Protocol

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

Sponsor: Nobelpharma Co., Ltd.
Precautions for Handling of This Protocol

The information included in this protocol is provided only to those involved in the study institutions participating in the trial of NPC-12G (directors of study institutions, investigators, subinvestigators, study collaborators, investigational product managers, members of Institutional Review Boards [IRBs], other appropriately designated persons). The information contained in this protocol must not be disclosed to third parties without written permission from Nobelpharma Co., Ltd., except in cases where it is necessary to disclose the information for the conduct of the study, such as cases where relevant information is disclosed to obtain consent from subjects wishing to participate in the study.

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## List of Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Spelled Out Expression</th>
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<tbody>
<tr>
<td>ALT (GPT)</td>
<td>Alanine Aminotransferase (Glutamic Pyruvate Transaminase)</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkaline Phosphatase</td>
</tr>
<tr>
<td>AML</td>
<td>Angiomyolipoma</td>
</tr>
<tr>
<td>AST (GOT)</td>
<td>Aspartate Aminotransferase (Glutamic Oxaloacetic Transaminase)</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
</tr>
<tr>
<td>CDLQI</td>
<td>Children’s Dermatology Life Quality Index</td>
</tr>
<tr>
<td>CK(CPK)</td>
<td>Creatine Kinase</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
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<tr>
<td>DLQI</td>
<td>Dermatology Life Quality Index</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>FA</td>
<td>Facial Angiofibroma</td>
</tr>
<tr>
<td>FAS</td>
<td>Full Analysis Set</td>
</tr>
<tr>
<td>FK506</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>FKBP12</td>
<td>12-kDa FK506-binding protein</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>IRC</td>
<td>Independent review committee on photograph assessment</td>
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<tr>
<td>JCOG</td>
<td>Japan Clinical Oncology Group</td>
</tr>
<tr>
<td>LAM</td>
<td>Lymphangioleiomyomatosis</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Drug Regulatory Activities</td>
</tr>
<tr>
<td>mTOR</td>
<td>Mammalian Target of Rapamycin</td>
</tr>
<tr>
<td>PPS</td>
<td>Per Protocol Set</td>
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<tr>
<td>PT</td>
<td>Preferred Term</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>SEGA</td>
<td>Subependymal Giant Cell Astrocytoma</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>SP</td>
<td>Safety Population</td>
</tr>
<tr>
<td>TSC</td>
<td>Tuberous Sclerosis Complex</td>
</tr>
<tr>
<td>YAG</td>
<td>Yttrium Aluminum Garnet</td>
</tr>
<tr>
<td>γ-GTP</td>
<td>γ-Glutamyl Transpeptidase</td>
</tr>
</tbody>
</table>
# Outline of Protocol

<table>
<thead>
<tr>
<th>Study title</th>
<th>A Phase III Study of NPC-12G in Patients with Skin Lesions Associated with Tuberous Sclerosis Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol number</td>
<td>NPC-12G-1</td>
</tr>
<tr>
<td>Study objectives</td>
<td>To verify the efficacy of sirolimus gel for angiofibroma associated with tuberous sclerosis complex and to investigate its efficacy and safety in patients with other skin lesions.</td>
</tr>
<tr>
<td>Study design</td>
<td>A multicenter, stratified, randomized, double-blind, placebo-controlled, comparative study</td>
</tr>
<tr>
<td>Target</td>
<td>Skin lesions associated with tuberous sclerosis complex</td>
</tr>
</tbody>
</table>

**Inclusion criteria**

1) Male or female patients 3 years old or greater at the time of informed consent  
2) Patients who are diagnosed as definite diagnosis according to diagnostic criteria for tuberous sclerosis complex (International Tuberous Sclerosis Complex Consensus Conference 2012)  
3) Patients with three or more reddish papules of angiofibroma (>= 2 mm in diameter) on the face at screening tests  
4) Patients who are not suitable for therapy with laser or surgery (including liquid nitrogen therapy and phototherapy) for angiofibroma, or who do not want therapy with laser or surgery  
5) Patients who (or whose guardian) give a written informed consent in understanding and willingness after having received enough explanation regarding the study participation. 

**Exclusion criteria**

1) Patients who (or whose guardian) are hard to apply the test drug topically with keeping compliance  
2) Patients with clinical findings such as erosion, ulcer and eruption on or around the lesion of angiofibroma, which may affect assessment of safety or efficacy  
3) Patients who are hard to be taken pictures of their lesions adequately in such cases that they may not follow instruction of stillness  
4) Patients with a history of hypersensitivity to alcohol or allergy to sirolimus  
5) Patients who have complications such as malignant tumor, infection, serious heart disease, hepatic function disorder, renal function disorder or blood disorders (selected by the investigator or subinvestigator [hereinafter referred to collectively as "investigator"] with reference to grade 2 or more serious disease defined in "Standards for Classification of Seriousness of Adverse Drug Reactions by Drugs etc.")  
6) Patients who have complications such as diseases unsuitable for the trial participation, for examples, uncontrolled diabetes (fasting blood glucose level >140 mg/dL or postprandial blood glucose level > 200 mg/dL), dyslipidemia (cholesterol level > 300 mg/dL or > 7.75 mmol/L, triglycerides level > 300 mg/dL or > 3.42 mmol/L), etc.  
7) Patients who have taken drugs with mTOR inhibitory action (including sirolimus, everolimus or tamsirolimus) within 12 months before the initial registration  
8) Patients who have applied topical tacrolimus on the lesion of angiofibroma within 3 months before the initial registration  
9) Patients who have received therapy with laser or surgery (including liquid nitrogen therapy and phototherapy) to the lesion of angiofibroma within 6 months before the initial registration
10) Female patients who are pregnant, may be pregnant, or are lactating
11) Patients who cannot agree to take appropriate measures of contraception until completion of the follow-up period or the follow-up after withdrawal from informed consent
12) Patients who have participated in other clinical trial and have taken a trial drug within 6 months before the initial registration
13) Other patients who are considered by the investigator as unsuitable for participation in the trial

<table>
<thead>
<tr>
<th>Investigational product</th>
<th>Test product</th>
<th>NPC-12G gel : An aqueous gel containing 2 mg (0.2%) of sirolimus in 1 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control drug</td>
<td>A placebo gel that does not contain sirolimus and is indistinguishable from the test drug in appearance</td>
<td></td>
</tr>
</tbody>
</table>

**Dosage**

NPC-12G gel (0.2%) or the placebo gel will be evenly applied to facial angiofibroma lesions twice daily (in the morning and at bedtime).

The amount of application will be 125 mg (approximately 0.5 to 1 cm as the length of gel extruded from the tube) per lesion of 50 cm², as a rough standard, and should not exceed the upper limit of the amount of daily application prescribed for the age category.

Application on the lesions of hypomelanotic macule and plaque on the head (above the neck), in addition to angiofibroma lesion, will be permitted, with the following limitations on the upper limit of the amount of daily application and the number of tubes that can be prescribed before the next prescribed visit (in approximately 1 month) being specified in accordance with the age category for safety reasons. For subjects who sharply deviate from the standard physique (body surface area) for the age category, the upper limit of the amount of application and the number of tubes will be defined not in accordance with age category but in accordance with body surface area category.

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Standard Body Surface Area</th>
<th>Upper Limit of the Amount of Daily Application</th>
<th>Upper Limit of the Number of Tubes That Can Be Prescribed before the Next Prescribed Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years or younger</td>
<td>Less than 0.8 m²</td>
<td>400 mg (corresponding approximately to 2 to 3 cm)</td>
<td>Two 10-g tubes</td>
</tr>
<tr>
<td>6 to 11 years</td>
<td>0.8 m² or more Less than 1.3 m²</td>
<td>600 mg (corresponding approximately to 3 to 4 cm)</td>
<td>Three 10-g tubes</td>
</tr>
<tr>
<td>12 years or older</td>
<td>1.3 m² or more</td>
<td>800 mg (corresponding approximately to 4 to 5 cm)</td>
<td>Four 10-g tubes</td>
</tr>
</tbody>
</table>

**Duration of treatment**

12 weeks (follow-up period after treatment, 4 weeks)

