| | |
|---|---|
| **Study Title:** | **A Phase 2, Multi-Center Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Evaluate the Safety and Efficacy of a Topical Formulation of Sirolimus for Cutaneous Angiofibromas in Subjects with Tuberous Sclerosis Complex (TSC) Followed by an Optional Open-label Phase** |
| **Drug Name/Dosage:** | **Sirolimus Ointment** |
| **Protocol No:** | **AUCTA-UAP006-PH2** |
| **IND Number:** | **125130** |
| **Author(s):** | Carol Udell<br>Senior Director<br>Clinical Data Management and Biostatistics<br>TKL Research, Inc. |
| **Development phase:** | 2 |
| **Document status:** | FINAL |
| **Document version and date:** | Version 8 – 16April2021 |
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## SIGNATURE PAGE

**Protocol number: AUCTA-UAP006-PH2**

The signatures of the representatives below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations stated in the protocol, including all statements as to confidentiality. It is also agreed that the study will not be initiated without the approval of an appropriate Institutional Review Board or Ethics Review Committee.

**Signatures:**

| | | |
|---|---|---|
| | shoufengli | April 28, 2021 |
| Shoufeng Li<br>Chief Executive Officer<br>Aucta Pharmaceuticals | Signature | Date |
| | Yunrong Wei | April 29, 2021 |
| Yunrong Wei, MD<br>Medical Monitor<br>dMed Biopharmaceutical Co., Ltd | Signature | Date |

## SIGNATURE PAGE FOR INVESTIGATOR(S)

**Product:** **Sirolimus Ointment**

**Protocol number:** **AUCTA-UAP006-PH2**

**Protocol title:** **A Phase 2, Multi-Center Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Evaluate the Safety and Efficacy of a Topical Formulation of Sirolimus for Cutaneous Angiofibromas in Subjects with Tuberous Sclerosis Complex (TSC) Followed by an Optional Open-label Phase**

The signature of the study investigator below constitutes his/her approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations, clinically and administratively, as detailed in the protocol. It is agreed that the conduct and results of this study will be kept confidential.

| | |
|---|---|
| Principal Investigator's Signature | Date |

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| ALT | Alanine transaminase |
| AST | Aspartate transaminase |
| BUN | Blood urea nitrogen |
| CRF | Case report form |
| CRO | Contract Research Organization |
| DMC | Data Monitoring Committee |
| DMSO | Dimethyl sulfoxide |
| eCRF | Electronic case report form |
| EOS | End of study |
| EOT | End of treatment |
| ET | Early termination |
| EU | European Union |
| FASI | Facial Angiofibromas Severity Index |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| ID | Identification |
| IEC | Independent Ethics Committee |
| IGA | Investigator's Global Assessment |
| IP | Investigational product |
| IRB | Institutional Review Board |
| IRC | Independent Review Committee |
| ITT | Intent to treat |
| MCH | Mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| mTOR | Mammalian target of rapamycin |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OTC | Over the counter |

| Abbreviation | Definition |
|---|---|
| PgP inhibitor | Permeability glycoprotein 1 inhibitors |
| PIND | Pre-IND (meeting with FDA) |
| PK | Pharmacokinetic(s) |
| PP | Per-Protocol |
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SAR | Suspected adverse reaction |
| SD | Standard deviation |
| SOP | Standard operating procedure |
| SUSAR | Suspected unexpected serious adverse reaction |
| TSC | Tuberous sclerosis complex |
| UPT | Urine pregnancy test |
| US | United States |
| WBC | White blood cell |

## 1.0 SYNOPSIS

| | |
|---|---|
| Study Title: | A Phase 2, Multi-Center Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Evaluate the Safety and Efficacy of a Topical Formulation of Sirolimus for Cutaneous Angiofibromas in Subjects with Tuberous Sclerosis Complex (TSC) Followed by an Optional Open-label Phase |
| Protocol Number: | AUCTA-UAP006-PH2 |
| Sponsor: | Aucta Pharmaceuticals, Inc. |
| Development Phase: | Phase 2 |
| Study Objectives: | The objective of this study is to evaluate the safety and efficacy of sirolimus (0.2% and 0.4% formulations) and its vehicle when applied topically once daily for 12 weeks for the treatment of cutaneous angiofibromas in pediatric subjects with tuberous sclerosis complex (TSC). |
| Study Design: | This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study designed to assess the safety and efficacy of topically-applied sirolimus for the treatment of cutaneous angiofibromas in pediatric subjects with TSC. Approximately 45 subjects will be enrolled at investigational sites in the United States (US) and China, though other countries may be added in the future. Approximately 45 subjects who meet the study entry criteria will randomly be assigned in a 1:1:1 ratio to receive 1 of 3 treatments: sirolimus 0.2% ointment, sirolimus 0.4% ointment, or placebo ointment. The randomization is stratified by site. Subjects, or a parent/guardian, will apply the study medication topically to the cutaneous angiofibromas on the face once daily at night before going to bed for 12 weeks. Subjects who complete the double-blind phase of the study, with an overall compliance rate >80% as determined by the dosing diary, will be offered entry into an open-label period for an additional 12 weeks. |

| | |
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| | The maximum study duration for each subject will be approximately 30 weeks and includes a screening period of up to 4 weeks, a blinded treatment period of 12 weeks, optional open-label period of 12 weeks, and a follow-up period of 2 weeks. |
| Planned Sample Size: | 45 subjects evaluable for analysis |

| | |
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| Study Population: | Subjects must meet all of the following criteria to be eligible for participation in the study:<br>1. Generally healthy males or non-pregnant females aged 2 to 21 years, inclusive, at the time of screening.<br>2. Diagnosis of TSC with visible facial angiofibromas of at least grade 3 up to grade 5, inclusive, based on the IGA.<br>3. Subjects with 3 or more isolated, measurable lesions of facial angiofibroma, with color grading score ≥2 for each of the 3 lesions.<br>4. Females of childbearing potential must have a negative urine pregnancy test (or a negative serum pregnancy test if a urine pregnancy test cannot be obtained) (For China, different pregnancy test procedure would be followed) and if sexually active or become sexually active during the study, must agree to use an effective form of birth control for the duration of the study. Females using oral contraceptives must also use a barrier method of contraception during the study. Sexually active male subjects and/or their female partners should also use appropriate contraception.<br>Effective contraception is defined as follows:<br>• Oral/implant/injectable/transdermal/estrogenic vaginal ring contraceptives, intrauterine device, condom with spermicide, diaphragm with spermicide.<br>• Abstinence or partner's vasectomy are acceptable if the female agrees to implement one of the other acceptable methods of birth control if her partner changes.<br>5. The subject and/or their parent or guardian must be willing and able to provide written informed consent/assent.<br>6. Willing and able to comply with all trial requirements. |

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| | 7. Subject or parent/guardian must be able to complete the subject self-assessment survey and subject diary in English or another language into which the documents have been officially translated.<br>8. Subjects should be in good general health based on the subject's medical history, physical exam, and impression of the study doctor.<br><br>A subject who fulfills any of the following criteria will be ineligible to participate in the study:<br><br>9. Has any chronic or acute medical condition, that in the opinion of the investigator, may pose a risk to the safety of the subject during the trial period, or may interfere with the assessment of safety or efficacy in this trial.<br>10. Has received oral or topical therapy with an mTOR inhibitor (sirolimus, temsirolimus, or everolimus) within 1 month of Baseline or other dermatologic treatment to facial angiofibromas within 1 month of Baseline. (Sunscreen is expected to be used in this patient population and is not considered treatment).<br>11. Is currently receiving any form of immunosuppression therapy or has previously experienced significant immune dysfunction.<br>12. Has a history of sensitivity to any component of the investigational product.<br>13. Is pregnant, plans to become pregnant during the course of the study, or is breastfeeding.<br>14. Has other dermatologic conditions, pigmentation, scarring, pigmented lesions or sunburn in the treatment area that would preclude or prevent adequate assessment of changes to their facial angiofibromas.<br>15. Has facial hair (e.g., beard, sideburns, mustache) that could interfere with study assessments.<br>16. Has had laser surgery or cryotherapy to facial angiofibromas, within 6 months preceding study entry. |

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|---|---|
| | 17. Requires the use of any concomitant medication that, in the investigator's opinion, has the potential to cause an adverse effect when given with the investigational product or will interfere with the interpretation of the study results (see Section 16.1 Appendix 1 for Potential Drug Interactions).<br>18. Has participated in another clinical trial or received an investigational product within 3 months prior to screening. |
| Investigational Product(s): | The investigational product is sirolimus (0.2% and 0.4%) administered as an ointment formulation for topical administration during the double-blind treatment period. Subjects entering the open-label treatment period will receive sirolimus 0.2% administered as an ointment formulation for topical administration. |
| Reference Product(s): | Not applicable. |
| Control Product(s): | Placebo ointment that contains the same ingredients as the active formulations without the active ingredient. |
| Efficacy Evaluation Criteria: | The primary efficacy endpoint will be the proportion of subjects with a clinical response of treatment success at Week 12. Treatment success is defined as:<br>• At least a 2-grade improvement on the Week 12 Investigator Global Assessment (IGA) of the facial skin lesions assessed by investigator.<br>Secondary efficacy endpoints will be the following:<br>• The proportion of subjects with an investigator assessed IGA score of clear or almost clear with at least a 2-grade improvement on the Week 12 IGA of the facial skin lesions;<br>• The proportion of subjects with at least 30% improvement at Week 12 as compared to Baseline in the Facial Angiofibromas Severity Index (FASI) |

| | |
|---|---|
| | score, which is based on lesion erythema, size, and extension (Salido et.al. 2012);[20]<br>• The time to reach at least 30% improvement from Baseline in the FASI score for angiofibroma severity;<br>• The proportion of subjects with at least 2-grade improvement at Week 12 as compared to Baseline in categorical lesion counts (scored as follows: No lesion = 0; <25 lesions = 1; 25-50 lesions = 2; 51-75 lesions = 3, >75 lesions = 4);<br>• The proportion of subjects with at least 2-grade improvement at Week 12 as compared to Baseline in lesion elevation score;<br>• The proportion of subjects with at least 2-grade improvement at Week 12 as compared to Baseline in the subject self-assessment survey;<br>• Overall Response of angiofibroma assessed by the investigator at Week 12 as compared to baseline based on Modified Nobel Scoring System;<br>• Overall Response of angiofibroma assessed by the IRC at Week 12 as compared to baseline based on Modified Nobel Scoring System;<br>• The proportion of subjects with at least Moderate Improvement (a score of 2) on Modified Nobel Scoring System assessed by the investigator at Week 12;<br>• The proportion of subjects with at least Moderate Improvement (a score of 2) on Modified Nobel Scoring System assessed by the IRC at Week 12;<br>• The proportion of subjects with at least a 2-grade improvement on the Week 12 Investigator Global Assessment (IGA) of the facial skin lesions assessed by IRC. |

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| Safety Evaluation Criteria: | Adverse event incidence and severity, laboratory test results (hematology, clinical chemistry, urinalysis), vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate), physical examination. |
| Statistical Methods: | **Primary efficacy endpoint:** The primary efficacy endpoint will be the proportion of subjects with a clinical response of treatment success on Week 12, defined as:<br>• At least a 2-grade improvement on the Week 12 Investigator Global Assessment (IGA) of the facial skin lesions assessed by investigator. The primary efficacy endpoint will be analyzed using Fisher's exact test, making all pairwise treatment comparisons.<br>**Secondary efficacy endpoints:** Treatment comparison of the proportion of treatment success with clear or almost clear will be conducted using Fisher's exact test at each time point, making all pair-wise comparisons. Descriptive statistics for observed values, absolute changes and percent changes from Baseline for Facial Angiofibromas Severity Index [FASI] lesion score, and Number and percentage of subjects reached overall response level for Modified Nobel Scoring System score will be summarized by treatment group at each time point during the double-blind period. Student's t-test will be used for pairwise comparison of continuous endpoints at each time point. Wilcoxon rank sum test will be used to compare Modified Nobel Scoring System score. Fisher's exact test will be used for categorical endpoints. Time to reach at least 30% improvement from Baseline in the Composite score or FASI score will be analyzed using Kaplan-Meier method, making all pairwise treatment comparisons. Proportion of subjects with at least Moderate Improvement on Modified Nobel Scoring System will be analyzed using Fisher's exact test, making all pair-wise comparison. Proportion of subjects with at least a 2-grade improvement on the Week 12 IGA will be analyzed using Fisher's exact test, making all pair-wise comparisons. Hazard ratio and 95% CI will be calculated using Cox model. Blood samples for pharmacokinetic analyses will be collected to confirm systemic pharmacokinetics.<br>**Safety:** The assessment of safety will be based mainly on the frequency of adverse events (AEs) and on the number of laboratory values that fall outside of predetermined ranges. |

