in writing) as soon as possible but no later than 7 calendar days after the first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible with 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same of similar medicinal products.

All other serious, unexpected ADRs

Serious, unexpected reaction (ADRs) that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

9 PROTOCOL DEVIATIONS

This study will be conducted, within reasonable limits, as described in this protocol, except for emergency situations in which the protection, safety, and well-being of the participant requires immediate intervention, based on the judgement of the Investigator (or a responsible, appropriately trained professional designated by the Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact the Sponsor, or the Sponsor's agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the best way to proceed with the study. The Investigator and the Sponsor will document this decision. The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) will be informed of all protocol changes by the Investigator in accordance with the IRB or IEC established procedure. No significant planned or deliberate deviations from the protocol of any type will be made without the Sponsor's agreement and complying with all the IRB or IEC established procedures.

10 PLAN FOR STATISTICAL AND OTHER CALCULATIONS

10.1 Populations of Interest

The Intent-To-Treat (ITT) population will consist of all subjects who receive at least one dose of study drug. Subjects will be included in the group to which they were randomized irrespective of the treatment actually taken. The ITT population is the primary population for the efficacy analysis.

The Per-Protocol (PP) population will consist of all ITT subjects who remain in the study for at least 26 weeks (i.e. complete the double-blind treatment period) and who do not incur a major protocol violation that would challenge the validity of their data.

The safety population is the population for all safety assessments. The safety population will include all subjects who are treated with study drug. Subjects will be included in the treatment group according to the treatment actually taken.

10.2 Sample Size

This is the first randomized clinical trial of *Rapamycin cream, topical* applied to patients and the first time that the Investigator's Global Assessment (IGA) scale will be used for the assessment of the severity of facial angiofibroma.

It is anticipated that no more than 10% of the placebo group will achieve the primary endpoint, a successful treatment according to IGA scale after 26 weeks treatment and that each dose of *Rapamycin cream, topical* will achieve at least 40% successful treatment (42). Including the Holm-Bonferroni adjustment of the type I error rate for multiple comparisons ($\alpha = 0.025$), a sample size of 40 participants is required in each randomized group to achieve >80% power for these comparisons.

10.3 Statistical Analyses

10.3.1 Primary Efficacy Endpoint

The data for the primary endpoint, the percentage of patients obtaining successful treatment based on the blind assessment using the IGA scale after 26 weeks or at last visit if early withdrawal/discontinuation, will be summarized by treatment group. Success is defined as clear or almost clear with an improvement of at least two grades from baseline, i.e. 2 to 0; 3 to 1. Statistical analysis of the primary endpoint will be performed using a logistic regression model which will include treatment effect and stratum as fixed factors and baseline IGA score as a covariate. This model will be used to generate the odds ratios and 95% confidence intervals of the individual dose treatments compared with placebo, with the p-values for these comparisons adjusted using the Holm-Bonferroni adjustment.

An exploratory analysis will compare the two active groups in the same manner as the primary endpoint, with no adjustment for multiple comparisons. This analysis will be summarized with the Odds ratio and 95% confidence interval.

10.3.2 Secondary Efficacy Endpoints

The time-to-treatment success will be summarized using Kaplan-Meier analyses and compared between each dose group and placebo using the stratified log-rank test. The secondary endpoints change in IGA and FASI from baseline to 26 weeks/last assessment, and objective and subject improvement from baseline to 26 weeks/last assessment, will be summarized by treatment group using means, medians, standard deviations, interquartile ranges and minima and maxima. These changes will be analyzed using ANOVA including treatment and stratum as main effect fixed factors, with planned pairwise comparisons between each dose group and placebo. If the data is not adequately normally distributed the Kruskal-Wallis non-parametric ANOVA, and Mann-Whitney U tests comparing changes between treatment groups will be used for the analysis. Baseline for the IGA and FASI scores is defined as the last pre-treatment assessment, whether obtained at screening, randomization or V0.

Categorical Improvement scores will be compared amongst study groups using the Kruskal-Wallis non-parametric ANOVA, and Mann-Whitney U tests comparing changes between each dose group and placebo.

The type I error rate associated with the testing of the six secondary endpoints will be strictly controlled using the Hochberg procedure. This will involve ranking the 6 p-values derived from the testing of each dose group with placebo from highest to lowest. If the highest p-value is <0.05, then all six comparisons are considered statistically significant if not significant then the next highest is tested at p=0.025. The p-value continues to reduce at each non-significant step based on the Bonferroni adjustment.