**Prohibited concomitant drugs**

The concomitant use of the following drugs and therapies will be prohibited from 4 weeks before the date of definitive registration through completion of the follow-up period because such use is considered to affect the evaluation of efficacy or safety in this trial. However, the use of such drugs or therapies after withdrawal from this trial will be permitted if they are necessary for purposes such as treatment.
<table>
<thead>
<tr>
<th>Therapies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- All investigational products other than those used in this trial</td>
<td></td>
</tr>
<tr>
<td>- Drugs that inhibit mTOR (such as sirolimus, everolimus, and temsirolimus)</td>
<td></td>
</tr>
<tr>
<td>- Use of tacrolimus ointment, topical steroids, topical antibacterial agents, topical vitamin D3 preparations on the site of application of the investigational products</td>
<td></td>
</tr>
<tr>
<td>- Use of adapalene, benzoyl peroxide, ibuprofen piconol, resorcin, zinc oxide/salicylic acid ointment on the site of application of the investigational products</td>
<td></td>
</tr>
<tr>
<td>- Surgical treatment, laser treatment, phototherapy, and liquid nitrogen therapy on the site of application of the investigational products</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary outcome measures</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvements in angiofibroma assessed using photographs by the Independent review committee on photograph assessment (IRC) at 12 weeks after the start of administration</td>
<td></td>
</tr>
</tbody>
</table>

| Secondary outcome measures                                                                                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| 1) Improvements in angiofibroma assessed using photographs by the IRC at 4 and 8 weeks after the start of administration and 4 weeks after the completion of administration |                                                                 |
| 2) Improvements in angiofibroma assessed by the investigator at 4, 8, and 12 weeks after the start of administration and 4 weeks after the completion of administration |                                                                 |
| 3) Improvements in the size of angiofibroma assessed by the IRC and the investigator at 4, 8, and 12 weeks after the start of administration and 4 weeks after the completion of administration |                                                                 |
| 4) Improvements in the color (reddishness) of angiofibroma assessed by the IRC and the investigator at 4, 8, and 12 weeks after the start of administration and 4 weeks after the completion of administration |                                                                 |
| 5) Improvements in hypomelanotic macule and plaque on the head (above the neck) assessed by the IRC and the investigator at 4, 8, and 12 weeks after the start of administration and 4 weeks after the completion of administration |                                                                 |
| 6) Proportion of subjects assessed as "improved" or a better category (improvement rate) in each improvement parameter (the primary outcome measure and secondary outcome measures 1) to 5)) at 4, 8, and 12 weeks after the start of administration and 4 weeks after the completion of administration |                                                                 |
| 7) Change from baseline in the total score for DLQI and CDLQI at 4, 8, and 12 weeks after the start of administration and 4 weeks after the completion of administration |                                                                 |

<table>
<thead>
<tr>
<th>Assessment of safety</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Incidence of adverse events and adverse drug reactions</td>
<td></td>
</tr>
<tr>
<td>2) Serious adverse events and adverse drug reactions</td>
<td></td>
</tr>
<tr>
<td>3) Significant adverse events and adverse drug reactions</td>
<td></td>
</tr>
<tr>
<td>4) Laboratory findings and vital signs</td>
<td></td>
</tr>
<tr>
<td>5) Sirolimus blood concentration</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target number of subjects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>60 (30 per group as the number of subjects who are registered definitively)</td>
<td></td>
</tr>
<tr>
<td>Both groups in total should include at least 20 children and 25 adults and at least the following number of subjects in each age category:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Standard Body Surface Area</th>
<th>Minimum Number of Subjects to Be Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to 5 years</td>
<td>Less than 0.8 m²</td>
<td>3</td>
</tr>
<tr>
<td>6 to 11 years</td>
<td>Not less than 0.8 m² and less than 1.3 m²</td>
<td>6</td>
</tr>
<tr>
<td>Age Category</td>
<td>Weight Requirement</td>
<td>Median Age</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------</td>
<td>------------</td>
</tr>
<tr>
<td>12 to 18 years</td>
<td>1.3 m² or more</td>
<td>6</td>
</tr>
<tr>
<td>19 years or older</td>
<td></td>
<td>25</td>
</tr>
</tbody>
</table>

**Medical expert**
Hiroyuki Murota, Assistant Professor, Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University

**Trial Period**
- Time of start of trial: November 2015
- Time of final subject registration (definitive registration): June 2016
- Time of completion of trial: October 2016 (time of completion of the follow-up of the final subject)
## 2 Trial Schedule

### [Tests and Observations and Study Schedule]

<table>
<thead>
<tr>
<th>Timing of Visit</th>
<th>Informed Consent</th>
<th>Screening Period</th>
<th>Double-blind Period</th>
<th>Follow-up Period</th>
<th>Time of Withdrawal</th>
<th>Follow up after withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Visit 1</td>
<td>Visit 2</td>
<td>Visi t 3</td>
<td>W4</td>
<td>W8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Screenin g</td>
<td>Baselin e</td>
<td>W1</td>
<td>±1 W</td>
<td>±1 W</td>
</tr>
</tbody>
</table>

#### Acceptable window for tests and observations

-4W to 0⁴  -1W to 0⁴  ±1 W  ±1 W  ±1 W  +1W  -1 to +2W

#### Informed consent
- No

#### Initial registration
- No

#### Definitive registration/assignment
- No

#### Application of the investigational product
- No

#### TSC diagnosis
- No

#### Verification of eligibility
- No

#### Subject characteristics
- No

#### Body height
- No

#### Pregnancy test
- No

#### Body weight
- No

#### Inspection
- No

#### Vital signs
- No

#### Laboratory tests
- No

#### Urinalysis
- No

#### Assessment of efficacy
- No

#### Measurement of blood concentration
- No

#### Checking of the status of application
- No

#### Checking of concomitant medication/therapy
- No

#### Checking of adverse events
- No

**Δ**: To be performed in possible when the subject was withdrawn at a prescribed visit during the double-blind period.

**▲**: Will be performed in possible when the subject was withdrawn during the double-blind period.

- a: The day when the application of the investigational product is started is defined as Day 0, and 1 W of the acceptable window is 7 days.

- b: The pregnancy test will be performed on women of childbearing potential only.
c: If the screening test was performed 1 week before the date of the initial application of the investigational product or later, the data of the screening test may be used.
d: If a follow-up visit after withdrawal is impossible, the subject will be followed up by telephone etc., and the measurement of vital signs will not be required.
e: Efficacy assessments on the basis of the photographs of each lesion, improvements in angiofibroma and its size and color and improvements in hypomelanotic macule and plaque on the head, and DLQI/CDLQI
f: The time and date of the latest application will be checked in the measurement of sirolimus blood concentration. The status of application will be checked also by patient diary cards.

3 Trial Organization

3.1 Sponsor

3.1.1 Sponsor
Nobelpharma Co., Ltd.
Jin Shiomura, President and CEO
12-10, Nihonbashi-kobunacho, Chuo-Ku, Tokyo 103-0024, Japan

3.1.2 Clinical Development Manager
The manager provides overall directions and supervision to trial-related activities and is solely responsible for smooth conduct of the trial.

Nobelpharma Co., Ltd.
Shigeki Shimazaki, Director of the Department of Research and Development
12-10, Nihonbashi-kobunacho, Chuo-Ku, Tokyo 103-0024, Japan

3.1.3 Director of Clinical Study
The director is responsible for the promotion and control of the activities of this trial. The director also gives directions on the activities to be outsourced to the contract research organization (hereinafter referred to as "CRO") and controls the activities.

Taihei Hio, Department of Development, Nobelpharma Co., Ltd.
12-10, Nihonbashi-kobunacho, Chuo-Ku, Tokyo 103-0024, Japan

3.1.4 Coordinating Investigator
The investigator is in charge of coordination between the study institutions involved in multicenter trials, such as coordination between multiple institutions on the details of the protocol and coordination of the interpretation of protocol in cases where questions arise during the trial.

Mari Kaneda, Instructor, Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University
3.1.5 Medical Expert

The expert provides the sponsor advice about preparation and revision of the investigator's brochure, the protocol, the electronic CRFs (CRFs), and the informed consent documents, guidance on the continuous assessment of safety information related to the investigational products and the actions to be taken for its results, medical evaluation of the data obtained with the investigational products, and guidance on the preparation of the clinical trial report, from the medical and technical viewpoints.

Hiroyuki Murota, Assistant Professor, Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University

3.1.6 Members of the Independent review committee on photograph assessment (IRC)

Independently of the assessment of improvements by the investigator, the committee members blindly assess and judge the improvements in each skin lesion from the medical and technical viewpoints, using the photographs of the skin lesions of individual subjects.

Chikako Nishigori, Professor, Department of Dermatology, Course of Internal Medicine, Kobe University Graduate School of Medicine,
Daisuke Tsuruta, Professor, Department of Skin Pathology, Osaka City University Graduate School of Medicine
Nanako Yamada, Deputy Director, Center for Clinical Residency Program, Tottori University Hospital

3.1.7 Monitor

The monitor performs monitoring in accordance with the monitoring method and the standard operating procedure (SOP) described in the protocol. The monitor also gives directions on the activities to be outsourced to the CRO and controls the activities.

Department of Development, Nobelpharma Co., Ltd.
Representative of the monitor: Taihei Hinoo
12-10, Nihonbashi-kobunacho, Chuo-Ku, Tokyo 103-0024, Japan

3.1.8 Quality Control Manager

The manager ensures that the trial-related documents have been prepared in accordance with GCP and the SOP.

Yusaku Ishizuka, Quality Control Group, Department of Development, Nobelpharma Co., Ltd.
12-10, Nihonbashi-kobunacho, Chuo-Ku, Tokyo 103-0024, Japan
3.1.9 Data Management Manager/Statistical Analysis Manager

The managers outsource data management and statistical analysis activities to the CRO and controls the activities.

Data Science Office, Nobelpharma Co., Ltd.
Yuko Ishikawa (data management manager)
Izumi Hamada (statistical analysis manager)
12-10, Nihonbashi-kobunacho, Chuo-Ku, Tokyo 103-0024, Japan

3.1.10 Audit Manager

The manager outsources the auditing activities to the contract audit organization and controls the activities in accordance with the SOP of Nobelpharma Co., Ltd. The activities to be outsourced include auditing of the appropriateness of the trial systems of the sponsor, the study institutions, and the CRO, the appropriateness of the activities performed, and the reliability of data.