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| | Adverse events will be presented in data listings and summarized by frequency and severity for each treatment group. Laboratory and vital sign data will be presented in data listings. Abnormal laboratory findings will be presented. |
| Study Sites: | Up to 15 sites in United States and China, though other countries may be added in the future |
| Planned Dates of Study: | 5 Feb 2018 to 31 Dec 2021 |

## Table 1-1 Visit Schedule and Assessments

| | | | Blinded Phase | | | Open-label Phase | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Examination** | **Visit 1** | **Visit 2** | **Visit 3** | **Telephone Visit 4** | **Visit 5** | **Visit 6** | **Telephone Visit 7** | **Visit 8** | **Telephone End of Study (EOS)** | **Early Termination** |
| | **Screening** | **Baseline** | **Week 4** | **Week 8** | **Week 12 (EOT DB)** | **Week 16** | **Week 20** | **Week 24 (EOT OL)** | | |
| | **Up to Day –28** | **Day 1** | **Day 28 ± 7 d** | **Day 56 ± 7 d** | **Day 84 ± 7 d** | **Day 112 ± 7 d** | **Day 140 ± 7 d** | **Day 168 ± 7 d** | **14 ± 3 days after final dose of IP[a]** | |
| Informed consent/assent Photographic consent/assent | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | X[b] | | | | | |
| Demographics/background information | X | | | | | | | | | |
| Medical history | X | X | | | | | | | | |
| Prior and concomitant medication assessment | X | X | X | X | X | X | X | X | X | X |
| Physical examination | X | | | | | | | X | | X |
| Vital signs | X | X | X | | X | X | | X | | X |
| Samples (blood and urine) for clinical laboratory assessment | X | | X | | X | X | | X | | X |
| Pharmacokinetics | | | X | | | | | | | |
| Urine pregnancy test, if applicable[c] | X | X | X | | X | X | | X | | X |
| Randomization | | X | | | | | | | | |
| Weigh study product; dispense to subject | | X | X | | X | X | | | | |

| | | | Blinded Phase | | | Open-label Phase | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Examination** | **Visit 1** | **Visit 2** | **Visit 3** | **Telephone Visit 4** | **Visit 5** | **Visit 6** | **Telephone Visit 7** | **Visit 8** | **Telephone End of Study (EOS)** | **Early Termination** |
| | **Screening** | **Baseline** | **Week 4** | **Week 8** | **Week 12 (EOT DB)** | **Week 16** | **Week 20** | **Week 24 (EOT OL)** | | |
| | **Up to Day –28** | **Day 1** | **Day 28 ± 7 d** | **Day 56 ± 7 d** | **Day 84 ± 7 d** | **Day 112 ± 7 d** | **Day 140 ± 7 d** | **Day 168 ± 7 d** | **14 ± 3 days after final dose of IP[a]** | |
| Dispense subject diary | | X | X | | X | X | | | | |
| IGA | X | X | X | | X | X | | X | | X |
| FASI (assessment of erythema, size, extension) | X | X | X | | X | | | X | | X |
| Modified Nobel Scoring System | | X | X | | X | X | | X | | X |
| Lesion count | X | X | X | | X | | | X | | X |
| Assessment of lesion elevation | X | X | X | | X | | | X | | X |
| Photography | X | X | X | | X | X | | X | | X |
| Subject self-assessment survey | X | X | X | | X | X | | X | | X |
| Collect used study medication; weigh the medication tube | | | X | Query Compliance | X | X | Query Compliance | X | | X |
| Review subject diary | | | X | Query Compliance | X | X | Query Compliance | X | | X |
| Record adverse events | X | X | X | X | X | X | X | X | X | X |

EOT = End of Treatment; EOS = End of Study; DB = Double-blind; OL = Open-label; IGA = Investigator's Global Assessment; FASI = Facial Angiofibromas Severity Index; IP = Investigational product.

a: Subjects who do not enter the open-label phase of the trial will complete the End of Study visit 14 ± 3 days after the final double-blind dose at Visit 5 (Week 12). Subjects who do enter the open-label phase of the trial will complete the End of Study visit 14 ± 3 days after the final open-label dose at Visit 8 (Week 24).

b: Inclusion criteria only are assessed for entry into the Open-label phase.

c: Urine pregnancy tests are to be performed on females of childbearing potential. In the unlikely event that a urine pregnancy test cannot be obtained, a serum pregnancy test should be conducted using the serum sample collected (For China, different pregnancy test procedure would be followed).

# 2.0 INTRODUCTION

## 2.1 Background

Tuberous sclerosis complex (TSC) is a rare genetic disease that causes benign tumors to grow in vital organs such as the brain, kidneys, heart, lungs, and skin. The disorder affects as many as 25,000 to 40,000 individuals in the United States (US) and about 1 to 2 million individuals worldwide, with an estimated prevalence of one in 6,000 newborns.[1]

Patients with TSC commonly have skin abnormalities which can be disfiguring, especially if they occur on the face. It is estimated that approximately 75% of TSC patients have facial angiofibromas,[2] which consist of blood vessels and fibrous tissue.[1] Facial angiofibromas can lead to bleeding, chronic irritation, and cosmetic disfigurement.[3]

The disease is caused by mutations on the TSC1 gene, the TSC2 gene, or both. The TSC1 gene produces hamartin and TSC2 produces tuberin. It is thought that these proteins inhibit the activity of mTOR (mammalian target of rapamycin), a kinase that regulates cellular metabolism, growth, and proliferation, and that the absence of these proteins leads to abnormal cellular differentiation and development.[1,4] mTOR is aberrantly activated in patients with TSC. This occurs in fibroblast-like cells located within the dermal layer of the skin; these cells produce an epidermal growth factor, epiregulin, which stimulates epidermal cell proliferation.[5] When epidermal cells are produced faster than dead cells are shed, the overproduction of skin cells in conjunction with angiogenesis result in initialization and progression of facial angiofibromas over time.

Current treatment options for facial angiofibromas include destructive approaches such as dermabrasion, surgical excision, and laser therapy.[6] The angiofibromas often recur, requiring repeated procedures and are unsuitable for early intervention. A more targeted therapeutic approach is needed because the invasive approaches have poor compliance, often need to be repeated, are not suitable for early intervention, and are not accessible for many patients.

Rapamycin (or sirolimus) binds to and inhibits the activity of mTOR. Everolimus is a derivative of rapamycin) that acts in a similar fashion to rapamycin.[7] There are a number of reports in the literature of small case studies in which sirolimus or everolimus was used to treat facial angiofibromas.[8-18] In these reports, improvement in the facial skin tumors was noted in all cases, although complete clearance of the skin tumors is not possible due to the underlying mechanism of the disease (i.e., the aberrant activation of mTOR) and the treatment was well tolerated. Salido et al[14] reported that subjects with TSC-associated facial angiofibroma treated with topical sirolimus ointment (0.4%) once daily, 3 times a week for 9 months showed improvement in erythema and in the size and extension of tumors with no local or systemic adverse events.

## 2.2 Nonclinical Safety

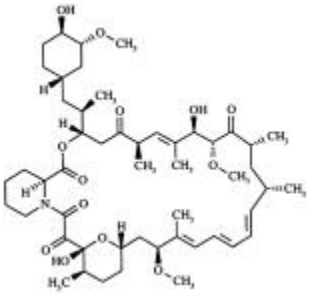
Repeated dermal application up to 13.6 mg/kg/day with 0.8% (w/w) Sirolimus Ointment or the vehicle to male and female minipigs once daily for 13 weeks was well tolerated did not cause any adverse effect in mortality, clinical signs, skin reaction, body weight, food consumption, body temperature, ophthalmic examinations, electrocardiography and clinical pathology.

Considering that the current GLP dermal toxicology study was given at a dose level 50-100 times higher than the anticipated clinical dose (1-2mg applied topically), and based on the oral sirolimus label where whole blood sirolimus trough concentration for 2mg/day is about 8.59 ng/mL (n=226), we expect the clinical plasma concentration to be close or below 0.1 ng/mL range, well below the observed oral sirolimus plasma concentration.

## 2.3 Name and Description of the Investigational Product

The investigational products are sirolimus formulated as an ointment for topical administration and the placebo ointment.

The chemical structure for sirolimus is



The chemical name of sirolimus (also known as rapamycin) is (3S,6R,7E,9R,10R,12R,14S, 15E,17E,19E,21S,23S,26R,27R,34aS)9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1R)-2[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacontine1,5,11,28,29(4H,6H,31H)-pentone. Its molecular formula is C51H79NO13 and its molecular weight is 914.2. [19]

## 2.4 Rationale of the Study

Facial angiofibromas are a common symptom in patients with TSC. They can be disfiguring and can have a negative psychological effect on pediatric patients. The current treatment options, such as dermabrasion, surgical removal, and laser treatment, can be painful, may require general anesthesia, and likely will need to be repeated. A medical treatment, such as a topically-applied medication, would be an easy long-term treatment option for a chronic disease. Such a treatment

option would improve patient compliance and reduce the healthcare burden since untreated skin tumors can progress until hospitalization and surgery are required.

Reports in the literature indicate that sirolimus is a promising candidate for the treatment of TSC-related cutaneous angiofibromas. Concentrations of 0.2% and 0.4% sirolimus were chosen based on literature reports and recommendations from experts in the field.

The study is designed to evaluate the safety and efficacy of sirolimus ointment (0.2% and 0.4% formulations), applied once daily to facial angiofibromas, for 12 weeks. Subjects who complete the double-blind treatment period, who are eligible and willing, will have the option of entering an open-label treatment period of 12 weeks.

### 2.5 Benefit-risk Assessment

Sirolimus (Rapamune), an immunosuppressant, is approved in the US as an orally administered agent for the prophylaxis of organ rejection. The package insert reports that the most common (> 30%) adverse reactions are peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine increased, abdominal pain, diarrhea, headache, fever, urinary tract infection, anemia, nausea, arthralgia, pain, and thrombocytopenia. There is also a boxed warning that increased susceptibility to infection and the possible development of lymphoma and other malignancies may result from immunosuppression.

In the current study with topical administration of sirolimus, systemic exposure to sirolimus is expected to be very low. In literature reports of topically-applied sirolimus and everolimus for the treatment of facial angiofibromas,[8-18] only 1 subject had a detectable blood levels of sirolimus (0.8 mmol/L).[17] Additionally, the topical treatment was well tolerated and no systemic or local adverse effects were reported.

Patients might benefit from the trial, because it is expected that the facial angiofibromas will improve. There is currently no FDA approved pharmaceutical treatment for this disease condition. The risks of participation in the trial include the risks associated with the study procedures (e.g., blood drawing) which are similar to other trials of investigative agents. No systemic or local adverse effects were reported in previous clinical experience with topical sirolimus, although these studies were small. The study has been designed and will be conducted in such a manner as to minimize risks as much as possible. Therefore, the benefit-risk assessment is considered acceptable for a first multiple-dose trial in human.

## 3.0 TRIAL OBJECTIVES AND PURPOSE

The objective of this study is to evaluate the safety and efficacy of sirolimus (0.2% and 0.4% formulations) and its vehicle when applied topically once daily for 12 weeks for the treatment of cutaneous angiofibromas in pediatric subjects with tuberous sclerosis complex (TSC).

# 4.0 STUDY DESIGN

## 4.1 Overall Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study designed to assess the safety and efficacy of topically-applied sirolimus for the treatment of cutaneous angiofibromas in pediatric and adolescent subjects with tuberous sclerosis complex (TSC) with an option to enter an open-label treatment phase. Study subjects will be enrolled at investigational sites in the United States (US) and China, though other countries may be included. Approximately 45 subjects who meet the study entry criteria will be randomly assigned in a 1:1:1 ratio to receive 1 of 3 treatments: sirolimus 0.2% ointment, sirolimus 0.4% ointment, or placebo ointment. The randomization is stratified by site. Subjects will apply the study medication topically to the cutaneous angiofibromas on the face once daily at night for 12 weeks. Subjects who complete the double-blind phase of the study, with an overall compliance rate >80% as determined by the dosing diary, will be offered entry into the open-label period for an additional 12 weeks.