10.3.3 Exploratory Efficacy Analyses

The exploratory endpoints, including the change in IGA and FASI from week 26 to follow-up, will be analyzed in the same manner as the appropriate secondary endpoints. The p-values from these comparisons will not be reported but the differences between each dose group and placebo will be summarized as odds ratios or mean differences as appropriate with 95% confidence intervals.

10.3.4 Additional Analyses

A sensitivity analysis will be conducted using the Per-Protocol (PP) population to assess the robustness of the results for the primary endpoint.

An additional sensitivity analysis of the primary endpoint will be conducted in the portion of the ITT who complete the 26 week treatment period and have a 26 week assessment, if this population differs from the PP population.

A further sensitivity analysis will be conducted in which those patients who do not provide data at 26 weeks will be considered as treatment failures.

Analyses and summaries of the primary endpoint will also be presented by subgroup. These will include gender, age, site and baseline IGA score groups. As the sample sizes of subgroups are likely to be small,

these analyses will be presented for information purposes only, and statistically significant results are not anticipated.

10.3.5 Safety Endpoints

AEs will be collected for all randomized participants and will be listed with type of AE, severity and relationship for each treatment group, using the safety population. Adverse event data will be summarized for each treatment groups using frequencies and percentages (% of participants with each specific AE). If frequencies permit, Chi-square tests or fisher's exact tests may be used to compare the rates of occurrence between treatment groups. Known AEs specific to oral or topical rapamycin will be individually summarized by treatment group.

Between-treatment comparisons will be made for changes in vital signs, hematology, biochemistry, blood lipids and urinalysis from baseline at visits V1-5. Baseline is defined as the last pre-treatment assessment, whether obtained at screening, randomization or V0. Changes between V5 and Follow-up will also be examined.

Blood rapamycin concentrations will be summarized for each of the treatment groups at all scheduled timepoints using standard descriptive statistics (means, medians, geometric means, ranges, standard deviations and standard errors), as appropriate.

Adverse events will be monitored up to 4 weeks after administration of the final dose of study medication.

10.3.6 Demographic and Background Characteristics

Participant demographic and background characteristics will be descriptively summarized by treatment group using means, medians, standard deviations, ranges, frequencies and percentages as appropriate. No formal statistical comparisons will be made between treatment groups.

10.4 Treatment Compliance

To evaluate the degree of treatment compliance during the trial, tabular summaries of study drug usage will be presented for each randomized group.

Participants whose study drug usage exceed the limitations provided by the study protocol will be included in a list of protocol deviations. The potential effect of such deviations on the resulting clinical evaluations will be discussed in the study report.

10.5 Missing data

Every effort will be made to obtain all assessments at the appropriate time points from all randomized participants, especially to obtain assessments from early withdrawals. Where early withdrawals occur between visits without a visit to confirm subject withdrawal, assessments completed at the visit preceding withdrawal will be considered the assessment at discontinuation/withdrawal.

For the exploratory analyses, intermittent missing values in the analysis of IGA, FASI and percentage improvement scores will be imputed by linear interpolation of adjacent scores (i.e. immediately preceding and immediately following the missing value). No attempt will be made to impute missing data for Overall Improvement/Patient Satisfaction (recorded only at V5, or at last visit where withdrawal was confirmed).

10.6 Procedure for Amendments to Statistical Plan

It is intended that all statistical analyses specified in this protocol will be performed. However, it is conceivable that some scheduled analyses may not be performed. In addition, study observations or analysis results may suggest the need for additional statistical analyses of the collected study data, or changes to the procedures for handling missing data. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final clinical study report.

10.7 Data collection

The Case Report Form (CRF) will be used to collect all data that will be used for evaluation of specified analyses. The CRF should be completed in a timely fashion.

As this study will be conducted under International Conference on Harmonization (ICH) GCP guidelines, these guidelines require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years following the date after the last approval of a marketing application in an ICH region and until there are not any pending or contemplated marketing applications in an ICH region.
- A period of at least 2 years after the formal discontinuation of clinical development of the investigational product.

Should countries participating in this study have other guidelines for record retention, the period of record retention should follow the strictest guidelines, for example, New Zealand guidelines require documents to be retained for 10 years and Australian guidelines for 15 years.