GCP Audit Office, Nobelpharma Co., Ltd.
12-10, Nihonbashi-kobunacho, Chuo-Ku, Tokyo 103-0024, Japan

3.1.11 Investigational Product Control Manager

The manager controls storing, delivery, recovery, and disposal of the investigational products in accordance with the SOP of Nobelpharma Co., Ltd. and the procedure manual for handling the investigational products.

Toyonari Torihata, Department of Development, Nobelpharma Co., Ltd.
12-10, Nihonbashi-kobunacho, Chuo-Ku, Tokyo 103-0024, Japan

3.2 Contract Research Organization (CRO)

3.2.1 Monitoring

The CRO will perform monitoring in accordance with the monitoring method described in the protocol and the SOP (including the monitoring procedure manual specific to this trial).

Department of Clinical Development, intellim Corporation
Representative of the monitor: Kazuaki Takahashix
Akihabara Bldg. 4F, 19 Kandamatsunaga-cho, Chiyoda-ku, Tokyo 101-0023, Japan

3.2.2 Assignment

The CRO will perform the following activities in accordance with the assignment procedure manual:
1) Assurance of the indistinguishability of investigational products
2) Blinding of investigational products
3) Preparation and storage of randomization schedule
4) Preparation and storage of emergency keys  
5) Sampling of investigational products for GCP compliance review  
6) Opening of the randomization schedule

Hiroyuki Hosokawa, Department of Safety Information Control, intelliom Corporation  
Akihabara Bldg. 4F, 19 Kandamatsunaga-cho, Chiyoda-ku, Tokyo 101-0023, Japan

3.2.3 Data Management  
The CRO will prepare a data management plan and check data in accordance with the plan. The CRO will perform a logical check and finalize data. If any correction is to be made in the electronic CRFs after finalization, the CRO will correct the entry data and finalize them again. In performing these activities, the CRO shall hold adequate consultations and discussions with the persons in charge of data management and statistical analysis at the sponsor and comply with their instructions.

Masayuki Aono, Data Science Department, intelliom Corporation  
Akihabara Bldg. 4F, 19 Kandamatsunaga-cho, Chiyoda-ku, Tokyo 101-0023, Japan

3.2.4 Statistical Analysis  
The CRO will prepare a statistical analysis plan in accordance with the analysis methods described in the protocol and perform analyses and tabulation in accordance with the plan. In performing these activities, the CRO shall hold adequate consultations and discussions with the persons in charge of data management and statistical analysis at the sponsor and comply with their instructions.

Tetsuhide Inoue, Data Science Department, intelliom Corporation  
Akihabara Bldg. 4F, 19 Kandamatsunaga-cho, Chiyoda-ku, Tokyo 101-0023, Japan

3.2.5 Audit  
The CRO will check the appropriateness of the study system of this trial, the appropriateness of the activities performed, and the reliability of data after consultations with the audit manager of the sponsor.

Hiroki Iwahara, Reliability Assurance Office, intelliom Corporation  
Akihabara Bldg. 4F, 19 Kandamatsunaga-cho, Chiyoda-ku, Tokyo 101-0023, Japan

3.2.6 Blood Drug Concentration  
The CRO will measure blood sirolimus concentration using the samples collected from the study institutions.

LSI Medience Corporation  
1-13-4 Uchikanda, Chiyoda-ku, Tokyo 101-8517, Japan
3.2.7 Control and Compensation of Image Files
The CRO will take photographs for the assessment by the IRC, transfer image files, prepare various procedure manuals related to the IRC, and perform activities, such as storage and control of the image files used for assessment by the IRC, and image processing including tone correction, and preparation of the meetings of the IRC, in accordance with the manuals.

Shinya Maruyama, Medical Imaging Group, Data Science Department, Drug Information Headquarters Mediscience Planning Inc.
HF Nihonbashi-hamacho Bldg., 1-2-1 Nihonbashi-hamacho, Chuo-ku, Tokyo 103-0007, Japan

3.3 Study Institutions and Investigators
Study institutions will be selected from institutions that can conduct the trial in compliance with GCP, and investigators will be selected from specialists in the field of this disease or those with equivalent experience and knowledge.
Investigators will put together all the trial-related activities and, if the trial is conducted by a team consisting of multiple members, control and guide the members such as subinvestigators and study collaborators as the manager of the team.
The study institutions and the investigator are listed in Annex 1.

4 Background Information

4.1 Skin Lesions Associated with Tuberous Sclerosis Complex
Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by systemic hamartoma, causing benign tumors in nearly the whole body, including the skin, brain, kidney, lung, and heart, and CNS symptoms such as behavior disorders including autism, mental retardation, and epilepsy. The estimated prevalence in Japan is approximately 1 in 10000,\(^1\) and the estimated number of the patients is approximately 15000.
Facial angiofibroma is a facial skin lesion specific to tuberous sclerosis complex and is hamartoma caused by an increase in the connective tissue component and the vascular component of the skin. The disease appears as a spider angiomatoid lesion in infancy and takes the final shape around the age of 5 years, with manifestation of a marked skin eruption and an increase in the number starting around adolescence. Skin eruption appears left-right symmetrically in the central and mandibular regions of the face, including the nasal region, the nasolabial groove, and the buccal region. In severe cases, the eruption not only is aesthetically damaging but also conglomerates around the nostril, causing nasal obstruction or bleeding in some cases. Skin eruption is reported to occur in approximately 75\% of patients with tuberous sclerosis complex worldwide and in at least 80\% of patients with tuberous sclerosis complex aged 5 years or more in Japan. Of 166 patients with tuberous sclerosis complex who visited the Department of Dermatology, Osaka University, 93\% reportedly had facial angiofibroma,\(^2\) and the estimated number of patients with angiofibroma associated with tuberous sclerosis complex in Japan is approximately 12000.

Other skin lesions associated with tuberous sclerosis complex include hypomelanotic macule, plaque on the head (such as the forehead, head, and lower jaw), shagreen patch, and periungual fibroma. Hypomelanotic macule is an obscure nonpigmented skin lesion that occurs at birth or within several months
after birth and is reported in at least 80% of patients with tuberous sclerosis complex. Fibrous plaque on the head is considered a lesion specific to tuberous sclerosis complex and occurs in approximately 25% of patients with the disease. Shagreen patch is a plaque that occurs commonly in the dorsal, lumbosacral, and abdominal regions asymmetrically after adolescence and is reported in 50% of patients with tuberous sclerosis complex aged 5 years or more. The size of the patch ranges from several millimeters to as large as 10 cm or more. Periungual fibroma is an oblong and cartilage-like hard mass that develops from the base of the nails or the nail plate or the edge of the nail plate and is reported to occur in 88% of patients with tuberous sclerosis complex aged 30 years or more. Periungual fibroma occurs more often in toenails than in fingernails and recurs soon after surgical excision.

4.2 Current Treatments

Table 4.2-1 shows treatments for skin lesions associated with tuberous sclerosis complex. In Japan, no drug has been approved for the indication "skin lesions associated with tuberous sclerosis complex" including angiofibroma. Treatments are indicated for angiofibroma that is aesthetically damaging or that causes frequent bleeding, but the treatment modalities are limited to laser treatment or surgical treatment. Yttrium aluminum garnet laser (YAG laser) is used for angiofibroma with a large number of blood vessels and a strong reddishness, and liquid nitrogen therapy, laser ablation using CO2 laser, etc. are performed for skin eruption consisting of clustered or dispersed small papules. Moreover, surgical excision is indicated for a severe lesion with plaque that looks like mulberry or a bunch of grapes. However, the level of satisfaction with the current treatments is not sufficiently high because all these treatments lack evidence for the choice of treatment and are associated with a high rate of recurrence and risks of pigmenat changes, scarring, and infection. For other skin lesions, the current therapeutic options are extremely limited: Surgical excision and follow up are the only treatments.

In addition, patients with tuberous sclerosis complex include a large number of children and often have concurrent mental retardation and autistic symptoms. In patients with these comorbid diseases, laser treatment or surgical treatment using local anesthesia and postoperative wound management are difficult. Moreover, high-risk treatments under general anesthesia are not easy in patients with comorbid diseases such as severe epilepsy, lung lesions, and renal lesions. Furthermore, oral administration of mammalian target of rapamycin (mTOR) inhibitors (everolimus, sirolimus) for renal angiomyolipomas (renal AML), subependymal giant cell astrocytoma (SEGA), and LAM accompanying tuberous sclerosis complex is associated with concern of systemic adverse drug reactions such as interstitial lung disease and infection due to immunosuppression. For these reasons, there is a strong demand for the development of an external medicine for skin lesions associated with tuberous sclerosis complex that can be locally administered with no systemic adverse drug reactions.
Table 4.2-1: Current Treatments for Skin Lesions Associated with Tuberous Sclerosis Complex

<table>
<thead>
<tr>
<th>Cutaneous Symptom</th>
<th>Frequency of Complications</th>
<th>Indication for Treatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomelanotic macule</td>
<td>&gt; 80%</td>
<td>A large number of blood vessels and a strong reddishness</td>
<td>Follow up</td>
</tr>
<tr>
<td>Facial angiofibroma</td>
<td>&gt; 80%</td>
<td>Aesthetically damaging, frequent bleeding</td>
<td>YAG laser</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small papules</td>
<td>Liquid nitrogen therapy, CO₂ laser</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mulberry</td>
<td>Surgical excision</td>
</tr>
<tr>
<td>Frontal, cephalic, and mandibular plaque</td>
<td>25%</td>
<td>Aesthetically damaging</td>
<td>Surgical therapy</td>
</tr>
<tr>
<td>Shagreen patch</td>
<td>&lt; 5 years: 25%</td>
<td>Large patch</td>
<td>Surgical excision in several operations</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 years: 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periungual fibroma</td>
<td>&gt; 30 years: 88%</td>
<td>Hemorrhagic tumor, functional impairment</td>
<td>Surgical excision (for tumors that are likely to recur)</td>
</tr>
</tbody>
</table>

4.3 History of Development

As genes responsible for tuberous sclerosis complex, 2 genes, TSC1 and TSC2, have been identified, and the dysfunction of the hamartin-tuberin complex, the proteins that are produced by these genes, results in a constant activation of downstream mTOR, causing systemic hamartoma. Sirolimus not only has a macrolide antibacterial action but also selectively binds to FKBP12 to form a complex with mTOR, inhibiting its function. Thus, as an external preparation, sirolimus is expected to be an extremely useful therapeutic drug for skin lesions associated with tuberous sclerosis complex, including angiofibroma, with reduced systemic adverse drug reactions.