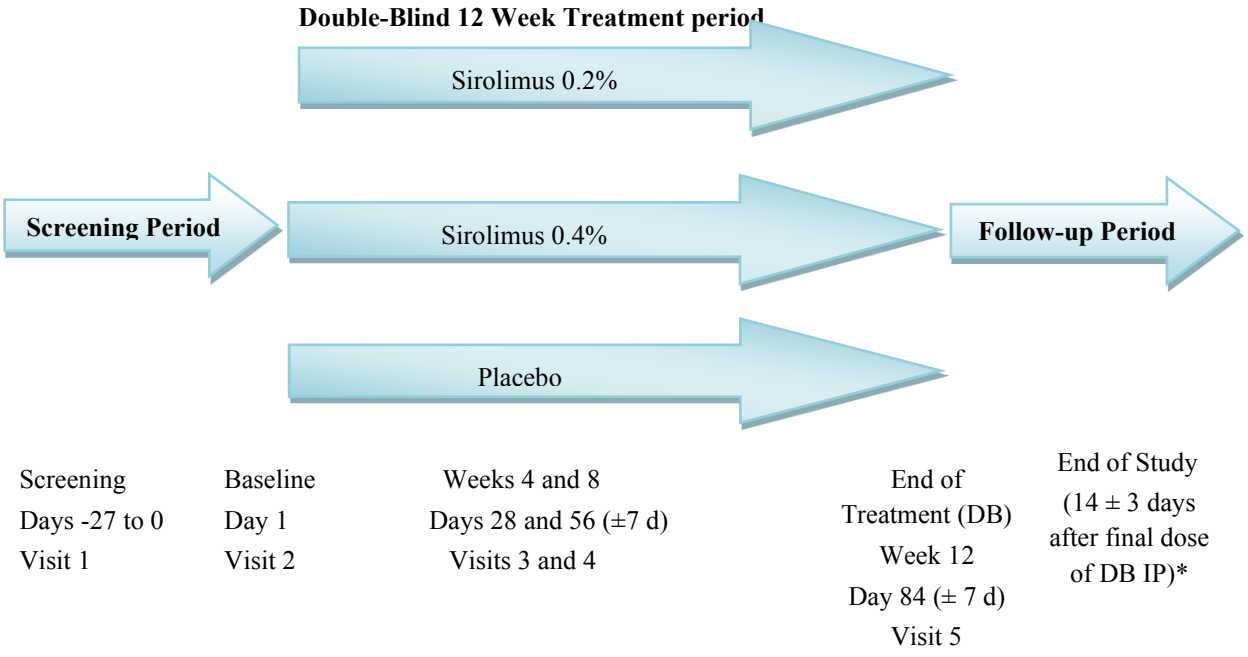
The maximum study duration for each subject will be approximately 30 weeks and includes a screening period of up to 4 weeks, a blinded treatment period of 12 weeks, optional open-label period of 12 weeks, and a follow-up period of 2 weeks. After the parent/guardian has provided written informed consent and the subject has assented (for subjects younger than 18 years) or after the subject has provided informed consent (for subjects 18 years of age), the subject will undergo screening procedures.

At the end of the screening period, eligible subjects will be randomly assigned to one of the study treatment groups on Day 1 (Baseline) of the treatment period. The randomization is stratified by site.

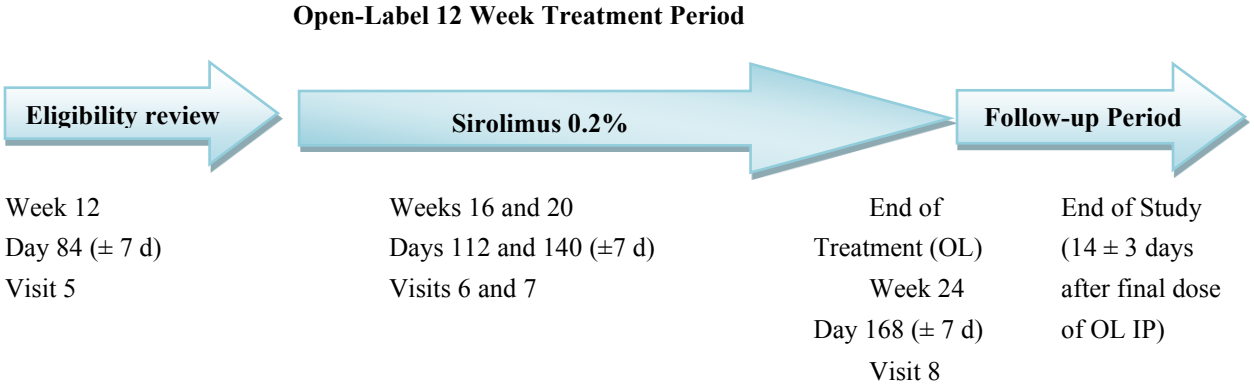
During the double-blind treatment period, subjects will return to the study site according to the study schedule for interim efficacy assessments and review of concomitant medications, the dosing diary, vital signs, and adverse events (AEs). At each clinic visit, subjects will be rated by the investigator on an Investigator's Global Assessment (IGA) as well as undergo specified safety assessments. At each clinic visit, subjects (or their parent/guardian) will be asked to complete a subject self-assessment questionnaire. Blood samples for pharmacokinetic analyses will be collected. In addition, a telephone visit will be conducted at Week 8 (Visit 4) for a review of concomitant medications, IP compliance and adverse events (AEs).

The study design is summarized in Figure 4-1.

**Figure 4-1 Study Design**




*Subjects participating in the open-label treatment period will not enter into the follow-up period or have an End of Study visit until the completion of the open-label treatment period.




## 4.2 Study Endpoints

The primary efficacy endpoint will be the proportion of subjects with a clinical response of treatment success at Week 12. Treatment success is defined as:

- At least a 2-grade improvement on the Week 12 Investigator Global Assessment (IGA) of the facial skin lesions assessed by the investigator.

Secondary efficacy endpoints will be the following:

- The proportion of subjects with an investigator assessed IGA score of clear or almost clear with at least a 2-grade improvement on the Week 12 IGA of the facial skin lesions;
- The proportion of subjects with at least 30% improvement at Week 12 as compared to Baseline in the Facial Angiofibromas Severity Index (FASI) score, which is based on lesion erythema, size, and extension (Salido et.al. 2012);[20]
- The time to reach at least 30% improvement from Baseline in the FASI score for angiofibroma severity;
- The proportion of subjects with at least 2-grade improvement at Week 12 as compared to Baseline in categorical lesion counts (scored as follows: No lesion = 0; <25 lesions = 1; 25-50 lesions = 2; 51-75 lesions = 3, >75 lesions = 4);
- The proportion of subjects with at least 2-grade improvement at Week 12 as compared to Baseline in lesion elevation score;
- The proportion of subjects with at least 2-grade improvement at Week 12 as compared to Baseline in the subject self-assessment survey;
- Overall Response of angiofibroma assessed by the investigator at Week 12 as compared to baseline based on Modified Nobel Scoring System;
- Overall Response of angiofibroma assessed by the IRC at Week 12 as compared to baseline based on Modified Nobel Scoring System;
- The proportion of subjects with at least Moderate Improvement (a score of 2) on Modified Nobel Scoring System assessed by the investigator at Week 12;
- The proportion of subjects with at least Moderate Improvement (a score of 2) on Modified Nobel Scoring System assessed by the IRC at Week 12;
- The proportion of subjects with at least a 2-grade improvement on the Week 12 Investigator Global Assessment (IGA) of the facial skin lesions assessed by the IRC.

Blood samples for pharmacokinetic analyses will be collected to confirm systemic pharmacokinetics.

Safety will be assessed through the monitoring of AEs, laboratory test results, vital signs, and physical examinations.

# 5.0 SELECTION OF STUDY POPULATION

## 5.1 Subject Population

A sufficient number of subjects will be enrolled in order to provide 45 subjects randomized. An individual subject will be allowed to participate in the study one time only. A rationale for the choice of sample size is provided in Section 8.2 of this protocol.

Each potential subject will sign and date an informed consent document before any study-specified procedures are performed. For subjects younger than age 18, the parent/guardian must provide written informed consent and the subjects will provide assent in conformance with the Institutional Review Board (IRB) requirements.

## 5.2 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for participation in the study:

1. Generally healthy males or non-pregnant females aged 2 to 21 years, inclusive, at the time of screening.
2. Diagnosis of TSC with visible facial angiofibromas of at least grade 3 up to grade 5, inclusive, based on the IGA, at the time of screening.
3. Subjects with 3 or more isolated, measurable lesions of facial angiofibroma, with color grading score ≥2 for each of the 3 lesions.
4. Females of childbearing potential must have a negative urine pregnancy test (or a negative serum pregnancy test if a urine pregnancy test cannot be obtained) (For China, different pregnancy test procedure would be followed) and if sexually active or become sexually active during the study, must agree to use an effective form of birth control for the duration of the study. Females using oral contraceptives must also use a barrier method of contraception during the study. Sexually active male subjects and/or their female partners should also use appropriate contraception.

   Effective contraception is defined as follows:

   - Oral/implant/injectable/transdermal/estrogenic vaginal ring contraceptives, intrauterine device, condom with spermicide, diaphragm with spermicide.
   - Abstinence or partner's vasectomy are acceptable if the female agrees to implement one of the other acceptable methods of birth control if her partner changes.

5. The subject and/or their parent or guardian must be willing and able to provide written informed consent/assent.
6. Willing and able to comply with all trial requirements.

7. Subject or parent/guardian must be able to complete the subject self-assessment survey and subject diary in English or another language into which the documents have been officially translated.
8. Subjects should be in good general health based on the subject's medical history, physical exam, and impression of the study doctor.

### 5.3 Exclusion Criteria

A subject who fulfills any of the following criteria will be ineligible to participate in the study:

9. Has any chronic or acute medical condition, that in the opinion of the investigator, may pose a risk to the safety of the subject during the trial period, or may interfere with the assessment of safety or efficacy in this trial.
10. Has received oral or topical therapy of an mTOR inhibitor (sirolimus, temsirolimus, or everolimus) within 1 month of Baseline or dermatologic treatment for facial angiofibromas within 1 month of Baseline. (Note: Sunscreen is not considered treatment for this condition and is expected to be used for skin protection in this patient population.)
11. Is currently receiving any form of immunosuppression therapy or has previously experienced significant immune dysfunction.
12. Has a history of sensitivity to any component of the investigational product.
13. Is pregnant, plans to become pregnant during the course of the study, or is breastfeeding.
14. Has other dermatologic conditions, pigmentation, scarring, pigmented lesions or sunburn in the treatment area that would preclude or prevent adequate assessment of changes to their facial angiofibromas.
15. Has facial hair (e.g., beard, sideburns, mustache) that could interfere with study assessments.
16. Has had laser surgery or cryotherapy to facial angiofibromas within 6 months preceding study entry.
17. Requires the use of any concomitant medication that, in the investigator's opinion, has the potential to cause an adverse effect when given with the investigational product or will interfere with the interpretation of the study results (see Section 16.1 Appendix 1 for Potential Drug Interactions).
18. Has participated in another clinical trial or received an investigational product within 3 months prior to screening.

## 5.4 Discontinuation of Treatment

In accordance with legal requirements and International Conference on Harmonization (ICH) – Good Clinical Practice (GCP) guidelines, every subject has the right to refuse further participation in this study at any time and without providing reasons (see also Section 9.2). A subject's participation is to be terminated immediately upon his/her request. The investigator should seek to obtain the reason and record this on the case report form (CRF) whenever possible.

If, at the time of refusal, a study product has already been administered, the subject should be advised on follow-up safety investigations.

The termination of an individual's participation should be considered in case of a serious adverse event (SAE). Should a subject develop conditions during the course of the study that would have prevented his/her entry into the study according to the safety-related medical exclusion criteria, he/she must be withdrawn immediately.

A subject may be withdrawn from the study at any time at the discretion of the investigator for medical reasons and/or due to non-adherence to the treatment scheme and other duties stipulated in the study protocol. The reasons for early termination are to be fully documented on the CRF.

In addition, the sponsor reserves the right to end or suspend the study at any time or a subject's participation due to a protocol amendment (see Section 9.2).

If a subject withdraws from the study, all efforts will be made to bring the subject in for completion of an Early Withdrawal visit.

Subjects discontinued for an AE will be monitored until the AE is resolved, a reasonable explanation is provided for the event, or the subject is referred to his/her own primary medical doctor. The specific AE in question will be recorded on the appropriate CRF.

## 5.5 Replacement Policy

There will be no replacements in this study. Dropouts will be addressed by additional enrollment if necessary.

## 5.6 Dietary and Lifestyle Restrictions

Subjects should avoid alterations to their diet, level of activity and lifestyle that would affect their participation during the study.

Subjects should avoid excessive sun exposure to the face.

# 6.0 STUDY TREATMENTS

## 6.1 Investigational Products and Controls

The study product under investigation in this study is sirolimus administered as an ointment formulation for topical administration. Two concentrations/dosages of sirolimus (0.2% and 0.4%) will be studied.

The ointment contains sirolimus (0.2% and 0.4%) as API, 4~10% white mineral oil as emollient, ~5% Labrasol® as surfactant, 2-6% Compritol® 888 ATO as thickener, 4.5% propylene carbonate (PC) and dimethyl sulfoxide (DMSO) as solvent and the remaining ingredients will be white petrolatum as the ointment base.

The placebo/vehicle contains the same ingredients as the active formulation(s) without the active ingredient.

For the open-label treatment period, sirolimus 0.2% will be administered as an ointment formulation for topical administration.