It is agreed that the Investigator and the Sponsor will share in the responsibility to maintain these records. Each will maintain a complete set. Neither the Investigator nor the Sponsor will dispose of any records relevant to this study without either written permission from the other and from the relevant authorities. The Investigator and Sponsor shall both be responsible for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including any data clarification forms (DCFs) received from the Sponsor. Such documentation is subject to inspection by the Sponsor or its agents, and/or regulatory agencies. The Investigator may work with the Sponsor to ensure that archiving facilities are provided during the archiving period.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

The Sponsor has ethical, legal, and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and applicable regulations. As part of a concerted effort to fulfil these obligations (maintain current personal knowledge of the progress of the study), the Sponsor's monitor will visit the center(s) during the study in accordance with the Monitoring Plan set forth for this trial as well as maintain frequent telephone and written communication. The Investigator expects that the Sponsor will fulfil this obligation and provide early opportunity for the Investigator to correct any deficiencies identified in the data.

11.2 Auditing

The Sponsor may conduct audits at the study center(s). Audits may include, but not be limited to: drug supply, presence of required documents, the informed consent process, and comparison of case report forms with source documents. The Investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact the Sponsor immediately if this occurs and must fully cooperate with regulatory authority audits conducted at a reasonable time in a reasonable manner.

The Sponsor agrees to meet all reasonable costs that arise out of such audits, including reasonable remuneration of staff involved in complying with the requirements of such audits.

12 ETHICS AND RESPONSIBILITY

12.1 Informed Consent

Written informed consent will be obtained from the participant before any study-related procedures (including any pre-treatment procedures) are performed. The Investigator(s) has both ethical and legal responsibility to ensure that each participant being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same IRB or IEC responsible for approval of this protocol. Each informed consent form shall include the elements required by ICH GCP guidelines. The Investigator agrees to obtain approval from the Sponsor of any written informed consent form used in the study, preferably prior to submission to the IRB or IEC.

Once the appropriate essential information has been provided to the participant and fully explained by the investigators (or a qualified designee) and it is felt that the participant understands the implications of participating, the participant and the Investigator (or a medically qualified designee) shall sign the IRB- or IEC-approved written informed consent form. The participants shall be given a copy of the signed informed consent form, and the original shall be kept in the site’s regulatory file. A second copy may be filed in the participant's medical record, if allowed by the institution.

12.2 Institutional Review Board/Independent Ethics Committee

This protocol and the written informed consent form shall be submitted to the IRB or IEC identified with this responsibility at the research facility. Notification in writing of approval must come from the IRB or IEC chairman or secretary, to the Investigator, either as a letter or as a copy of the appropriate section of the IRB or IEC meeting minutes where this protocol and associated informed consent form were discussed. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, the written approval must indicate such non-participation. The Investigator will submit status reports to the IRB or IEC at least annually (when applicable). The IRB or IEC must be notified by the Investigator in writing of the interruption and/or completion of the study; the Investigator must promptly report to the IRB or IEC all changes in research (protocol amendments) and will not make such changes without IRB or IEC approval except where necessary to eliminate apparent immediate hazards to participants. In these cases, the IRB or IEC must be notified within 5 days of the change. The Investigator will promptly report to the IRB or IEC all unanticipated problems involving risk to participants or others. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB or IEC and must agree to share all such documents and reports with the Sponsor.

12.3 Governance of Study and Publication Policy

The Governance of the study will be the responsibility of the Principal Investigator/s and the Sponsor, in collaboration.

It is the intention of the Sponsor to publish the results of this study. Authorship of all publications and communications will reflect the contribution of the investigators and sponsors and will be inclusive where possible.

13 CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed by either the Investigator or the Sponsor to any persons not directly concerned with the study without written prior permission from the Sponsor and Investigator (as the case may be). However, authorized regulatory officials, the Investigator personnel and Sponsor personnel will be allowed full access to the records. All medications provided and participant bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor and the Investigator, and in compliance with all relevant regulations.

Only the unique participant number in case report forms will identify participants. Their full names may, however, be made known to a product regulatory agency or other authorized official if necessary.

14 INVESTIGATOR AGREEMENT

Certain responsibilities devolve to the Principal Investigator (notably those of signing the Statutory Declarations related to the Ethics Committee, the requirement to retain records, and oversight and governance of the study). Other responsibilities apply to all named co-investigators.

I have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I understand the potential risks and side effects of the drug. I will personally conduct the study as described, with the assistance of co-investigators and study personnel. I will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel responsible to me who will participate in the study. Together with the Sponsor, I will arrange briefing sessions and will discuss the protocol with them, to assure myself that they are appropriately informed regarding the investigational new drug- Rapamycin Topical Cream, the concurrent medications, the efficacy and safety parameters and the conduct of the study in general. I agree to make all reasonable efforts to adhere to the attached protocol. I understand that this EC approved protocol will be submitted to the regulatory authorities by the Sponsor's Contractor, as appropriate. I agree to allow Sponsor monitors and auditors full access to all medical records at the research facility for participants screened or randomized in the study. In return the Sponsor agrees to undertake audits regularly and assist me in identifying any deficiencies in the conduct of the study as early as possible, and in instituting appropriate measures to address these.