In fact, in an investigation using a nude mouse model of tuberous sclerosis complex, local administration of sirolimus ointment, as compared with the control, has shown significant tumor inhibitory effects and prolongation of lifetime. In addition, in clinical trials, many Japanese and overseas reports have been reported since 2010 about the results of local administration of various dosage forms (gel, ointment, cream, liquid; obtained by such means as grinding tablets and mixing with a base to form an external preparation) of sirolimus at various concentrations (0.003% to 1%) to patients with angiofibroma associated with tuberous sclerosis complex. A report of an integrative analysis of these literature reports has shown that in a total of 84 patients who received external sirolimus in the world, angiofibroma was improved in a remarkable 94% of patients without serious adverse events except 1 case of aspiration pneumonia and has concluded that external sirolimus can be a safe and effective therapeutic drug for angiofibroma. In addition, multiple papers have reported improvements in hypomelanotic macule and periungual fibroma. On the basis of these results, the latest International Consensus Conference (2012) recommends local administration of an mTOR inhibitor for skin lesions associated with tuberous sclerosis complex, although the evidence level is low because of the lack of reports of the results of verification studies.

In Japan, Kaneda et al. at Osaka University conducted an investigator-initiated phase I/II study of a gel (OSD-001) manufactured from a bulk powder of sirolimus in patients with skin lesions due to tuberous sclerosis complex from December 2013 through July 2014. The sirolimus gel showed significant
improvements against placebo in both the volume and color of angiofibroma. In addition, the gel had good tolerability with no adverse events leading to withdrawal or no severe adverse drug reactions.

This trial was planned as a verification study because the above-described actions and clinical/nonclinical results suggest that the sirolimus gel is a heretofore non-existent promising therapy for skin lesions associated with tuberous sclerosis complex, including angiofibroma.

4.4 Summary of Clinically Significant Findings Obtained from Nonclinical Studies

In an in vitro study to investigate inhibition of vascular endothelial growth factor using cultured cells derived angiofibroma and epidermal keratinocytes obtained from patients with tuberous sclerosis complex, sirolimus inhibited the production of vascular endothelial growth factor in a manner dependent on the concentration of the amount added. In addition, sirolimus increased the mRNA of MITF, TYR, and TYRP1, which are involved in the production of melanin in melanocytes. Moreover, according to a literature report, local administration of sirolimus ointment, as compared with the control, has shown significant tumor inhibitory effects and prolongation of lifetime in an investigation using a nude mouse model of tuberous sclerosis complex.

With respect to safety, sirolimus was not stimulatory at concentrations of up to 0.2% in an investigation of local stimulation on the skin and the eye using rabbits. In addition, sirolimus showed no phototoxicity in an in vitro phototoxicity study of sirolimus using 3T3 cells and was negative for skin sensitization with no erythema or edema in a skin sensitization study (adjuvant and patch test method) using guinea pigs. On the other hand, a skin photosensitization study (adjuvant and strip method) using guinea pigs suggested that sirolimus or the base component may cause skin photosensitization or induce photosensitivity, and a subsequent supplemental investigation did not rule out the possibility. Although no report has heretofore shown any photosensitivity symptom in a clinical setting, we will instruct subjects to take measures such as avoiding direct sunlight in this study.

4.5 Summary of Japanese Investigator-initiated Phase I/II Study

An investigator-initiated, placebo-controlled, randomized, double-blind study (phase I/II) to estimate the safety and effective doses of a sirolimus gel (OSD-001) for facial skin lesions due to tuberous sclerosis complex was conducted from December 2013 through July 2014 at Osaka University Hospital.

The study was conducted in 36 patients with facial angiofibroma associated with tuberous sclerosis complex (adults, 18 patients; children, 18 patients), to whom the sirolimus gel (0.05%, 0.1%, 0.2%) or placebo was applied twice daily on facial lesions for 12 weeks. In each concentration group, 8 patients were included in the sirolimus gel group (4 patients each of adults and children), and 4 patients in the placebo group (2 patients each of adults and children). In adult patients (aged not less than 19 years and less than 65 years), the 0.1% gel was applied after the safety of the 0.05% gel was ascertained, and the 0.2% was applied after the safety of the 0.1% gel was ascertained. In pediatric patients (aged 3 to 18 years), application of the gel of each concentration was performed after the safety of that concentration was ascertained in adult patients. The safety of each concentration was judged by the investigator on the basis of data up to 4 weeks after the start of application. The tumors to be used for efficacy assessment are 3 largest tumors at locations distant from each other selected from solitary papules with a longitudinal diameter of at least 2 mm and reddishness.
In comparison with the placebo group in the frequency distribution of the primary efficacy outcome measure "composite variable consisting of the degree of shrinkage of the tumors assessed (improvements in tumor volume) and improvements in the redness of the tumors assessed from baseline to 12 weeks (total score of improvements based on improvements in the volume and redness of the 3 target tumors)," significant improvements in angiofibroma were observed in the 0.2% group ($p = 0.047$) in adults, in all of the sirolimus gel groups (0.05%, $p = 0.029$; 0.1%, $p = 0.038$; 0.2%, $p = 0.014$) in children, and in the 0.05% group ($p = 0.010$) and the 0.2% group ($p < 0.001$) in adults and children combined (Wilcoxon test).

In addition, of the secondary outcome measures, similar results were observed in improvements in the redness and overall improvements in the 3 target tumors. With respect to improvements in tumor volume, although no significant improvement against placebo was observed in any test drug group in adults, a significant improvement against placebo was observed in the 0.2% group ($p = 0.029$) in children and in the 0.05% group ($p = 0.031$) and the 0.2% group ($p = 0.004$) in adults and children combined (Wilcoxon test). With respect to patient satisfaction, although no significant difference from placebo was observed in adults and in adults and children combined, a significantly high satisfaction against placebo was observed in all test drug groups in children (Wilcoxon test: 0.05%, $p = 0.043$; 0.1%, $p = 0.024$; 0.2%, $p = 0.024$).

With respect to adverse events (adults and children combined), 11 cases occurred in 7 patients (58.3%) in the the placebo group, 11 cases in 6 patients (75.0%) in the 0.05% group, 10 cases in 7 patients (87.5%) in the 0.1% group, and 25 cases in 7 patients (87.5%) in the 0.2% group. As adverse events (adverse drug reactions) whose causal relationship with the investigational products cannot be ruled out, 4 cases occurred in 3 patients (25.0%) in the placebo group, 5 cases in 3 patients (37.5%) in the 0.05% group, 5 cases in 4 patients (50.0%) in the 0.1% group, and 8 cases in 7 patients (87.5%) in the 0.2% group. Adverse events that occurred in at least 2 patients in the sirolimus gel groups (8 patients/group × 3 groups) were dry skin (0.2% group, 4/8 patients; 0.1% group, 3/8 patients; 0.05% group, 3/8 patients; placebo group, 1/12 patients), nasopharyngitis (0.2% group, 1/8 patients; 0.1% group, 2/8 patients; 0.05% group, 3/8 patients; placebo group, 2/12 patients), dermatitis aceneiform (0.2% group, 3/8 patients; other groups, 0 patient), procedural pain (0.2% group, 1/8 patients; 0.1% group, 1/8 patients; 0.05% group, 0/8 patients; placebo group, 0/12 patients), and irritability (0.2% group, 0/8 patients; 0.1% group, 1/8 patients; 0.05% group, 1/8 patients; placebo group, 2/12 patients).

As serious adverse events, epilepsy (1 case in 1 patient; adult; placebo group) and pneumothorax (2 cases in 1 patient; adult; 0.2% group) were reported. Both events are complications of the primary disease, and the causal relationship of both events with the investigational products was ruled out. Skin irritation symptoms defined as significant adverse events were observed in 17/36 patients (0.2% group, 7/8 patients; 0.1% group, 4/8 patients; 0.05% group, 3/8 patients; placebo group, 3/12 patients). Of them, dry skin was observed most frequently and occurred in 11 patients (0.2% group, 4/8 patients; 0.1% group, 3/8 patients; 0.05% group, 3/8 patients; placebo group, 1/12 patients), and the causal relationship was not ruled out in all patients. All events of skin irritation symptoms were nonserious and mild or moderate and were not considered clinically significant adverse events because these events were treatable with vaseline or heparinoid, and the outcome was "recovered" in all events.