## 6.2 Dosing Regimen

Subjects are to apply the study product topically to the affected areas on the face, once daily at bedtime after thorough washing of the face. The study medication should be applied in sufficient quantity to cover the facial lesion. The typical dose of the medication is about 1.0 cm of ointment, which is about a pea-size or fingertip amount of medication. The recommended dose for application to the lesions on the face is a minimum of 0.5 cm. Subjects are to continue to apply study medication for the entire treatment period.

If subjects are night workers, they may apply the medication in the morning after they have showered and are preparing for sleep. Medication application should be consistently applied at near the same time each day.

Detailed application instructions will be provided in the subject instructions.

If a subject misses a dose >4 hours, that dose should be counted as missed and the subject should wait to apply investigational product at the next scheduled time of dosing.

Should the study product come in contact with the eyes, the eyes should be flushed with tepid to warm water for approximately five minutes.

## 6.3 Packaging, Labeling and Storage

The investigational product will be packaged and distributed by Bellwyck Packaging Solutions and will be labeled according to all applicable federal regulations.

The study medication will be supplied to the clinical site(s) as tubes containing 30 g of ointment.

For the double-blind treatment period, study medication will be packaged as kits containing seven (7) tubes. For the open-label treatment period, appropriately labeled study medication will be supplied to each site.

Study medication will be refrigerated in a secure environment under the control of the investigator, pharmacist, or a study coordinator/nurse, and maintained at a controlled temperature (35.6°F to 46.4°F or 2°C to 8°C). Excursions up to 86°F or 30°C are permitted.

Study medication will be kept by the subject in a refrigerator. When traveling and during application, the study medication may be kept at room temperature.

## 6.4 Assignment to Treatment

### 6.4.1 Randomization

At the Screening Visit and throughout the trial, subjects will be identified by a subject number that will consist of the three-digit site number and a three-digit sequential number, beginning with 001. Site numbers will be 100-1500.

A subject who fulfills the trial eligibility requirements will be randomly assigned to treatment at the Baseline visit. Treatment assignment to randomization numbers will be stratified at the site level. Both the kit and treatment tubes within a kit will have a label containing the randomization number for the double-blind treatment period. When a subject is to be randomized, site personnel will sequentially choose the kit with the lowest randomization number from their stock of double-blind kits, unless otherwise instructed by the study team.

Randomization data will be kept strictly confidential, accessible only to authorized persons as defined below, until the time of unblinding.

### 6.4.2 Blinding

This is a double-blind study with the treatment assignment concealed from the subjects, the investigators and their staff, and the clinical research team. All active and placebo investigational products will be of identical appearance, regardless of the dose, during the double-blind phase. Study materials will be packaged and issued in a manner designed to maintain the blind.

In an emergency, when knowledge of the subject's treatment assignment is essential for the clinical management or welfare of the subject, the investigator must contact the Medical Monitor (or designee). Since there is no antidote to sirolimus, the knowledge of treatment is unlikely to be medically valuable.

Prior to unblinding the subject's treatment assignment, the investigator should assess the relationship of an AE to the administration of the study drug. The investigator must then follow the unblinding procedures outlined for the study. If the blind is broken for any reason, the investigator must record the date and reason for breaking the blind on the appropriate CRF and source documents.

If the treatment assignment is unblinded during the double-blind period, the subject will not be allowed participation in the open-label treatment period of the study.

For details of the procedure for unblinding of individual subjects in cases of emergency see Section 13.1.

## 6.5 Study Drug Dispensation

Two tubes of sirolimus/placebo from the kit assigned to the subject based on the randomization number will be dispensed at Baseline during the double-blind treatment period. Four tubes of sirolimus/placebo from the kit assigned to the subject based on the randomization number will be dispensed at Week 4. One additional tube will be provided in each double-blind kit to be used as a replacement tube should the subject lose or misplace a dispensed tube.

Two tubes of sirolimus 0.2% will be dispensed at Week 12 during the open-label treatment period. Four tubes of sirolimus 0.2% will be dispensed at Week 16. For the open-label treatment period, tubes will be available as open stock. At the time of dispensation to the subject, the clinical site will record the Subject Number, Study Visit and sequential number of tube dispensed on the label and drug accountability record.

## 6.6 Replacement Procedure for Study Drug

For the double-blind treatment period, one additional tube will be packaged in each kit for the purpose of replacing a lost or misplaced tube. For the open-label treatment period, a tube from the open stock may be used as a replacement.

## 6.7 Prior and Concomitant Therapy

All medications, including over-the-counter (OTC) drugs, taken within 30 days prior to the start of the study will be recorded at Screening. Thereafter, a record of all medications and supportive therapy taken during the course of the study will be made. Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be recorded on the subject's CRF.

Restrictions regarding prior and concomitant therapies as listed in the Exclusion Criteria must be observed during the study, including the double-blind and open-label treatment and follow-up periods. Subjects that are screen failures due to prohibited concomitant medications, may be re-

screened at a later time if they are no longer exposed to the prohibited products and are otherwise eligible.

Use of the following medication within 1 month prior to the Baseline visit will exclude a potential subject from participation and is prohibited during the study:

- oral therapy with an mTOR inhibitor (sirolimus, temsirolimus, or everolimus)
- topical therapy with an mTOR inhibitor.

Use of the following medications within 1 month prior to the Baseline visit will exclude a potential subject from participation and is prohibited during the study:

- retinoids.

Use of the following medications within 1 month prior to the Baseline visit should be used with caution during the study, though not exclusionary. Subjects on stable doses of these medications must be discussed in advance with the medical monitor prior to inclusion in the study:

- medications that are strong CYP3A4/PgP inhibitors (see Appendix 16.1).

The use of any topical anti-acne agents on the face must be discontinued from at least 1 month prior to the start of study drug dosing through 1 month after the last dose of study drug. Use of the following medications within 1 month prior to the screening visit will exclude a potential subject from participation and is prohibited during the study:

- salicylic acid,
- corticosteroids,
- topical antibiotics,
- other topical treatment in the treatment area.

Laser surgery or cryotherapy to the facial angiofibromas within 6 months prior to the screening visit will exclude a subject from participation and is prohibited during the study.

(Note: Sunscreen is not considered treatment for this condition and is expected to be used for skin protection in this patient population.)

Questions regarding concomitant drugs or therapies should be discussed with the Medical Monitor.

## 6.8 Rescue Medications

There are no rescue medications for this study.

## 6.9 Treatment Compliance

Records of study product used and dosages administered will be kept during the study. Product accountability will be checked by the study monitor during site visits and at the completion of the trial.

The tubes of study medication will be weighed prior to dispensation to the subject. Subjects will be asked to return all unopened, partially used and empty ointment tubes to the study site at each clinic visit. The tubes will be weighed and the weight difference will be analyzed as a measure of product usage. Subjects or their parent/guardian will be asked to complete a simple dosing diary on a daily basis recording the times at which they administered the treatments. A missed dose should also be recorded upon realization that the dose was missed.

Compliance at each visit will be determined as follows:

(# of Dose Days / Total # of Days between visits) * 100

Subjects who are estimated to have missed on average >1.5 doses per week, as recorded in the dosing diary, will be considered non-compliant. All attempts should be made to improve the subject's compliance, including counseling. Subjects may be withdrawn/early terminated from the study due to non-compliance.

An overall compliance rate will be calculated for the double-blind treatment period, at the conclusion of Visit 5, to determine the subject's eligibility for the open-label treatment period. Subjects with an overall compliance rate that is > 80%, as determined by the dosing diary, will be allowed to continue on to the open-label phase of the trial.

Investigators may temporarily suspend dosing at their discretion, however the time subject is off study drug should be minimized. If study drug use is suspended more than 7 days (consecutive or in aggregate in either the double-blind or open-label phase of the trial), the investigator should contact the Medical Monitor to review medical reasons and steps to be taken to assure patient's adherence to study requirements. The exact dates of investigator approved stopping and re-starting study drug will be recorded in the CRF. Investigator initiated suspension of study drug will not count toward overall compliance.

Subjects will be asked to return all unused product at the end of the study.

## 7.0 VISIT SCHEDULE AND ASSESSMENTS

### 7.1 Study Procedures

The visit schedule and assessments are summarized in Table 1-1 Visit Schedule and Assessments

| | | | Blinded Phase | | | Open-label Phase | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Examination** | **Visit 1** | **Visit 2** | **Visit 3** | **Telephone Visit 4** | **Visit 5** | **Visit 6** | **Telephone Visit 7** | **Visit 8** | **Telephone End of Study (EOS)** | **Early Termination** |
| | **Screening** | **Baseline** | **Week 4** | **Week 8** | **Week 12 (EOT DB)** | **Week 16** | **Week 20** | **Week 24 (EOT OL)** | | |
| | **Up to Day –28** | **Day 1** | **Day 28 ± 7 d** | **Day 56 ± 7 d** | **Day 84 ± 7 d** | **Day 112 ± 7 d** | **Day 140 ± 7 d** | **Day 168 ± 7 d** | **14 ± 3 days after final dose of IP[a]** | |
| Informed consent/assent Photographic consent/assent | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | X[b] | | | | | |
| Demographics/background information | X | | | | | | | | | |
| Medical history | X | X | | | | | | | | |
| Prior and concomitant medication assessment | X | X | X | X | X | X | X | X | X | X |
| Physical examination | X | | | | | | | X | | X |
| Vital signs | X | X | X | | X | X | | X | | X |
| Samples (blood and urine) for clinical laboratory assessment | X | | X | | X | X | | X | | X |
| Pharmacokinetics | | | X | | | | | | | |
| Urine pregnancy test, if applicable[c] | X | X | X | | X | X | | X | | X |
| Randomization | | X | | | | | | | | |
| Weigh study product; dispense to subject | | X | X | | X | X | | | | |

## 7.2 Study Visits and Assessments

### 7.2.1 Visit 1 Screening (Visit 1, up to Day –28)

Screening procedures should be completed no more than 28 days prior to the randomization visit (Day 1). The following screening procedures are to be performed:

- Review study information with subject and his/her parent/guardian (for subjects <18 years of age). Obtain written informed consent (including photographic consent) and, for subjects <18 years of age, assent in accordance with the IRB requirements.
- Review inclusion and exclusion criteria with the subject to determine the subject's eligibility.
- Collect medical history and demographic information.
- Review and record prior medication (used within the previous 30 days) and concomitant medication (medications currently used).
- Perform a physical examination, including height and weight.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position.
- Perform the following efficacy assessments:
    - Investigator's Global Assessment (IGA);
    - Facial Angiofibroma Severity Index (FASI) (assessment of erythema, size, and extension);
    - Categorical lesion count using the following categories: (0) no lesion; (1) <25 lesions; (2) 25-50 lesions; (3) 51-75 lesions; (4) >75 lesions;
    - Assessment of lesion elevation.
- Have the subject (or parent/guardian for subjects under the developmental age of 7 years) complete the subject self-assessment survey.
- Obtain blood samples and optional urine samples for a laboratory profile including hematology, clinical chemistry, and urinalysis.
- Perform a urine pregnancy test (UPT) in female subjects of childbearing potential. Instruct all sexually-active female subjects to use approved form(s) of contraception. Instruct sexually active male subjects that they (and/or their female partners) should use appropriate contraception. (In the unlikely event that a urine pregnancy test cannot be obtained, a serum pregnancy test can be run from the serum sample collected.) (For China, different pregnancy test procedure would be followed).

- If subject meets the inclusion/exclusion criteria, schedule Visit 2.
- Take a photograph of the angiofibroma according to the Standardized Operation Procedure (Appendix 2).
- Record any AEs.

### 7.2.2 Visit 2 Randomization/Baseline (Day 1)

- Review inclusion and exclusion criteria to ensure that the subject is qualified for study participation, including laboratory test results from Visit 1.
- Review and record medication used since the Screening visit.
- Record any new medical history since the Screening visit.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position.
- Perform a UPT for females of childbearing potential. Remind sexually-active female subjects of childbearing potential to use approved method(s) of contraception. Remind sexually active male subjects that they (or their female partners) should use appropriate contraception. (In the unlikely event that a urine pregnancy test cannot be obtained, a serum pregnancy test can be run from the serum sample collected.) (For China, different pregnancy test procedure would be followed).
- Perform the following efficacy assessments:
    - Investigator's Global Assessment (IGA);
    - Facial Angiofibroma Severity Index (FASI) (assessment of erythema, size, and extension);
    - Modified Nobel Scoring System (assessment of target lesions and non-target lesions response);
    - Categorical lesion count using the following categories: (0) no lesion; (1) <25 lesions; (2) 25-50 lesions; (3) 51-75 lesions; (4) >75 lesions.
    - Assessment of lesion elevation.
- Have the subject (or parent/guardian for subjects under the developmental age of 7 years) complete the subject self-assessment survey.
- Take a photograph of the angiofibroma according to the Standardized Operation Procedure (Appendix 2).
- Record any AEs.