I agree to inform any patients that the study drugs are being used for investigational purposes and I agree to provide all participants with informed consent forms, as required by government and ICH regulations. I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol and FDA regulation, 21 CFR 312.64. I commit to conducting this trial in compliance with local laws and regulations and ICH GCP.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

Principal Investigator	Date

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APPENDIX 1: INVESTIGATORS GLOBAL ASSESSMENT

Grade	Short Description	Detailed Description
0	Clear	No signs of facial angiofibroma
1	Almost Clear	Few small angiofibromas (< 2 mm); normal to pink coloration in affected area*
2	Mild	Predominantly small angiofibromas (< 2 mm) with few intermediate tumors (2-4 mm); pink to red coloration in affected area
3	Moderate	Predominantly intermediate angiofibromas (2-4 mm) with few large tumors (> 4 mm); red coloration in affected area
4	Severe	Mix of intermediate (2-4 mm) and large angiofibromas (>4 mm) present diffusely on face; intense and generalized redness on the whole face

* Note: coloration refers to both the FA lesions and the background facial skin tone
Where lesion size and coloration are discrepant within the grade, emphasis should be placed on lesion size.

APPENDIX 2: FACIAL ANGIOFIBROMA SEVERITY INDEX (FASI)

Feature	Presentation	Score
Erythema	Skin color	0
	Light Red	1
	Red	2
	Dark Red/purple	3
Size	None	0
	Small (< 5mm)	1
	Large (> 5mm)	2
	Confluent	3
Extension	<50 % cheek surface	2
	>50% cheek surface	3

The score of the predominant tumors are taken in cases in which the same patient presented lesions with varying degrees of severity. A patient's FASI is the sum of scores assigned to each feature. Mild, moderate and severe FA corresponded score ranges on the FASI of $\leqslant$ 5, 6-7, and $\geqslant$ 8, respectively.

The scores assigned to each feature will be recorded in the case report form, as well as the overall summed FASI score. Please refer to (15) for further information on the FASI.

APPENDIX 3: SUBJECTIVE AND OBJECTIVE IMPROVEMENT RATINGS

The following assessments will be completed at V1-V5. The subjective improvement rating will be evaluated by the parent/caregiver for patients under the age of 18 years.

Subjective Percentage Improvement Assessment

Please rate the change in facial angiofibroma appearance since Visit 0:

Percentage improved since Visit 0: ___ ___ ___ %

(Minimal: <30%, Moderate: 30-59%, Good: 60-90%, Excellent: > 90%)

Objective Percentage Improvement Assessment

Please rate the change in the participant's facial angiofibroma appearance since Visit 0:

Percentage improved since Visit 0: ___ ___ ___ %

(Minimal: <30%, Moderate: 30-59%, Good: 60-90%, Excellent: > 90%)

APPENDIX 4: CATEGORICAL IMPROVEMENT OF FACIAL ANGIOFIBROMA

This will be completed at V5, or at the time of early discontinuation. The categorical improvement rating will be evaluated by the parent/caregiver for patients under the age of 18 years.

Categorical Improvement Assessment

Please tick ONE of the following statements that you agree with:

☐	3	I got significantly better on the treatment
☐	2	I got moderately better on the treatment
☐	1	I got slightly better on the treatment
☐	0	The treatment made no difference
☐	-1	I got worse on the treatment

APPENDIX 5: GRADING OF ADVERSE EVENTS

A copy of the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, published November 27 2017 will be provided to each site, and is also available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Common Terminology Criteria for Adverse Events (CTCAE v 5.0)

Grade[1]	Definition
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.[2]
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.[3]
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event (not appropriate for some adverse events).

1: not all grades are appropriate for all AEs.

2: Instrumental activities of daily living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

3: Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Relationship	Definition
Not related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is unlikely or not reasonable. Or where another cause can explain the occurrence of the event by itself.
Unlikely	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is unlikely but cannot be ruled out.
Possibly Related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable, but the event could have been due to an equally likely cause.
Probably Related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable and the event is more likely to be explained by the medicinal product than by another cause.
Definitely Related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable and there is no other cause to explain the event. Cause to explain the event, or a re-challenge is positive.