In conclusion, the sirolimus gel at up to 0.2% showed a significant improvement of angiofibroma and tolerability.
5 Study Objectives

To verify the efficacy of sirolimus gel for angiofibroma associated with tuberous sclerosis complex and to investigate its efficacy and safety in patients with other skin lesions.

6 Target

Skin lesions associated with tuberous sclerosis complex

6.1 Inclusion Criteria

1) Male or female patients 3 years old or greater at the time of informed consent
2) Patients corresponding to "definite diagnosis" according to the diagnostic criteria for tuberous sclerosis complex (International Tuberous Sclerosis Complex Consensus Conference 2012, Appendix 1).
3) Patients with three or more reddish papules of angiofibroma (≥ 2 mm in diameter) on the face at screening tests
4) Patients who are not suitable for therapy with laser or surgery (including liquid nitrogen therapy and phototherapy) for angiofibroma, or who do not want therapy with laser or surgery
5) Patients who (or whose guardian) give a written informed consent in understanding and willingness after having received enough explanation regarding the study participation.

6.2 Exclusion Criteria

1) Patients who (or whose guardian) are hard to apply the test drug topically with keeping compliance
2) Patients with clinical findings such as erosion, ulcer and eruption on or around the lesion of angiofibroma, which may affect assessment of safety or efficacy
3) Patients who are hard to be taken pictures of their lesions adequately in such cases that they may not follow instruction of stillness
4) Patients with a history of hypersensitivity to alcohol or allergy to sirolimus
5) Patients who have complications such as malignant tumor, infection, serious heart disease, hepatic function disorder, renal function disorder or blood disorders (selected by the investigator or subinvestigator [hereinafter referred to collectively as "investigator"] with reference to grade 2 or more serious disease defined in "Standards for Classification of Seriousness of Adverse Drug Reactions by Drugs etc. (Appendix 2)."
6) Patients who have complications such as diseases unsuitable for the trial participation, for examples, uncontrolled diabetes (fasting blood glucose level >140 mg/dL or postprandial blood glucose level > 200 mg/dL), dyslipidemia (cholesterol level > 300 mg/dL or > 7.75 mmol/L, triglycerides level > 300 mg/dL or > 3.42 mmol/L), etc.
7) Patients who have taken drugs with mTOR inhibitory action (including sirolimus, everolimus or temsirolimus) within 12 months before the initial registration
8) Patients who have applied topical tacrolimus on the lesion of angiofibroma within 3 months before the initial registration
9) Patients who have received therapy with laser or surgery (including liquid nitrogen therapy and phototherapy) to the lesion of angiofibroma within 6 months before the initial registration
10) Female patients who are pregnant, may be pregnant, or are lactating
11) Patients who cannot agree to take appropriate measures of contraception until completion of the follow-up period or the follow up after withdrawal from informed consent
12) Patients who have participated in other clinical trial and have taken a trial drug within 6 months before the initial registration
13) Other patients who are considered by the investigator as unsuitable for participation in the trial

7 Informed Consent by Subjects

7.1 Preparation of Informed Consent Documents

Prior to the conduct of this trial, the investigator, in cooperation with the sponsor, will prepare informed consent documents and assent documents, submit them to the head of the study institutions to obtain approval by the IRB, and also submit them to the sponsor. The informed consent documents shall contain the following information defined by GCP:

1) That the trial involves research.
2) Study objectives
3) Trial method (including the experimental aspects of the trial, subject inclusion criteria, and the probability for random assignment to each treatment).
4) The expected duration of the subject's participation in the trial.
5) Planned number of subjects participating in the trial.
6) Expected clinical benefits and risks or disadvantages.
7) Presence or absence of alternative treatments and their important expected benefits and risks.
8) The compensation and/or treatment available to the subject in the event of trial-related injury.
9) That the subject's participation in the trial is voluntary and that the subject or the patient's legally acceptable representative may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
10) That the subject or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
11) The conditions and/or reasons under which the subject's participation in the trial are terminated.
12) That the monitor(s), the auditor(s), the IRB, and the regulatory authority(ies) will be granted access to the subject's original medical records without violating the confidentiality of the subject and that, by signing a written informed consent form, the subject or the patient's legally acceptable representative is authorizing such access.
13) If the results of the trial are published, the subject's confidentiality will be maintained.
14) The details of the anticipated expenses, if any, to the subject.
15) The details of the anticipated prorated payment, if any, to the subject (such as an arrangement on the calculation of the payment).
16) Name, affiliation, and contact information of the investigator or subinvestigator
(17) The person(s) at the study institution whom the subject and the subject's legally acceptable representative should make inquiries to or contact for further information regarding the trial and the rights of trial subjects and in the event of trial-related injury.

(18) The subject's responsibilities.

(19) The type of the IRB that will investigate and discuss the advisability of this trial etc., the matters investigated and discussed in the IRB, and other trial-related matters about the IRB.

(20) That the written procedure for the IRB etc. can be checked. The website address if the procedure for the IRB etc. are open to the public on the website of the study institution etc. or the fact that the procedure for the IRB etc. have been made available for public access by such means as providing them at the office, if they are not open to the public. Subjects may make a request if they want to check the procedure for the IRB etc.

7.2 Timing and Method of Obtaining Consent

7.2.1 Explaining the Trial Etc. and Obtaining Consent

After the study institution and the sponsor concluded the study contract and before the conduct of the tests and observations described in the protocol, the investigator will explain the trial to patients who are candidates for subjects using the informed consent documents, give them opportunities to ask questions and ample time to determine whether or not to participate in the trial, and obtain written voluntary consent.

However, if the patient who is a candidate of subject is aged less than 20 years, or is aged 20 years or more but is not judged by the investigator to be sufficiently capable of giving consent due to concurrent mental retardation etc., the investigator will give the patient's legally acceptable appropriate representative (a person who exercises parental power over the patient who is a candidate for subject, a legal guardian, or other equivalent persons who can work for the patient's best benefits) adequate explanation using the informed consent documents, give them opportunities to ask questions and ample time to determine whether or not to participate in the trial, and obtain written voluntary consent from the patient's legally acceptable representative. In this instance, the investigator will record the relationship of the patient's legally acceptable representative and the patient who is a candidate for subject. Even in such cases, the investigator will give the patient an explanation corresponding to the patient's power of comprehension using the informed consent documents or an appropriate assent document and, if possible, obtain a written voluntary consent also from the patient. If the patient refuses to participate in the trial, the investigator may not include the subject in the trial on the basis of the sole consent of the patient's legally acceptable representative.

7.2.2 Delivery of Informed Consent Forms

After the explanation is completed, the investigator will sign the informed consent form with the date of explanation and hand it, together with the informed consent documents, to the patient who is a candidate for subject and the patient's legally acceptable representative. Before obtaining consent, the investigator will give the patient who is a candidate for subject and the patient's legally acceptable representative opportunities to ask questions and ample time to determine whether or not to participate in the trial. To all questions, the investigator will provide answers that satisfy the patient who is a candidate for subject and the patient's legally acceptable representative.
7.2.3 Obtainment of Informed Consent Forms

Before performing the tests and observations necessary for the trial, the investigator will obtain the informed consent form signed and dated by the patient who is a candidate for subject or the patient's legally acceptable representative and hand a copy of the form, together with the informed consent documents, to the subject or the subject's legally acceptable representative.

If it was impossible to obtain the signature of the patient because of difficulty in understanding the explanation due to the patient's condition or age or if an oral assent was obtained from the patient, the investigator will record the fact and the reasons that obtaining of the signature was considered impossible in the informed consent form signed by the patient's legally acceptable representative or the medical record.

7.3 Acquisition of New Information and Revision of "Informed Consent Documents"

If new information becomes available that may be relevant to the willingness of the subjects and the subjects' legally acceptable representatives to continue participation in the trial, the investigator will revise the informed consent documents and, if necessary, the assent documents in accordance with the information and obtain the approval from the IRB.

Furthermore, the investigator will promptly inform the subjects and the subjects' legally acceptable representatives about the information, ascertain again the willingness of the subjects and the subjects' legally acceptable representatives to continue participation in the trial, and record the ascertained information in the medical record etc. In addition, the investigator will explain the informed consent documents and the assent documents again to the subjects and the subjects' legally acceptable representatives and obtain written consent again in accordance with the rules described in Section 7.2 "Timing and Method of Obtaining Consent."

7.4 Other Matters

The investigator will obtain consent from the patient who is a candidate for subject and the patient's legally acceptable representative in compliance with the following:

1. The investigator must not coerce or unduly influence the patient who is a candidate for subject and the patient's legally acceptable representative about participation or the continuation of participation in the trial.

2. The information provided orally or by the informed consent documents or the assent documents must not contain any phrase that causes or appears to cause the patient who is a candidate for subject and the patient's legally acceptable representative to waive any legal rights or any phrase that releases or appears to release the investigator, the study institution, or the sponsor from legal liability.