- Perform randomization by sequentially choosing the kit with the lowest randomization number.
- Weigh the study medication and dispense to the subject or their parent/guardian with dosing instructions.
- Dispense the dosing diary to the subject or parent/guardian.
- Schedule the next visit; instruct the subjects to bring the study medication to the study visit.

### 7.2.3 Blinded Phase

#### 7.2.3.1 Visit 3 (Week 4 ± 7 days)

- Collect the used tubes of study medication from the subject (or parent/guardian) and weigh the tubes.
- Collect and review the dosing diary.
- Review any concomitant medication used since the previous study visit.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position.
- Obtain blood samples and optional urine samples for a laboratory profile including hematology, clinical chemistry, and urinalysis.
- Obtain blood sample for pharmacokinetic analysis.
- Perform a UPT for females of childbearing potential. Remind sexually-active female subjects of childbearing potential to use approved method(s) of contraception. Remind sexually active male subjects that they (or their female partners) should use appropriate contraception. (In the unlikely event that a urine pregnancy test cannot be obtained, a serum pregnancy test can be run from the serum sample collected.) (For China, different pregnancy test procedure would be followed).
- Perform the following efficacy assessments:
    - Investigator's Global Assessment (IGA);
    - Facial Angiofibroma Severity Index (FASI) (assessment of erythema, size, and extension);
    - Modified Nobel Scoring System (assessment of target lesions and non-target lesions response);
    - Categorical lesion count using the following categories: (0) no lesion; (1) <25 lesions; (2) 25-50 lesions; (3) 51-75 lesions; (4) >75 lesions.

- Assessment of lesion elevation.

- Have the subject (or parent/guardian for subjects under the developmental age of 7 years) complete the subject self-assessment survey.
- Take a photograph of the angiofibroma according to the Standardized Operation Procedure (Appendix 2).
- Record any AEs.
- Weigh the study medication and dispense to the subject (or parent/guardian).
- Dispense the dosing diary to the subject.
- Schedule the next study visit; instruct the subjects (or their parent/guardian) to bring the study medication to the study visit.

#### 7.2.3.2 Telephone Visit 4 (Week 8 ± 7 days)

- Review any concomitant medication used since the previous study visit.
- Record any AEs.
- Assess subject's compliance with study medication.
- Assess subject's compliance with maintaining the dosing diary.
- Schedule the next visit; instruct the subject (or parent/guardian) to bring the study medication to the study visit.

#### 7.2.3.3 Visit 5 (Week 12 ± 7 days)

- Collect and review the dosing diary.
- Collect all study materials from the subject (or parent/guardian), including unused study medication, etc.
- Weigh the used tubes of study medication collected from the subject (or parent/guardian).
- Review any concomitant medication used since the previous study visit.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position.
- Obtain blood samples and optional urine samples for a laboratory profile including hematology, clinical chemistry, and urinalysis.
- Perform a UPT for females of childbearing potential. Remind sexually-active female subjects of childbearing potential to use approved method(s) of contraception. Remind sexually active male subjects that they (or their female partners) should use appropriate contraception. (In

the unlikely event that a urine pregnancy test cannot be obtained, a serum pregnancy test can be run from the serum sample collected.) (For China, different pregnancy test procedure would be followed).

- Perform the following efficacy assessments:
  - Investigator's Global Assessment (IGA);
  - Facial Angiofibroma Severity Index (FASI) (assessment of erythema, size, and extension);
  - Modified Nobel Scoring System (assessment of target lesions and non-target lesions response);
  - Categorical lesion count using the following categories: (0) no lesion; (1) <25 lesions; (2) 25-50 lesions; (3) 51-75 lesions; (4) >75 lesions;
  - Assessment of lesion elevation.
- Have the subject (or parent/guardian for subjects under the developmental age of 7 years) complete the subject self-assessment survey.
- Take a photograph of the angiofibroma according to the Standardized Operation Procedure (Appendix 2).
- Record any AEs.
- If subject will not be participating in the open-label treatment period, schedule the End of Study Visit.
- If the subject will be participating in the open-label treatment period:
  - Subject must have completed the double-blind treatment period, with an overall compliance rate that is > 80%, as determined by the dosing diary.
  - Weigh the open-label study medication and dispense to the subject or their parent/guardian.
  - Dispense the dosing diary to the subject.
  - Schedule the next visit; instruct the subject to bring the study medication to the study visit.

### 7.2.4 Open-label Phase

#### 7.2.4.1 Visit 6 (Week 16 ± 7 days)

- Collect the used tubes of study medication from the subject (or parent/guardian) and weigh the tubes.
- Collect and review the dosing diary.

- Review any concomitant medication used since the previous study visit.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position.
- Obtain blood samples and optional urine samples for a laboratory profile including hematology, clinical chemistry, and urinalysis.
- Perform a UPT for females of childbearing potential. Remind sexually-active female subjects of childbearing potential to use approved method(s) of contraception. Remind sexually active male subjects that they (or their female partners) should use appropriate contraception. (In the unlikely event that a urine pregnancy test cannot be obtained, a serum pregnancy test can be run from the serum sample collected.) (For China, different pregnancy test procedure would be followed).
- Perform the Investigator's Global Assessment (IGA).
- Perform the Modified Nobel Scoring System (assessment of target lesions and non-target lesions response).
- Have the subject (or parent/guardian for subjects under the developmental age of 7 years) complete the subject self-assessment survey.
- Take a photograph of the angiofibroma according to the Standardized Operation Procedure (Appendix 2).
- Record any AEs.
- Weigh the study medication and dispense to the subject (or parent/guardian).
- Dispense the dosing diary.
- Schedule the next visit; instruct the subjects (or parent/guardian) to bring the study medication to the study visit.

#### 7.2.4.2 Telephone Visit 7 (Week 20 ± 7 days)

- Review any concomitant medication used since the previous study visit.
- Record any AEs.
- Assess subject's compliance with study medication.
- Assess subject's compliance with maintaining the dosing diary.
- Schedule the next visit; instruct the subjects (or parent/guardian) to bring the study medication to the study visit.

#### 7.2.4.3 Visit 8 (Week 24 ± 7 days)

- Collect and review the dosing diary.
- Collect all study materials from the subject (or parent/guardian), including unused study medication, etc.
- Weigh the used tubes of study medication collected from the subject (or parent/guardian).
- Review any concomitant medication used since the previous study visit.
- Perform a physical examination, including height and weight.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position.
- Obtain blood samples and optional urine samples for a laboratory profile including hematology, clinical chemistry, and urinalysis.
- Perform a UPT for females of childbearing potential. Remind sexually-active female subjects of childbearing potential to use approved method(s) of contraception. Remind sexually active male subjects that they (or their female partners) should use appropriate contraception. (In the unlikely event that a urine pregnancy test cannot be obtained, a serum pregnancy test can be run from the serum sample collected.) (For China, different pregnancy test procedure would be followed).
- Perform the following efficacy assessments:
    - Investigator's Global Assessment (IGA);
    - Facial Angiofibroma Severity Index (FASI) (assessment of erythema, size, and extension);
    - Modified Nobel Scoring System (assessment of target lesions and non-target lesions response);
    - Categorical lesion count using the following categories: (0) no lesion; (1) <25 lesions; (2) 25-50 lesions; (3) 51-75 lesions; (4) >75 lesions;
    - Assessment of lesion elevation.
- Take a photograph of the angiofibroma according to the Standardized Operation Procedure (Appendix 2).
- Have the subject (or parent/guardian for subjects under the developmental age of 7 years) complete the subject self-assessment survey.
- Record any AEs.

- Schedule the End of Study Visit.

### 7.2.5 Telephone End of Study Visit (14 ± 3 days after final dose of IP) – Both Blinded and Open-Label Participants

- Review any concomitant medication used since the previous study visit.
- Record any AEs.
- Inform Subjects that they may be approached to participate in future trials with this product.
- Dismiss the subject from the study.

### 7.2.6 Early Termination (Blinded and Open-Label)

If a subject withdraws from the study prior to the End of Study visit, the subject is to return to the site. The early termination procedures should be performed, as specified below:

- Collect all study materials from the subject (or parent/guardian), including used and unused study medication, subject dosing diary, etc.
- Weigh the used tubes of study medication collected from the subject.
- Review any concomitant medication used since the previous study visit.
- Perform a physical examination, including height and weight.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position.
- Obtain blood samples and optional urine samples for a laboratory profile including hematology, clinical chemistry, and urinalysis.
- Perform a UPT for females of childbearing potential. Remind sexually-active female subjects of childbearing potential to use approved method(s) of contraception. Remind sexually active male subjects that they (or their female partners) should use appropriate contraception. (In the unlikely event that a urine pregnancy test cannot be obtained, a serum pregnancy test can be run from the serum sample collected.) (For China, different pregnancy test procedure would be followed).
- Perform the following efficacy assessments:
    - Investigator's Global Assessment (IGA);
    - Facial Angiofibroma Severity Index (FASI) (assessment of erythema, size, and extension);
    - Modified Nobel Scoring System (assessment of target lesions and non-target lesions response);

- Categorical lesion count using the following categories: (0) no lesion; (1) <25 lesions; (2) 25-50 lesions; (3) 51-75 lesions; (4) >75 lesions;
- Assessment of lesion elevation.

- Have the subject (or parent/guardian for subjects under the developmental age of 7 years) complete the subject self-assessment survey.
- Take a photograph of the angiofibroma according to the Standardized Operation Procedure (Appendix 2).
- Record any AEs.
- Inform Subjects that they may be approached to participate in future trials with this product.
- Dismiss the subject from the study.

## 7.3 Efficacy Assessments

Efficacy will be assessed using the Investigator's Global Assessment (IGA) of the facial skin lesions; the facial angiofibromas severity index (FASI), a composite score based on erythema, size, and lesion extension scores; time to and proportion of subjects with a 30% improvement of the composite score (FASI); lesion counts; proportion of subjects with at least 2-grade improvement in categorical lesion counts; proportion of subjects with at least 2-grade improvement in lesion elevation score; and proportion of subjects with at least 2-grade improvement in the subject self-assessment survey; overall response assessment of target lesions and non-target lesions including the size and color based on Modified Nobel Scoring System; proportion of subjects with at least Moderate Improvement on Modified Nobel Scoring System; and proportion of subjects with at least a 2-grade improvement on the Week 12 IGA. Photographs will be taken of the involved area for documentation purposes at clinic visits.

### 7.3.1 Primary Efficacy Assessment: Investigator's Global Assessment

The investigator will perform the IGA at Screening, Visit 2 (Baseline), Visit 3 (Week 4), Visit 5 (Week 12), Visit 6 (Week 16), Visit 8 (Week 24) and Early Withdrawal. The scale in Table 7-1 will be used; the IGA was developed based on discussion with FDA during the PIND meeting, the agency's guidance for Acne Vulgaris and recent FDA approved products (i.e., Mirvaso):

Reference: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM071292.pdf

**Table 7-1 Investigator's Global Assessment (IGA)**

| Description | Grade | Disease Status |
|---|---|---|
| Clear | 0 | Clear skin with no signs of erythema and no disease related lesions |
| Almost clear | 1 | Slight redness with few disease related lesions, |
| Mild | 2 | Greater than Grade 1; definite redness with scattered, some disease related lesions |
| Moderate | 3 | Greater than Grade 2; marked redness, concentrated, many disease related lesions |
| Severe | 4 | Greater than Grade 3; Very bright redness, confluent, highly concentrated disease related lesions |
| Very severe | 5 | Greater than Grade 4; fiery redness, very extensive disease related lesions covering very large area of the face |

### 7.3.2 Secondary Efficacy Assessment: Facial Angiofibroma Severity Index (FASI)

At study visits (Visit 1 through Visit 3, Visit 5 Visit 8 and Early Termination), the investigator will grade the treatment area for erythema, average size, and degree of involved skin (lesion extension). The grades for erythema, size, and extension are presented in Table 7-2. A composite score, the Facial Angiofibromas Severity Index (FASI), will be derived from these measurements.

**Table 7-2 Scoring for Erythema, Size, and Extension**

| Score | Description |
|---|---|
| **Erythema** | |
| 0 | Clear skin with no signs of erythema |
| 1 | Almost clear; slight redness |
| 2 | Mild erythema; definite redness |
| 3 | Moderate erythema; marked redness |
| 4 | Severe erythema; very bright redness |
| **Size** | |
| 0 | No lesions |
| 1 | Few lesions, average lesion size ≤ 2mm |
| 2 | Scattered, some lesions, average lesion size >2 to ≤5mm |
| 3 | Concentrated, many lesions, average lesion size >5mm to ≤10mm |
| 4 | Confluent, highly concentrated lesions |
| **Extension** | |
| 0 | No lesions |
| 2 | ≤ 50% of the cheek surface |
| 3 | > 50% of the cheek surface |

### 7.3.3 Secondary Efficacy Assessment: Lesion Count

At Visit 1 through Visit 3, Visit 5 Visit 8 and Early Termination the investigator will perform a lesion count, based on the categories presented in Table 7-3.