APPENDIX 6: SAE REPORTING FORM

Protocol: DSLP-01 **SAE Number:** _____ **Fax to:** + 64 9 488 0234	**Site:** _____ _____	**Report Type:** ☐ Initial Report ☐ Follow-up ☐ Revised / additional information ☐ Final Report	**Date of Initial Report:** _____ / _____ /_____ *dd mmm yyyy* **Date of Follow-up Report:** _____ / _____ /_____ *dd mmm yyyy*
PATIENT INFORMATION			
Patient #: _____	**Gender:** ☐ Male ☐ Female	**DOB:**_____/_____ / ____ *dd mmm yyyy*	**Weight:** _____ ☐ lbs ☐ kg
STUDY DRUG INFORMATION			
Study Drug & Dose administered:		**Start Date and Time:** _____/ _____/ _____ *dd mmm yyyy* _____: _____ *(24 hr clock)*	**Stop Date and Time:** _____/ _____/ _____ *dd mmm / yyyy* _____: _____ *(24 hr clock)*
Blind broken? ☐Yes ☐No ☐ N/A If yes, please specify the treatment: _____			

ADVERSE EVENT (AE)*
* List only one adverse event. Additional serious AEs are to be reported separately.

Adverse Event: (diagnosis)	**Date and Time of Event Onset:** _____ / _____ / _____ _____ : _____ *dd mmm yyyy (24 hr clock)* **Date and Time of Last Dose Prior to Event Onset:** _____ / _____ / _____ _____ : _____ *dd mmm yyyy (24 hr clock)*

Serious Criteria (check <u>all</u> that apply):

☐ Death
☐ Life-threatening
☐ Hospitalization – initial or prolonged
☐ Medically significant (specify) _____
☐ Persistent or significant disability
☐ Congenital anomaly or birth defect

(i.e. may require intervention to prevent permanent impairment / damage or one of the other outcomes listed)

Protocol: DSLP-01	**Site Name: _____** **Patient No: _____**

Relationship to Study Drug:	**Outcome of AE: (check only one)**	**Action Taken with Study Drug:**
☐ Not related, possible etiology: _____ ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definitely	☐ Death (*dd/mmm/yyyy*): ____/ ____ / ____ ☐ Resolved (*dd/mmm/yyyy):*____ / _____ / ____ ☐ Permanent sequelae (specify in description) ☐ Ongoing ☐ Unknown/Lost to follow-up	☐ None ☐ Discontinued permanently ☐ Temporarily interrupted ☐ Dose adjusted ☐ Not applicable

Description of Event* (including symptoms, diagnosis, chronology, treatment, re-challenge / dechallenge):**

* List only one adverse event. Additional serious AEs are to be reported separately.
** Attach additional sheet if necessary

Relevant Tests/Laboratory Data (including dates, lab units):

If lab reports are attached, please tick here: ☐

Other Relevant History (including pre-existing medical conditions):

Protocol: DSLP-01	**Site Name:** ______________________________ **Patient No:** _________

CONCOMITANT MEDICATION(S)* *(List all administered at onset of SAE, attach additional sheet of necessary)*

Name & Indication	**Dose & Regimen**	**Route Of Administration**	**Start Date/Time & Stop Date/Time *(dd/mm/yyyy, 24 hr clock)***	**Causal Relationship to AE**
Name (generic): **Indication:**	______ dose ______ units ______ regimen	☐ iv ☐ sc ☐ im ☐ oral ☐ sublingual ☐ inhalation ☐ other (specify) __________	**Start:** _____/ _____ / _____ *dd mmm yyyy* ________: ______ *24 hr clock* **Stop:** _____/ _____ / _____ *dd mmm yyyy* ________: ______ *24 hr clock*	☐ Not Related ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definitely
Name (generic): **Indication:**	______ dose ______ units ______ regimen	☐ iv ☐ sc ☐ im ☐ oral ☐ sublingual ☐ inhalation ☐ other (specify) __________	**Start:** _____/ _____ / _____ *dd mmm yyyy* ________: ______ *24 hr clock* **Stop:** _____/ _____ / _____ *dd mmm yyyy* ________: ______ *24 hr clock*	☐ Not Related ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definitely
Name (generic): **Indication:**	______ dose ______ units ______ regimen	☐ iv ☐ sc ☐ im ☐ oral ☐ sublingual ☐ inhalation ☐ other (specify) __________	**Start:** _____/ _____ / _____ *dd mmm yyyy* ________: ______ *24 hr clock* **Stop:** _____/ _____ / _____ *dd mmm yyyy* ________: ______ *24 hr clock*	☐ Not Related ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definitely

INVESTIGATOR'S SIGNATURE

____
Name

___________________________________ **Date** _____/ _____ / _________
Signature *dd mmm yyyy*