3. The language used in the information provided orally or by the informed consent documents or the assent documents must be understandable to patients who are candidates for subject and the patients' legally acceptable representative and must be as non-technical as practical.

4. For any reason, the trial must not be started on the basis of oral consent alone.
7.5 Allocation of Subject Identification Codes and Preparation of Screening List

The investigator will allocate a "subject identification code" to all patients from whom consent was obtained, in accordance with the order in which consent was obtained, and record the following information in the fanfold "screening list."

[First sheet]

The date of consent, patient's name, subject identification code, medical record number, group number for investigational products, and whether the subject completed or discontinued the trial (in the case of discontinuation, the date thereof and the reasons therefor) will be recorded, and the sheet will be stored at the study institution.

[Second sheet]

The information contained in the first sheet, except the patient's name and the medical record number, will be reproduced. After checking the information, the investigator affixes his/her name and seal or signature on the sheet and submits it to the sponsor.

8 Investigational Product

8.1 Test product

<table>
<thead>
<tr>
<th>Non-proprietary name</th>
<th>Sirolimus (JAN), Sirolimus (INN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational product code</td>
<td>NPC-12G</td>
</tr>
<tr>
<td>Structural formula</td>
<td>![Structural formula image]</td>
</tr>
<tr>
<td>Strength and dosage form</td>
<td>Aqueous gel containing 2 mg of sirolimus in 1 g</td>
</tr>
<tr>
<td>Appearance</td>
<td>Colorless and transparent gel</td>
</tr>
<tr>
<td>Container</td>
<td>Aluminum-laminated tube</td>
</tr>
<tr>
<td>Storage condition</td>
<td>Refrigerate (2°C to 8°C)</td>
</tr>
<tr>
<td>Manufacturing number</td>
<td>NP12G1581*, NP12G1611*2</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Nobelpharma Co., Ltd.</td>
</tr>
</tbody>
</table>

### 8.2 Control Drug (Placebo)

<table>
<thead>
<tr>
<th>Strength and dosage form</th>
<th>A placebo gel that does not contain sirolimus and is indistinguishable from the test drug in appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Colorless and transparent gel</td>
</tr>
<tr>
<td>Container</td>
<td>Aluminum-laminated tube</td>
</tr>
<tr>
<td>Storage condition</td>
<td>Refrigerate (2°C to 8°C)</td>
</tr>
<tr>
<td>Manufacturing number</td>
<td>NP12G1581</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Nobelpharma Co., Ltd.</td>
</tr>
</tbody>
</table>

### 8.3 Packaging and Labeling of the Investigational Products

A total of 15 tubes, each containing 10 g of the investigational product, will be put in an inner box, which will be sealed as a unit for 1 patient. Inner boxes corresponding to units for 4 patients will be put in an outer box, which will be used as a unit for 1 group.

The following information will be displayed on the inner and outer boxes.
- That the products are for the trial.
- Number of the allocation group (outer box) or the allocation group order (inner box)
- Name and address of the sponsor
- Identification number
- Protocol number
- Manufacturing number
- Storage condition
- Quantity

### 8.4 Delivery, Storage, Control, and Recovery of the Investigational Products

1. After the study contract was concluded with the study institution, the sponsor will deliver the investigational products, together with "Investigational Products Handling Procedure," to the investigational product manager.

2. In accordance with "Investigational Products Handling Procedure," the investigational product managers will store and control the investigational products and record the prescriptions at the study institutions, drug use for each subject, and return to the sponsor in the investigational products administration table.

3. After the trial is completed, the investigational product managers will promptly return the used tubes of the investigational products, the unused investigational products, and the empty boxes (inner and outer boxes) to the sponsor together with the investigational products administration table (copy). If the remaining drugs are to be recovered before unblinding, the investigational product manager will seal the investigational products and return them to the sponsor.

4. The investigational products shall not be disposed of at the study institutions.
9 Trial Method

9.1 Study Design
A multicenter, stratified, randomized, double-blind, placebo-controlled, comparative study

9.2 Randomization and Blinding

9.2.1 Confirmation of the Indistinguishability of Investigational Products
Before the allocation of the investigational products, the allocation manager will confirm the indistinguishability of the test drug and the placebo gel in appearance, packaging, etc. and record the result.

9.2.2 Method of Randomization and Blinding
Randomization will be performed for each of the adult age group (aged 19 years or more) and the pediatric age group (aged less than 19 years) by the allocation manager using the permuted block method. Blinding will be achieved by using in combination a placebo gel and the test drug that are indistinguishable in appearance.

9.2.3 Allocation of Investigational Products
The allocation manager will randomly allocate the investigational products in accordance with the allocation procedure manual and prepare a randomization schedule for the investigational products. The randomization schedule and the electronic files and documents used for preparing the schedule will be sealed and securely stored and controlled by the allocation manager until unblinding.

9.2.4 Preparation of Emergency Keys
The allocation manager will prepare 2 copies of emergency keys for each patient to enable immediate identification of the administered investigational product in a state of emergency, store the top copy, and send the duplicate copy to the Clinical Development Manager for storage by the manager.

9.2.5 Maintenance of the Blinding
The randomization schedule will be stored by the allocation manager until unblinding, and the allocation manager and the persons in charge of allocation will not disclose the allocation information learned in allocation operation until unblinding.
If the remaining drugs are to be recovered before unblinding, the investigational product manager will seal the investigational products and return them to the sponsor.
For the procedure for unblinding in an emergency, see Section 14.4 "Procedure for Opening Emergency Keys."
9.3 Subject Enrollment

9.3.1 Initial Registration

In accordance with the rules described in Section 7.2 "Timing and Method of Obtaining Consent," the investigator will perform the screening tests as the tests and observations for the first visit after obtaining written consent form patients who are candidates for subjects and the subjects' legally acceptable representatives. On the basis of the result of screening, the investigator will check that subjects meet the inclusion criteria and do not fall under the exclusion criteria (items 5 and 6 may be checked by the second visit) and enter necessary information in the electronic CRFs. A subject will be regarded as having been initially registered when this entry has been made.

If a subject met the withdrawal criteria described in Section 15.3.1 "Withdrawal Criteria between Initial Registration and Definitive Registration" after the initial registration and before the definitive registration, the investigator will promptly enter necessary information in the electronic CRF.

9.3.2 Definitive Registration

After checking that the laboratory findings at the first visit (screening tests) are satisfactory, the investigator will perform the tests and observations for the second visit, check that the patient who is a candidate for subject meets the inclusion criteria and does not fall under the exclusion criteria on the basis of the result, and enter necessary information in the electronic CRF. A subject will be regarded as having been definitively registered when this entry has been made. The investigator will check the group number of the investigational product allocated to the subject after the definitive registration and start the administration of the investigational product corresponding to the group number.

If a subject met the withdrawal criteria described in Section 15.3.2 "Withdrawal Criteria after Definitive Registration" after the definitive registration, the investigator will promptly enter necessary information in the electronic CRF.
9.3.3 Subject Registration Flow

Obtainment of written consent

At the first visit: Checking for the inclusion/exclusion criteria (screening)
Eligible patients only

[Initial registration]
The result of checking of eligibility is entered into the electronic CRF.

The sponsor checks entries and makes inquiries if necessary.

[If a subject meets the withdrawal criteria between the initial registration and the definitive registration.]

Within 4 weeks

At the second visit: Checking for the inclusion/exclusion criteria (including checking of
Eligible patients only

[Definitive registration]
The result of checking of eligibility is entered into the electronic CRF.

The sponsor checks entries and makes inquiries if necessary.

[If a subject meets the withdrawal criteria after the definitive registration]
The withdrawal information is entered into the electronic CRF.

Within 1 week

Start of application of the investigational product

[If a subject meets the withdrawal criteria after the definitive registration]
The withdrawal information is entered into the electronic CRF.
9.4 Dosing Regimen and Dose

The allocated investigational product, either NPC-12G gel (0.2%) or the placebo gel, will be evenly applied to facial angiofibroma lesions twice daily (in the morning and at bedtime). If a subject forgot to perform the morning application, the subject shall perform application immediately upon realization of the fact if the time of realization was before dinner on the same day and shall perform only the application before sleeping if the time of realization was after dinner. The application of the investigational product shall be started within 4 weeks from the first visit and 1 week from the second visit (baseline).

The amount of application will be 125 mg (approximately 0.5 to 1 cm as the length of gel extruded from the tube) per a lesion of 50 cm², as a rough standard, and the duration of treatment will be 12 weeks (allowable duration: 11 to 13 weeks).

Application on the lesions of hypomelanotic macule and plaque on the head (above the neck), in addition to angiofibroma lesion, will be permitted, with the limitations on the upper limit of the amount of daily application specified in accordance with the age category shown in Table 9.4-1 for safety reasons. For subjects who sharply deviate from the standard physique (body surface area) for the age category, the upper limit of the amount of application will be defined not in accordance with age category but in accordance with body surface area category. In addition, the upper limit for each subject will be determined by the second visit, and the result will be recorded. Moreover, from the viewpoint of compliance with the upper limit of the amount of application, the investigational products will be prescribed in such a manner that the number of tubes that be prescribed before the next prescribed visit (in approximately 1 month) does not exceed the upper limits defined in Table 9.4-1, and subjects and the subjects' legally acceptable representatives will be given the following guidance:

- From the start of application of the investigational products to the completion of the follow-up period or the follow up after withdrawal, the subjects will use a sunscreen and take such measures as prevention of direct sunlight.
- If possible, the method of skin care (such as application of a general humectant etc., makeup, and facial cleansing) should not be changed during participation in the trial.
- The investigational product must not be applied to lesions from scratches or skin infection.