**Table 7-3 Lesion Count Categories**

| Score | Description |
|---|---|
| 0 | No lesion |
| 1 | < 25 lesions |
| 2 | 25 to 50 lesions |
| 3 | 51 to 75 lesions |
| 4 | >75 lesions |

### 7.3.4 Secondary Efficacy Assessment: Lesion Elevation

At Visit 1 through Visit 3, Visit 5, Visit 8 and Early Termination, the investigator will assess the degree of lesion elevation in the area of interest.

**Table 7-4 Lesion Elevation Categories**

| Score | Description |
|---|---|
| 0 | No elevation over normal skin |
| 1 | Possible but difficult to ascertain whether there is slight elevation above normal skin |
| 2 | Slight but definite elevation |
| 3 | Moderate elevation |
| 4 | Marked elevation |

### 7.3.5 Secondary Efficacy Assessment: Subject Self-Assessment Survey

Subjects, or their parent/guardian for subjects under the developmental age of 7 years, will be asked to complete the subject self-assessment survey, displayed in Table 7-5, at each clinic visit.

**Table 7-5 Subject Self-Assessment Survey**

| Circle the number that best describes the status of your facial bumps RIGHT NOW. | |
|---|---|
| 0 | No redness and no disease-related bumps |
| 1 | Very mild redness with few very small bumps |
| 2 | Mild redness with some scattered bumps |
| 3 | Moderate redness with many small and medium sized bumps |
| 4 | Severe redness with numerous small, medium and large sized bumps |

### 7.3.6 Secondary Efficacy Assessment: Modified Nobel Scoring System

At study visits (Visit 2, Visit 3, Visit 5, Visit 6, Visit 8 and Early Termination), the investigator will perform response assessment of target lesions and non-target lesions including the size and color based on Modified Nobel Scoring System.

#### 7.3.6.1 Response for Target Lesions

Before scoring, the investigator should choose 3 of the largest isolated lesions as target lesions, then measure both the Volume and Color of each lesion as indicated below, using provided label:

- Measure lesion dimensions to the nearest 0.1 mm;
- Assess color of the lesion using provided color panel;
- Take a close-up photo of each lesion, including the color panel and mm scale label on the same plane;
- Volume of one lesion = (long diameter) x (short diameter) x (short diameter)/2.

Color scale of 1-6 as displayed in Table 7-6:

**Table 7-6 Color Scale for Color Assessment**

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

The investigator will calculate total volume and total color score of all 3 target lesions at baseline visit and each post-baseline visit, and calculate the percent change from baseline in total volume and percent change from baseline in total color then average these two percent change from baseline values to give improvement score. The scale in Table 7-7 will be used for response assessment of target lesions.

**Table 7-7 Scale for Response Assessment of Target Lesions**

| Score | Response Category | Criterion |
|---|---|---|
| -1 | Worsened | 20% or more increase |
| 0 | Unchanged | Less than 20% reduction |
| 1 | Slight improvement | ≥20% - <50% reduction |
| 2 | Moderate improvement | ≥50% - <75% reduction |
| 3 | Remarkable improvement | ≥75% reduction |

#### 7.3.6.2 Response for Non-Target Lesions

All lesions that are not selected as target lesions are defined as non-target lesions. Only three response categories will be defined.

The scale for non-target lesions response assessment as listed in Table 7-8.

**Table 7-8 Scale for Response Assessment of Non-Target Lesions**

| Score | Response Category | Criterion |
|---|---|---|

| | | |
|---|---|---|
| -1 | Worsened | Overall color increased by 1 grade or overall size/extent increased by 20% or new lesions |
| 0 | Not worsened, not remarkable improvement | |
| 1 | Remarkable improvement | Overall color decreased by at least 2 grades and overall size/extent decreased by 75% |

#### 7.3.6.3 Overall Response for Target and Non-Target Lesions

Before assessment, the investigator should add the scores from both target and non-target lesions evaluation. Overall response for Target and Non-Target lesions can be performed using the following scale in Table 7-9.

**Table 7-9 Scale for Overall Response Assessment**

| Score | Response Category |
|---|---|
| -1 or less | Worsened |
| 0 | Unchanged |
| 1 | Slight improvement |
| 2 | Moderate improvement |
| 3 or more | Remarkable improvement |

All measurements and scoring will be performed by investigator at each post-screening visit. At the baseline visit, only the measurements will be taken for comparison.

### 7.3.7 Independent Review Committee (IRC) on Photograph Assessment

#### 7.3.7.1 Members of the IRC

Independently of the assessment of IGA and Modified Nobel Scoring System by the investigator, an independent review committee will blindly assess and judge the status of each lesion from the medical and technical viewpoints, using the photographs of the skin lesions of individual subjects collected from investigational sites. The independent review committee members will be blinded

to treatment assignment. The members of the IRC will consist of two dermatologists who are independent from persons involved in the sponsorship or the conduct of the study, such as the investigator, sub-investigators, study collaborators, coordinating investigators, medical experts, and the sponsor, and who treat patients with angiofibroma in everyday practice and have no direct conflict of interest with the sponsor. In the event there is a discrepancy between the two members of the IRC, a third dermatologist will perform adjudication and select dermatologist 1 or dermatologist 2.

#### 7.3.7.2 Transmission, Control, Compensation, Masking, and Checking of Image Files

Canfield Scientific, Inc. will be responsible for transmission, control, compensation, masking, and checking of image files and will supply a written Work Instruction detailing the specific Photographic Review process in separate document. In accordance with separately prepared written procedures, the investigator or study collaborators will take the photographs of each lesion with provided label and color panel, mask images in the image files of the photographs if necessary, and transmit the image files to the CRO in charge of the control and compensation of the image files via a dedicated server. In accordance with separately prepared written procedures, the CRO in charge of the control and compensation of the image files will check, retain, and control the photographic image files stored on the dedicated server and store the image files that were compensated for color tone in the prescribed location on the dedicated server. The sponsor will periodically access the dedicated server as appropriate and ascertain if photographing and the transfer, retention, control, compensation, etc., of image files are being performed appropriately.

#### 7.3.7.3 IRC

The sponsor, the CRO in charge of the control and disposition of image files, and the members of the IRC will hold meetings of the IRC in accordance with the written procedure for holding meetings of the IRC, which is separately prepared.

## 7.4 Assessment of Safety

### 7.4.1 Adverse Events

#### 7.4.1.1 Adverse Events Assessments

An adverse event (AE) is an untoward medical occurrence in any subject during the study which does not necessarily have a causal relationship with the study drug treatment. Adverse events can be categorized as treatment-emergent or treatment-related. All AEs will be recorded and will be documented in the CRFs.

AEs will be collected from the time the subject signs informed consent/assent until 30 days after the last investigational product administration. Serious adverse events (SAEs) must be reported to the sponsor within 24 hours of awareness. The condition of the subject will be monitored

throughout the study for any signs or symptoms. The occurrence of AEs should be sought by nondirective questioning of the subject at each visit during the study. All AEs will be collected as:

- The subject's positive response to questions about their health.
- Symptoms spontaneously reported by the subject.
- Clinically relevant changes and abnormalities observed by the investigator (e.g., local and systemic tolerability, laboratory measurements, results of physical examinations, monitoring for infections and noninfectious pneumonitis).

If an AE worsens in intensity, it should be recorded as a new AE. Otherwise, it continues as the first report (counted as the same AE) until the subject is recovered.

The investigator or designee will record the following on the AE CRF:

- Adverse event and relevant clinical findings
- Time/date of onset
- Time/date of recovery
- Intensity
- Action taken on study drug/treatment
- Other action taken to treat the event
- Relation to study drug/treatment
- Seriousness of the AE

Adverse events requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Treatment due to an AE will be recorded.

All AEs with moderate or greater intensity and/or possibly or probably related to the study drug(s) or study procedure must be followed by the investigator until it is resolved or until the medical condition of the subject is stable; all relevant follow-up information will be reported to the sponsor.

The outcome of an AE will be classified as recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal or unknown.

Safety assessment will include assessment of local safety (e.g., through active assessment of local signs and symptoms, such as scaling, itching etc.) as well as systemic safety. If a subject experiences a generalized rash or other health issue in the treatment area, the subject (or

parent/guardian) should contact the study site and the subject should report to the study center for examination.

#### 7.4.1.2 Timing

Adverse events will be assessed after the subject signs informed consent/assent and at all study visits.

Treatment-emergent AEs include any untoward medical occurrence in a subject or clinical investigation subject after administration of an investigational study treatment, which does not necessarily have to have a causal relationship with this treatment. A treatment-emergent AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the product, whether or not related to the medicinal (investigational) product. It could also include accidents and reasons for changes in medication (drug and/or dose).

Treatment-related AEs are all treatment-emergent AEs that are considered by the investigator as causally related to administration of the study drug.

#### 7.4.1.3 Severity of Adverse Events

The investigator is to classify the severity (intensity) of an AE according to the following definitions:

- Mild – The subject was aware of the signs and symptoms but the signs and symptoms were easily tolerated.
- Moderate – The signs and symptoms were sufficient to restrict, but did not prevent, usual daily activity for the subject.
- Severe – The subject was unable to perform usual daily activity.

The maximum intensity of an AE (mild, moderate, or severe) will be assessed taking into account the possible range of intensity of the symptom(s).

#### 7.4.1.4 Relationship of an Adverse Event to Study Treatment

The investigator is to classify the relationship of an AE to the investigational product using good clinical judgment and the following definitions:

| | |
|---|---|
| Not Related | The AE is clearly explained by another cause not related to the study product. |

| | |
|---|---|
| Probably Not Related | A potential relationship between study product and the AE could exist (i.e., the possibility cannot be excluded), but the AE is most likely explained by causes other than the study agent. |
| Possibly Related | The AE and administration of study product are temporally related, but the AE can be explained equally well by causes other than the study product. |
| Probably Related | The AE and use of study product are temporally related, and the AE is more likely explained by study product than by other causes. |
| Related | The AE and use of study product are related in time, and a direct association can be demonstrated. |

#### 7.4.1.5 Unexpected Adverse Events

See the Investigator's Brochure to determine expectedness of serious adverse events for expedited reporting. An AE is considered "unexpected" if it is not listed in the Package Insert of the marketed sirolimus oral products or in the Investigator's Brochure, or is not listed at the specificity or severity that has been observed; or, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

#### 7.4.1.6 Adverse Events of Special Interest

There are currently no known adverse events of special interest. The investigator should evaluate any reactions in the treatment area. If a subject has any reaction in the treatment area, the subject should return to the site for evaluation.

#### 7.4.1.7 Adverse Events Causing Treatment Discontinuation

If a patient is withdrawn from the study as a consequence of an AE, this must be recorded and reason provided in the eCRF, and the patient must be followed until the resolution of the AE or as instructed by the Medical Monitor.

### 7.4.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- is life-threatening
- results in death
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

- is an important medical event.

The death of a subject enrolled in a study is per se not an event, but an outcome. Any event resulting in a fatal outcome must be fully documented and reported, regardless of the causality relationship to the investigational product.

The term life-threatening refers to an AE in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death, if it was more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of important medical events include AEs, which suggest a significant hazard, contraindication or precaution, occurrence of malignancy, or development of drug dependency or drug abuse.

Any SAE, whether or not deemed drug-related or expected, must be reported immediately to the sponsor or designee via email as soon as it becomes known to the investigator and not later than within 24 hours of his/her knowledge of the occurrence of an SAE. The investigator will document such events in the best possible detail on the SAE Report Form to be transmitted by email. SAEs will be collected from the time the subject signs informed consent/assent until 30 days after the last investigational product administration.

A pre-scheduled elective procedure is not to be considered an SAE, even if the subject is hospitalized, provided the condition requiring the pre-scheduled elective procedure was present before and did not worsen or progress between the subject's consent to participate in the study and the time of the procedure. In addition, the pre-scheduled elective procedure must be the sole reason for admission and intervention. An adverse event occurring during the pre-scheduled elective procedure should be recorded as an AE or SAE.

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is both unexpected (not consistent with the current Investigator's Brochure/product information) and for which there is evidence to suggest a causal relationship between the drug and the AE. As a minimum requirement, the Investigator must report all SUSARs to their IRB. All investigators participating in the trial will also be notified appropriately of SUSARs. The sponsor will report SUSARs and other events requiring expedited reporting to regulatory authorities as required.

Investigator instructions for reporting SAEs are provided in Section 13.2.

### 7.4.3 Dermatologic Stopping and Follow-up Criteria

Dermatologic stopping criteria are defined below:

If a subject has worsening angiofibromas where the investigator feels the worsening has a causal relationship to the study drug, the study drug should be stopped. If the investigator would like to restart the drug within 7 days as a re-challenge, they can do this in consultation with the Medical Monitor. A second re-challenge will not be allowed and the subject should be discontinued.

If the investigator feels that the angiofibromas are worsening (such as 2 grades higher on the IGA) that is abnormal in disease progression and the investigator feels it is not in the subject's best medical interest to continue in the study, they can schedule an early termination visit and discontinue the subject.

### 7.4.4 Safety Laboratory Assessments

Blood samples and optional urine samples will be collected for routine safety laboratory tests (hematology, serum biochemistry, and urinalysis) at Visit 1 (Screening), Visit 3 (Week 4), Visit 5/End of Double-blind Treatment, Visit 6 (Week 16), Visit 8 (Week 24) or at early termination from the study. Clinical laboratory specimens will be analyzed by a central licensed and accredited laboratory facility according to the laboratory's standard operating procedures (For China, clinical laboratory specimens will be analyzed by local lab). The following tests will be performed:

**Hematology:** hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV)

**Serum chemistry:** glucose (non-fasting, but for China, glucose will be tested under fasting state), blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorus, bicarbonate, uric acid, lactic dehydrogenase (LDH), total protein, albumin, bilirubin (total and direct), total cholesterol, triglycerides

**Urinalysis:** color/appearance, pH, specific gravity, glucose, ketones, protein, and microscopic appearance.

The investigator may collect additional blood or urine samples to repeat any laboratory test that was abnormal post-dosing, was within normal limits at Baseline, and is considered clinically significant. Abnormal laboratory results at the last scheduled visit may require additional collection of samples on an "as needed" basis until: a) the values return to the baseline value, b) the values are within normal limits, c) the values are clinically stable, or d) the investigator determines that further follow-up is unnecessary. The investigator will record the date and time of

all additional samples collected. If the investigator establishes a clear explanation for the laboratory abnormality, he or she will record this explanation in the CRFs.

### 7.4.5 Pregnancy Testing

Female subjects of child-bearing potential will undergo a UPT at the screening visit before any study-specific procedures are performed. If the UPT is positive, the subject will not be permitted to enroll in the study. In the unlikely event that a urine pregnancy test cannot be obtained, a serum pregnancy test can be run from the serum sample collected.

Pregnancy tests will be performed at all clinic study visits on female subjects of child-bearing potential. The pregnancy tests must have a sensitivity of at least 25 mIU/mL. If there is a suspicion of pregnancy at any time during the study, a urine sample will be obtained and tested. Should a subject become pregnant during the study, treatment must be discontinued. Subjects should continue with non-treatment and/or follow-up visits. For China, different pregnancy test procedure would be followed.

All pregnancies should be immediately reported to the sponsor/Contract Research Organization (CRO)/Medical Monitor and followed through to resolution (i.e., delivery, miscarriage, or abortion). The report should be submitted within the same timelines as an SAE (within 24 hours of knowledge), although a pregnancy per se is not considered an SAE. Information on the status of the fetus and the mother may be requested (see Section 7.4.2) to include outcome of delivery.

If the pregnancy is associated with an SAE (e.g., if the mother is hospitalized for dehydration), in addition to the pregnancy report form, a separate SAE report form must be filed. Miscarriage, stillbirth and any malformation/disease must be reported as a SAE. Any pregnancy leads to the immediate cessation of the study treatment.

### 7.4.6 Vital Signs

Measurements of vital signs, including blood pressure, pulse rate, and respiratory rate, will be taken at every clinic visit with the subject seated.

### 7.4.7 Physical Examination

At the screening visit, Visit 8, and Early Termination visits, the investigator or designee will complete an abbreviated general physical examination including measurements of weight (in pounds) and height (inches).

### 7.4.8 Pharmacokinetics

A single blood sample will be collected at Visit 3 (Week 4/Day 28) during the double-blind treatment period for plasma sirolimus determination.

The actual collection time of the blood sample must be recorded in the source data, collection tube and in the eCRF. Exact prior dosing must be recorded in the source data and in the eCRF.

The central laboratory will provide all materials and supplies to be used for the collection and shipment of biological samples.

Plasma samples for study medication measurements will be stored at the investigational site and shipped as specified in the study lab manual. Plasma samples will be packaged and shipped directly to the bioanalytical laboratory. Specific details on sample collection, processing, aliquoting, storage, and shipping instructions are provided in the laboratory manual.

Plasma sample PK analysis will be performed using validated procedures and methods.

### 7.5 Appropriateness of Measurements

The safety evaluations are the standardized and most widely accepted methods for evaluating safety in clinical trials. Methodology for evaluating efficacy in the treatment of TSC-related facial angiofibromas are not well established; the methodology in this study was developed according to reports in the literature.[8-18]

## 8.0 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE STATISTICAL AND ANALYTICAL PLANS

### 8.1 General Considerations for Data Analysis

The methodology presented below represents a brief overview of the statistical methods that will be fully detailed in the statistical analysis plan (SAP). The SAP will be finalized before the database is locked and unblinded. Any changes to the methods described in the final SAP will be described and justified in the clinical study report. It is planned that the data from all centers that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis. All statistical analyses will be performed using SAS statistical software (Version 9.2 above).

Statistical significance will be tested at the 2-sided 5% level. No adjustments for multiplicity are planned.

All efficacy and safety analyses will be performed on observed data with no imputation unless otherwise specified. For the analyses of treatment response, subjects having a missing responder status will be analyzed as non-responders.

## 8.2 Sample Size and Power Considerations

This study is exploratory in nature and the sample size is not based on a statistical rationale. For sample size calculation, reliable assumptions on the difference between treatments for the primary efficacy parameter must be present. However, currently no such data in subjects with TSC are available for sirolimus. Therefore, practical considerations were used for sample size calculation. The planned number of 45 subjects is considered to be sufficient to provide a reliable answer on the efficacy of sirolimus in concentrations of 0.2% and 0.4% in subjects with TSC compared to placebo (in a 1:1:1 ratio) and to achieve insight into the safety of sirolimus.

## 8.3 Analysis Populations

The primary statistical analyses will be performed on the Intent-to-Treat (ITT) population (efficacy), Per-Protocol population (efficacy) and Safety population (safety). The analysis populations are defined as:

- Intent-to-Treatment (ITT) population will include all randomized subjects. This will be the population for efficacy analysis.
- The Per-Protocol (PP) population will include all ITT subjects with no major protocol deviation and with >80% study drug compliance rate, where the drug compliance will only apply to active treatment groups. Efficacy analyses will be repeated on this population as a sensitivity analysis.
- Safety population will include all subjects who were randomized and dispensed the study medication at Randomization / Day 1, excluding subjects who return all of the study medication unused. This will be the population for safety analysis.

## 8.4 Interim Analysis

One interim analysis will be performed.

The interim analysis will be conducted by the study team when all subjects have completed the double-blind phase (Visit 5 - Week 12). The database will be locked and unblinded to assess for efficacy and safety. The results will be reported in the clinical study report (CSR).

In the event of early stopping due to interim analysis results, subjects will be brought to the investigational sites for a final visit. The final analysis will include all data collected up to and including the final visit.

## 8.5 Analysis of Efficacy

All original and derived efficacy parameters as well as population characteristics will be described using summary statistics. All primary and secondary efficacy endpoints will be analyzed for pairwise differences between treatment groups.

### 8.5.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint will be the proportion of subjects with a clinical response of treatment success on Week 12. Treatment success is defined as:

At least a 2-grade improvement on the Week 12 Investigator Global Assessment (IGA) of the facial skin lesions assessed by investigator. The primary efficacy endpoint will be analyzed using Fisher's exact test, making all pairwise treatment comparisons.

### 8.5.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will be the following:

- The proportion of subjects with an investigator assessed IGA score of clear or almost clear with at least a 2-grade improvement on the Week 12 IGA of the facial skin lesions;
- The proportion of subjects with at least 30% improvement at Week 12 as compared to Baseline in the Facial Angiofibromas Severity Index (FASI) score, which is based on lesion erythema, size, and extension (Salido et.al. 2012);[20]
- The time to reach at least 30% improvement from Baseline in the FASI score for angiofibroma severity;
- The proportion of subjects with at least 2-grade improvement at Week 12 as compared to Baseline in categorical lesion counts (scored as follows: No lesion = 0; <25 lesions = 1; 25-50 lesions = 2; 51-75 lesions = 3, >75 lesions = 4);
- The proportion of subjects with at least 2-grade improvement at Week 12 as compared to Baseline in lesion elevation score;
- The proportion of subjects with at least 2-grade improvement at Week 12 as compared to Baseline in the subject self-assessment survey;
- Overall Response of angiofibroma assessed by the investigator at Week 12 as compared to baseline based on Modified Nobel Scoring System;
- Overall Response of angiofibroma assessed by the IRC at Week 12 as compared to baseline based on Modified Nobel Scoring System;

- The proportion of subjects with at least Moderate Improvement (a score of 2) on Modified Nobel Scoring System assessed by the investigator at Week 12;

- The proportion of subjects with at least Moderate Improvement (a score of 2) on Modified Nobel Scoring System assessed by the IRC at Week 12;

- The proportion of subjects with at least a 2-grade improvement on Week 12 Investigator Global Assessment (IGA) of the facial skin lesions assessed by the IRC.

Treatment comparison of the proportion of treatment success with clear or almost clear will be conducted using Fisher's exact test at each time point, making all pair-wise comparisons. Descriptive statistics for observed values, absolute changes, and percent changes from Baseline (for FASI lesion score) and Number and percentage of subjects reached each overall response level for Modified Nobel Scoring System score will be summarized by treatment group at each time point. Student's t-test will be used for pairwise comparison of continuous endpoints at each time point. Wilcoxon rank sum test will be used to compare Modified Nobel Scoring System score. Fisher's exact test will be used for categorical endpoints. Time to reach at least 30% improvement from Baseline in the FASI score will be analyzed using Kaplan-Meier method, making all pairwise treatment comparisons. Proportion of subjects with at least Moderate Improvement on Modified Nobel Scoring System will be analyzed using Fisher's exact test, making all pair-wise comparison. Proportion of subjects with at least a 2-grade improvement on the Week 12 IGA will be analyzed using Fisher's exact test, making all pair-wise comparisons.

## 8.6 Analysis of Safety

The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of predetermined ranges. Adverse events will be presented in data listings and summarized by frequency and severity for each treatment group. Laboratory and vital sign data will be presented in data listings. Abnormal laboratory findings will be presented. The analysis of safety will be described in the SAP.

### 8.6.1 Adverse Events

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in an individual body system, and having each individual AE. Any other information collected (e.g., severity or relatedness to study medication) will be listed as appropriate.

Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The incidence of AEs (percent of subjects reporting the AE at least once) will be tabulated separately for each treatment group by severity and relationship to drug.

### 8.6.2 Other Safety Variables

Clinical laboratory values will be reported as complete listings of individual subject data. Clinical laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges), and by the flagging of notable values in data listings.

Data from other tests (e.g., vital signs, special tests) will be considered as appropriate and listed. Notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

## 8.7 Quality of Life Analysis

Not applicable.

# 9.0 CHANGES IN THE PLANNED STUDY

## 9.1 Protocol Amendments

With the exception of administrative changes, any changes or additions to this clinical study protocol require a written protocol amendment that must be approved by the sponsor, the Contract Research Organization (CRO), and the investigator(s) before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study, require additional approval by the IRB for each study center.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or the sponsor in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons, the sponsor should be notified and the IRB should be informed according to their reporting requirements.

## 9.2 Termination or Suspension of the Study

The sponsor reserves the right to terminate or suspend the study at any time or a subject's participation due to a protocol amendment. In case of premature termination or suspension of the study, the CRO project manager will promptly inform the investigators, regulatory authorities, and IRBs about the premature termination or suspension, including the reason for it. In terminating the study, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

# 10.0 DATA HANDLING AND RECORD KEEPING

## 10.1 Recording of Data

### 10.1.1 Source Documents

Source data are all the information in original records and copies of original records of clinical findings, observations, or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The identification of any data to be recorded directly on the CRFs is to be considered source data.

Study data collection procedures must ensure that each data element can be traced with a high level of confidence from its originator or recorder to its representation in the study database and then to its place in the analysis and report of study results. Once recorded, the study data must be protected from unauthorized modification or deletion, and all authorized modifications and deletions must be securely linked in the permanent record with their author, time of change, and reason for change (i.e., the audit trail must be maintained).

The investigator will permit study-related monitoring, audit(s), IRB/IEC review(s) and regulatory inspection(s), with direct access to all the required source records.

The principal investigator will certify the data to be accurate and complete and will release the data for transmittal to the sponsor or CRO.

Source records need to be preserved for the maximum period of time permitted by local requirements (see Section 10.2). For each subject enrolled, the investigator will indicate in the source record(s) that the subject participated in the study.