Body surface area will be calculated on the basis of the body height, body weight, and age at the first visit (at the time of screening tests) using the Fujimoto method shown below and, if necessary, in reference to the body surface area table (Appendix 3) published by the Japan Clinical Oncology Group (JCOG).

One to 5 years old: Body surface area (cm²) = body weight (kg)⁰.⁴²³ × body height (cm)⁰.³⁶² × 381.89
6 years old or older: Body surface area (cm²) = body weight (kg)⁰.⁴⁴⁴ × body height (cm)⁰.⁶⁶³ × 88.83
Table 9.4-1: Upper Limit of the Amount of Daily Application by Age Category and the Number of Tubes That Can Be Prescribed before the Next prescribed visit

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Standard Body Surface Area</th>
<th>Upper Limit of the Amount of Daily Application</th>
<th>Upper Limit of the Number of Tubes That Can Be Prescribed before the Next Prescribed Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years or younger</td>
<td>Less than 0.8 m²</td>
<td>400 mg (corresponding approximately to 2 to 3 cm)</td>
<td>Two 10-g tubes</td>
</tr>
<tr>
<td>6 to 11 years</td>
<td>Not less than 0.8 m² and less than 1.3 m²</td>
<td>600 mg (corresponding approximately to 3 to 4 cm)</td>
<td>Three 10-g tubes</td>
</tr>
<tr>
<td>12 years or older</td>
<td>1.3 m² or more</td>
<td>800 mg (corresponding approximately to 4 to 5 cm)</td>
<td>Four 10-g tubes</td>
</tr>
</tbody>
</table>

The status of application of the investigational product will be checked by the patient diary, and a subject will be withdrawn from this trial if the subject did not perform application consecutively for 8 days or more regardless of the reasons. During the 8 days starting from 7 days before the day of efficacy assessment through the day of assessment, missing applications for reasons that the subject forgot to perform application etc. (excluding applications suspended from the viewpoint of safety, e.g., to treat adverse events) must not occur 4 times or more.

[Rationale for Setting]
(1) Concentration of application and duration of treatment
In the investigator-initiated phase I/II study conducted prior to this trial, a significant improvement against the placebo group in "frequency distribution of the composite variable based on improvements in the tumor volume and reddishness at 12 weeks after the start of administration" was observed in the adult 0.2% group and all of the pediatric sirolimus gel groups (0.05% to 0.2%). In addition, a significant improvement against the placebo group was observed in "reddishness at 12 weeks after the start of administration" in the adult 0.2% group and the pediatric 0.05% and 0.2% groups and in "tumor volume at 12 weeks after the start of administration" in the pediatric 0.2% group.

With respect to safety, although the number of cases of adverse events (adults and children combined) was large in the 0.2% group, all these events were mild or moderate except pneumothorax that occurred in 1 adult patient, and no event was reported that occurred in a greatly different manner between adult and children. While dry skin, nasopharyngitis, dermatitis acniform, procedural pain, and irritability occurred in 2 patients or more in the sirolimus gel groups, the number of patients with adverse events was similar between concentrations, except in dermatitis acniform. While 3 cases of dermatitis acniform occurred in 3 patients in the 0.2% group alone, all these events were mild in severity, resolved without intervention, and did not recur. As serious adverse events, epilepsy and pneumothorax each occurred in 1 patient. Both events were complications of the the primary disease, and the causal relationship with the investigational products was ruled out. In addition, no adverse event was reported that led to withdrawal. Although skin irritation symptoms such as dry skin occurred in 17/36 patients, none of the events was considered clinically significant because all events were nonserious and mild or moderate, treatable with vaseline etc., and resolved, and it was possible to continue the trial.
In conclusion, the use of the 0.2% gel was judged appropriate in this trial because among the 3 concentrations in the range of 0.05% to 0.2% that were investigated in the I/II study, the recommended concentration was 0.2% for both adults and pediatric, and the tolerability of twice daily application of the gel for 12 weeks was considered satisfactory. With respect to the duration of treatment, it was considered possible to verify the efficacy of the present drug by studying for 12 weeks in accordance with the I/II study.

(2) Amount of application

With respect to the amount of application, the upper limit of the amount of daily application that is needed was considered to be approximately 2 times the amount prescribed in the phase I/II study (approximately 375 mg at the maximum as the sirolimus gel) in order to appropriately secure the amount necessary for application on skin lesions on the head (above the neck) including angiofibroma, and the safety after application of this upper limit was investigated as follows:

Since the amount of application at the lesion will be 125 mg per 50 cm² as a rough standard as is the case with the I/II study, the degree of increase in local drug concentration and the severity of the associated skin symptoms and their incidences were expected to be similar to those in the I/II study.

On the other hand, increasing the upper limit of the amount of application may increase the blood concentration of sirolimus. In the phase I/II study, the number of subjects in whom blood concentration was detected, as well as the blood concentration detected, was increased as the concentration of sirolimus gel was increased. In the 0.2% group, blood concentration tended to be slightly higher in children than in adults with a blood concentration of 0.1045 to 0.1952 ng/mL detected in 3/4 patients in adult patients and a blood concentration of 0.1103 to 0.2462 ng/mL detected in all 4 patients in pediatric patients. However, in both adults and children, the blood concentration after application of the sirolimus gel was extremely lower than the blood concentration after administration of 2 mg per day of sirolimus tablets to patients with LAM. In addition, the above-mentioned detected concentration was extremely low, i.e., approximately one 60th to one 20th of the target trough concentration (5 to 15 ng/mL) specified in the clinical study in patients with LAM or the lower limit of the trough concentration that is described in an overseas package insert as the concentration required to maintain immnosuppression with sirolimus alone (12 ng/mL) (chromatography method in both cases). Thus, if the upper limit of the amount of application in this trial is approximately 2 times the amount in the phase I/II study, the blood concentration may remain extremely low as is the case with the phase I/II study. In other words, any of the systemic adverse drug reactions that are of concern in the administration of tablets is considered extremely unlikely to occur, and concern over local skin symptoms and systemic adverse drug reactions may be similar to that in the I/II study.

However, since patients included in this trial vary greatly in physique, we thought that the upper limit of the amount of application should be specified in accordance with the age or physique of each patient. Thus, the criteria for body surface area were defined by age category on the basis of the mean body surface area for the pediatric generation by age category, which was calculated from the result of the school health statistical survey, and the upper limit of the number of tubes that can be prescribed before the next prescribed visit was prescribed in view of the upper limit of the amount of daily application in accordance with the criteria and the allowable range. From the viewpoint of feasibility, the upper limit of the amount of application for each age category was defined so that the upper limit of the amount of daily application can be understood in terms of integers.
10 Concomitant Drugs/Concomitant Therapies

10.1 Prohibited Concomitant Drugs/Prohibited Concomitant Therapies

The concomitant use of the following drugs and therapies will be prohibited from 4 weeks before the date of definitive registration through completion of the follow-up period because such use is considered to affect the evaluation of efficacy or safety in this trial. However, the use of such drugs or therapies after withdrawal from this trial will be permitted if they are necessary for purposes such as treatment.

(1) All investigational products other than those used in this trial
(2) Drugs that inhibit mTOR (such as sirolimus, everolimus, and temsirolimus)
(3) Use of tacrolimus ointment, topical steroids, topical antibacterial agents, topical vitamin D3 preparations on the site of application of the investigational products
(4) Use of adapalene, benzoyl peroxide, ibuprofen piconol, resorcin, zinc oxide/salicylic acid ointment on the site of application of the investigational products
(5) Surgical treatment, laser treatment, phototherapy, and liquid nitrogen therapy on the site of application of the investigational products

10.2 Concomitant Drugs/Concomitant Therapies

The investigator will examine the drugs and therapies used during the period from the day of the first administration of the investigational product to the completion of the follow-up period or the follow up after withdrawal and, if the use of any drug or therapy is found, record the following information:

- Name of drug (priority is given to product name or trade name) or therapy
- Dose
- Route of administration
- Period of use (day of the first use, day of completion of use)
- Indication

11 Guidance of Subjects

The investigator will provide guidance to subjects and the subjects' legally acceptable representatives on the following matters before the start of application of the investigational product and, if necessary, continuously thereafter.

[Application of Investigational Products]

- The investigational product must be applied twice daily (in the morning and before sleeping) in compliance with the prescribed upper limit and the investigator's instructions.
- In the application of the investigational product, the highest priority must be given to the application on the angiofibroma lesion including the target tumor.
- If a subject forgot to perform the morning application, the subject must perform application immediately upon realization of the fact if the time of realization was before dinner on the same day and must perform only the application before sleeping if the time of realization was after dinner.
- Be thoroughly careful not to forget application, particularly in the week before the day of prescribed visit.
- The investigational product must not be applied to lesions from scratches or skin infection.
[Matters Requiring Attention during the Trial]

- Comply with the rules concerning the prohibited concomitant drugs and the prohibited concomitant therapies when visiting a hospital other than the study institution.
- From the start of application of the investigational products to the completion of the follow-up period or the follow up after withdrawal, the subjects will use a sunscreen and take such measures as prevention of direct sunlight.
- If possible, the method of skin care (such as application of a general humectant etc., makeup, and facial cleansing) should not be changed during participation in the trial.
- Take appropriate measures of contraception between the day of consent to participate in the trial and the completion of the follow-up period or the follow up after withdrawal.