### 10.1.2 Case Report Forms

The primary data collection tool for the study is an electronic case report form (eCRF) designed specifically for the study. For each subject enrolled in the study, an eCRF will be completed by the study coordinator and signed by the investigator or his/her designate.

The investigator will be responsible for ensuring the accuracy of all data entered in the eCRFs. All eCRFs are to be completed in a timely manner.

Errors occurring in the eCRFs will be queried. Queries raised by data reviewers must be addressed by site personnel.

On request, the investigator will provide the sponsor with additional data relating to the study, or copies of relevant source records, duly anonymized (i.e., subject's name is redacted).

### 10.2 Retention of Documents

The United States Food and Drug Administration (FDA)/ ICH regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- at least two years following the date on which a Marketing Application is approved by the FDA/applicable regulatory or health authority, or
- two years after the sponsor notifies the investigator that no further application is to be filed with the health authorities

Similarly, ICH guidelines require that essential documents be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. European Union (EU) Directive 2001/63/EC requires that essential documents be retained for at least 15 years after completion or discontinuation of the trial.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the sponsor, or (2) providing an opportunity for the sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor or its agents, the FDA and/or other regulatory agencies.

## 11.0 QUALITY CONTROL AND QUALITY ASSURANCE

### 11.1 Direct Access to Source Documents

As specified in the investigator's agreement, the investigator agrees to allow study-related monitoring, audit(s), IRB/IEC review(s) and regulatory inspection(s), with direct access to all the required source records, and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues.

### 11.2 Monitoring Procedures

The Clinical Study Monitor will contact and/or visit the investigator site periodically to verify the adherence to the protocol, the maintenance of study-related source records, and the completeness and accuracy of all CRF entries compared to source data. The investigator will cooperate with the study monitor to ensure that any discrepancies that may be identified are resolved.

### 11.3 Audit and Inspection

The investigator will make all the study-related source data and records available to a quality assurance auditor mandated by the sponsor, or to domestic or foreign regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects have been adequately protected, and that all data relevant for the evaluation of the investigational product have been processed and reported in compliance with GCP/ICH and applicable regulatory requirements.

The investigator is to notify the sponsor/CRO immediately of any inspection by regulatory authorities or IRBs.

## 12.0 ETHICS

### 12.1 Ethical Conduct of the Study

This study must be carried out in compliance with the protocol and the applicable laws and regulatory requirements of the US Food and Drug Administration (FDA) as well as CFDA (China Food and Drug Administration). The study must be conducted in accordance with the ethical principles originating from the Declaration of Helsinki and amendments and the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines.

### 12.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

This protocol, the proposed informed consent form, and other information for subjects must be reviewed and approved by an IRB or IEC, before the start of the trial, in compliance with local regulations. This committee must also approve any amendments to the protocol, other than administrative ones, before initiation of the amendment procedures.

### 12.3 Subject Information and Consent

Before participation in the study, each subject and/or their parent/guardian is required to provide written consent to participate in the study. Subjects under the age of 18 years are required to provide assent, in accordance with IRB specifications. No study-specific procedures will be performed before a subject’s informed consent/assent is obtained.

### 12.4 Disclosure and Confidentiality

#### 12.4.1 Confidentiality of Study Documentation

By signing the protocol, the investigator agrees to keep all information provided by the sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB or IEC. Study documents provided by the study sponsor (i.e., protocols, Investigators' Brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization

from the sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

### 12.4.2 Privacy of Individual Health Information

The investigator will undertake to protect the privacy of all individually identifiable health information except as specifically authorized by each individual subject through the written informed consent. The Informed Consent document will include a request of the subject's consent to release the collected data for research purposes in such a way that the individual's identity remains masked. While all data records will be identified by the corresponding subject number, the identity of the subject will be held in confidential source documents at the study site. All study personnel with access to this information are legally bound not to disclose such information.

## 13.0 EMERGENCY PROCEDURES

### 13.1 Emergency Unblinding

Unblinding should only be performed in emergencies where knowledge of the subject's treatment assignment is essential for further management of the subject's medical care. Unblinding a subject's treatment assignment under any other circumstances will be considered a protocol violation.

The investigator should assess the relationship of any AEs to administration of the investigational product prior to unblinding.

The investigator is required to contact the study Medical Monitor before unblinding any subject's treatment assignment. Instructions for "breaking the blind" will be provided to the Investigator. The subject's treatment code should not be communicated to the Medical Monitor or designee. The unblinding will be documented by the investigator.

If the treatment assignment is unblinded during the double-blind treatment period, the subject will not be allowed participation in the open-label treatment period of the study.

### 13.2 Reporting of Serious Adverse Events and Pregnancies

#### 13.2.1 Contact Person(s) and Number(s)

Serious adverse events and pregnancies must be reported immediately (i.e., not later than 24 hours after first knowledge) to the sponsor or designee.

Contact Information:

**Email for reporting initial SAE: DRUGSAFETY-AUCTA@DMEDGLOBAL.COM**

**Email for reporting SAE follow-up information:**

DRUGSAFETY-AUCTA@DMEDGLOBAL.COM

### 13.2.2 Reporting Procedures

**Serious Adverse Events**

For each SAE, the investigator will complete a Serious Adverse Event Report Form and assess the relationship of each SAE to study treatment. The completed form(s) should be sent electronically to the designated SAE email within 24 hours of first knowledge of the SAE.

Follow-up reports regarding the status of the SAE and the subject's subsequent course should be submitted until the SAE has subsided, the condition stabilized (in the case of persistent impairment), the subject receives alternative therapy, or the subject dies. The form and email confirmation will be retained. Contacts for reporting SAEs and other safety concerns are provided to each site.

## 14.0 PUBLICATION POLICY

Written permission must be obtained from the Sponsor prior to submission to a publication or presentation.

If the data merit, the Investigator and the Sponsor will discuss the preparation of a manuscript for publication in a peer-reviewed professional journal or an abstract for presentation, oral or written, to a learned society or symposium. Authorship should reflect work done by the Investigators and personnel of the Sponsor, in accordance with generally recognized principles of scientific collaboration.

## 15.0 REFERENCE LIST

1. National Institute of Neurological Disorders and Stroke (NINDS). Tuberous sclerosis fact sheet, located at http://www.ninds.nih.gov/disorders/tuberous_sclerosis/detail_tuberous_sclerosis.htm. Accessed 17 May 2016.

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# 16.0 APPENDICES

## 16.1 APPENDIX 1: Potential Drug Interactions

Sirolimus is known to be a substrate for both cytochrome CYP3A4 and P-gp. The package insert for Rapamune (sirolimus) oral solution and tablets reports some known and potential drug interactions with orally-administered sirolimus. While the systemic absorption of topically-applied sirolimus in this study is expected to be negligible, co-administration of oral sirolimus with other known strong inhibitors of CYP3A4 and/or P-gp (such as voriconazole, itraconazole, telithromycin, or clarithromycin) or other known strong inducers of CYP3A4 and/or P-gp (such as rifabutin), though not necessarily exclusionary, should be used with caution, during the study. Subjects on stable doses of these medications should be discussed in advance with medical monitor prior to inclusion in the study.

Drugs shown to increase sirolimus blood concentrations in drug-interaction studies included:

- Cyclosporine.
- Diltiazem.
- Erythromycin.
- Ketoconazole.
- Verapamil.

Other drugs with the potential to increase sirolimus blood concentrations include (but are not limited to):

- Antifungal agents: clotrimazole, fluconazole.
- Antibiotics: troleandomycin.
- Gastrointestinal prokinetic agents: cisapride, metoclopramide.
- Other drugs: bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g., ritonavir, indinavir).

## 16.2 APPENDIX 2: Standardized Operation Procedure for Obtaining Digital Images in Sirolimus Ointment Clinical Trials for Cutaneous Angiofibromas in Subjects with Tuberous Sclerosis Complex

For all eligible subjects providing photographic consent, photographs of the target lesion areas will be taken at every visit including screening and baseline, end of the study or early termination at any time points for documentation purpose. All the photographs are required to be of high quality

and resolution upon enlargement of the image, correct prospective, neutral background and even lighting. The following procedure should be followed and checked each time when the image is obtained in order to ensure the precision and objectivity of recording.

**I. Quick check for equipment and camera settings**

- Before capturing pictures, make sure the location has adequate lighting (i.e. with celling light above subject) and all the equipment (refer to **Table I.)**.
- Confirm the information written on the identification card, check camera for the right settings to ensure standardization (refer to **Table II.**).

**II. Positioning of subjects**

- For consistency, photography should be taken from the same place in the facility.
- Remove anything that could hinder the direct and authentic photography of the lesion, such as a mask, hair or cosmetics.
- Gently cleanse the lesion with saline and dry face with tissue.
- Position the subject to stand in front of the background in a comfort way.

**III. Photography techniques**

- Take a picture of the subject with identification card to preserve blinding.
- The camera lens should be oriented parallel to the plane of the lesion.
- Photos were taken between 1-2 feet distance from the lesion from three directions, front, right 45° and left 45° (see **Figure 1.** for an example).
- Make sure the face is centered, press the shutter button halfway to focus. When the aligning focus frame turns green, hold camera still and tight, press the button all the way to record.
- At least two photos were taken from each direction.
- Check the photos immediately to ensure at least one photo from each direction is focused and clear after enlargement, otherwise additional photos should be taken.
- Photos of target lesions for Modified Nobel Scoring System should be close-up with mm scale label and color panel on the same plane as the lesion being measured.

**IV. Photograph processing and storage (For China, photograph processing and storage will follow canfield capture instructions provided by Canfield Scientific, Inc. and details will be supplied in a separate document)**

- Upload and save photos to the secure location with the cable provided.
- Rename the photos in the following format:
  Participant Number Site_Day&Visit_Date_Orientation

  Example:

  49_BostonChildren_Day30Visit3_8May17_Front or Right45 or Left45
- Delete photos from camera.

**Table I. Equipment and Materials**

| Items | Specific Choice | Features |
|---|---|---|

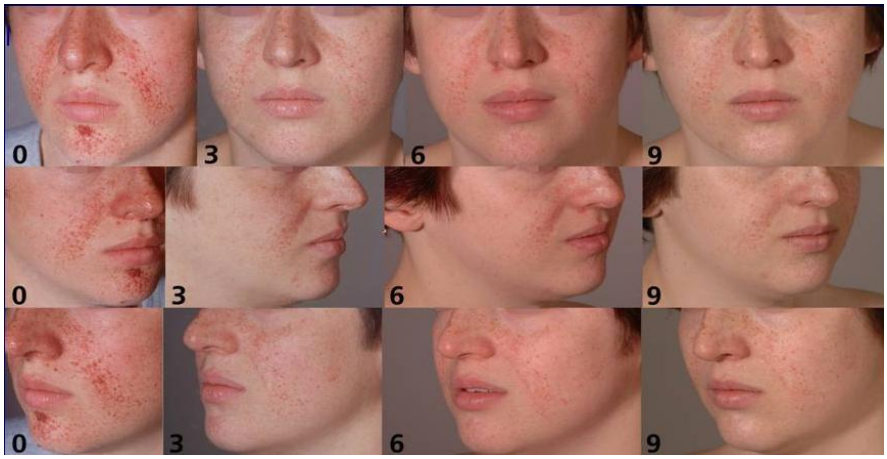
| | | |
|---|---|---|
| **Digital Camera** | Panasonic LUMIX DMC-ZS5 | 12x optical zoom lens (35mm camera equivalent: 25-300mm), built in flash, lithium ion rechargeable battery, 8GB memory card |
| **Background** | Blue surgical drapes | Light weight and transportable |
| **Identification card** | Cardboard handwritten card | Pre-formatted to add participant number, date and time of image, location, study day/visit, i.e.<br>Participant No: 49<br>Site: Boston Children<br>Day: 30 Visit: 3<br>Date:8-May-2017 Time: 2:28 PM |

**Table II. Camera Settings* and Lighting Conditions**

| Settings | Details |
|---|---|
| **Program Mode (P)**  | Taking pictures with the following setting |
| **Macro Zoom (down cursor button)**  | For taking close up photographs of the subjects |
| **Picture Size** | 12M |
| **Quality**  | High quality |
| **White Balance (WB)** | Set to AWB for appropriate light compensate |
| **International Organization for Standardization (ISO)** | Set to 100 |
| **Auto Focus Mode (AF mode)**  | Set to face detection |
| **Metering Mode**  | Set to multiple |
| **Stabilizer**  | Set to Auto |
| **AF Assist Lamp**  | On |
| **Flash (right cursor button)**  | Set to forced flash on |

*Unless specified in the Table II., all the settings should be set to off, auto or standard.

**Figure 1. An Example of Capturing Photos from Three Directions**




-Front

-Right 45°

-Left 45°

Note: This figure is solely used for the purpose of providing an example of capturing subject photos from three directions. Panels labelled 0, 3, 6, and 9 signify months after treatment from a separate study, and has no relation to this study.[3]

**References:**

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