[Descriptions in Patient Diary]

- In the patient diary, record everyday the status of application of the investigational product, the site of application, the reasons for missed application if any, and the number of tubes opened.
- The patient diary must be written by the subject or the subject's legally acceptable representative, and any correction of the description must be using double lines so that the original description is readable.
- Bring the patient diary for every prescribed visit, and submit it to the investigator or the study collaborator.
12 Schedule and Items of Tests and Observations

12.1 Schedule of Tests and Observations

<table>
<thead>
<tr>
<th>Timing of visit</th>
<th>Informed consent</th>
<th>Screening Period</th>
<th>Double-blind Period</th>
<th>Follow-up Period</th>
<th>Time of Withdrawal</th>
<th>Follow-up after withdrawalb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Visit 1 Screening</td>
<td>Baseline W4 Visit 3</td>
<td>Visit 4 W8 Visit 5</td>
<td>4 Weeks after Completion of Administration Date of Withdrawal</td>
<td>4 Weeks after Withdrawal</td>
</tr>
<tr>
<td>Acceptable window for tests and observations</td>
<td>-4W to 0a</td>
<td>-1W to 0b</td>
<td>±1W</td>
<td>±1W</td>
<td>±1W</td>
<td>+1W</td>
</tr>
<tr>
<td>Informed consent</td>
<td>•</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Initial registration</td>
<td>•</td>
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<td></td>
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<tr>
<td>Definitive registration/assignment</td>
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<tr>
<td>Application of the investigational product</td>
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<tr>
<td>TSC diagnosis</td>
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<tr>
<td>Verification of eligibility</td>
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<tr>
<td>Subject characteristics</td>
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<tr>
<td>Body height</td>
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<tr>
<td>Pregnancy test b</td>
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<tr>
<td>Body weight</td>
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<td></td>
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<tr>
<td>Inspection</td>
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<td>•••••</td>
<td>•</td>
<td></td>
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<tr>
<td>Vital sign</td>
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<td>•••••</td>
<td>•</td>
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<td>•</td>
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<tr>
<td>Laboratory Tests</td>
<td></td>
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<td></td>
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<tr>
<td>Urinalysis</td>
<td>•</td>
<td>•••</td>
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<td></td>
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<tr>
<td>Assessment of efficacye</td>
<td></td>
<td></td>
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<tr>
<td>Measurement of blood concentrationd</td>
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</tr>
<tr>
<td>Checking of the status of applicationf</td>
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</tr>
<tr>
<td>Checking of concomitant medication/therapy</td>
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<td></td>
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<tr>
<td>Checking of adverse events</td>
<td></td>
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</tr>
</tbody>
</table>

△: To be performed in possible when the subject was withdrawn at a prescribed visit during the double-blind period.

▲: Will be performed in possible when the subject was withdrawn during the double-blind period.
a: The day when the application of the investigational product is started is defined as day 0, and 1 W of the acceptable window is 7 days.
b: The pregnancy test will be performed on women of childbearing potential only.
c: If the screening test was performed within 1 week of the date of the initial application of the investigational product, the data of the screening test may be used.
d: If a follow-up visit after withdrawal is impossible, the subject will be followed up by telephone etc., and the measurement of vital signs will not be required.
e: Efficacy assessments on the basis of the photographs of each lesion, improvements in angiobroma and its size and color and improvements in hypomelanotic macule and plaque on the head, and DLQI/CDLQI
f: The time and date of the latest application will be checked in the measurement of sirolimus blood concentration. The status of application will be checked also by patient diary cards.
12.2 Tests and Observations

12.2.1 At the time of Obtainment of Consent

The investigator or the study collaborators will record the day when an explanation was given to the subject and the subject's legally acceptable representative and the day of obtainment of consent in the screening list and enter the information into the electronic CRF.

12.2.2 At the Time of the First Visit (Screening)

After obtaining consent to participate in the trial, the investigator will perform the following tests and observations as the screening tests within the 4 weeks before the day of the first application of the investigational product (before the start of application of the investigational product) and enter the result into the electronic CRF for initial registration. For any subject who was withdrawn after consent was obtained and before the initial registration, the investigator will record the fact of withdrawal, the date of withdrawal, and the reasons for withdrawal in the screening list.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Subject characteristics (sex, date of birth, current history, past history, complications)</td>
</tr>
<tr>
<td>2</td>
<td>Diagnosis of tuberous sclerosis complex (criteria of International TSC Consensus Conference 2012: Appendix 1)</td>
</tr>
<tr>
<td>3</td>
<td>Eligibility based on the inclusion and exclusion criteria</td>
</tr>
<tr>
<td>4</td>
<td>Body height, body weight</td>
</tr>
<tr>
<td>5</td>
<td>Inspection</td>
</tr>
<tr>
<td>6</td>
<td>Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate)</td>
</tr>
<tr>
<td>7</td>
<td>Laboratory tests (hematologic tests, biochemical tests)</td>
</tr>
<tr>
<td>8</td>
<td>Urinalysis</td>
</tr>
<tr>
<td>9</td>
<td>Pregnancy tests (for women of childbearing potential only)</td>
</tr>
<tr>
<td>10</td>
<td>Checking of concomitant medication/therapy and prior medications/pretreatments</td>
</tr>
<tr>
<td>11</td>
<td>Setting of the upper limit of the amount of application (to be set by the second visit and recorded in the source documents)</td>
</tr>
</tbody>
</table>

12.2.3 At the Second Visit (Baseline)

Within 1 week before the day of the first application of the investigational product (before the first application of the investigational product), the investigator will perform the following tests and observations, enter the obtained information into the electronic CRF for definitive registration, and check the allocation number.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eligibility based on the inclusion and exclusion criteria</td>
</tr>
<tr>
<td>2</td>
<td>Inspection</td>
</tr>
<tr>
<td>3</td>
<td>Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate)</td>
</tr>
<tr>
<td>4</td>
<td>Laboratory tests (hematologic tests, biochemical tests)</td>
</tr>
<tr>
<td>5</td>
<td>Urinalysis</td>
</tr>
<tr>
<td>6</td>
<td>Assessment of efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>1)</td>
<td>Angiofibroma, checking of hypomelanotic macule and plaque on the head, and setting of the site of application of the investigational product and the site of evaluation</td>
</tr>
<tr>
<td>2)</td>
<td>Taking photographs of lesions</td>
</tr>
</tbody>
</table>
3) DLQI/CDLQI
(7) Measurement of blood sirolimus concentration (before the first application)
(8) Checking of concomitant medication/therapy and prior medications/pretreatments
(9) Setting of the upper limit of the amount of application (the limit is to be set if it was not set at the first visit and is to be recorded in the source documents)
The data from the screening tests may be used for items (2) to (5) if the screening test was performed within 1 week of the date of the first application of the investigational product.

12.2.4 At the Time of the Third Visit (4 Weeks after the First Administration)
At 4 weeks (allowable range, 3 to 5 weeks) after the first application of the investigational product, the investigator will perform the following tests and observations and enter the result into the electronic CRF:

<table>
<thead>
<tr>
<th>Test/Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Inspection</td>
</tr>
<tr>
<td>(2) Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate)</td>
</tr>
<tr>
<td>(3) Laboratory tests (hematologic tests, biochemical tests)</td>
</tr>
<tr>
<td>(4) Urinalysis</td>
</tr>
<tr>
<td>(5) Assessment of efficacy</td>
</tr>
<tr>
<td>1) Taking photographs of lesions</td>
</tr>
<tr>
<td>2) Improvements in angiofibroma</td>
</tr>
<tr>
<td>3) Improvements in the size of angiofibroma</td>
</tr>
<tr>
<td>4) Improvements in the color of angiofibroma</td>
</tr>
<tr>
<td>5) Improvements in hypomelanotic macule and plaque on the head (if the subject has these diseases as complications)</td>
</tr>
<tr>
<td>6) DLQI/CDLQI</td>
</tr>
<tr>
<td>(6) Measurement of blood sirolimus concentration</td>
</tr>
<tr>
<td>(7) Checking of the date of the first application, the status of application of the investigational product, the date and time of the last application of the investigational product, and the descriptions in the patient diary</td>
</tr>
<tr>
<td>(8) Checking of concomitant medication/therapy</td>
</tr>
<tr>
<td>(9) Checking of the presence or absence of adverse events</td>
</tr>
</tbody>
</table>

12.2.5 At the Time of the Fourth Visit (8 Weeks after the First Administration)
At 8 weeks (allowable range, 7 to 9 weeks) after the first application of the investigational product, the investigator will perform the following tests and observations and enter the result into the electronic CRF:

<table>
<thead>
<tr>
<th>Test/Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Inspection</td>
</tr>
<tr>
<td>(2) Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate)</td>
</tr>
<tr>
<td>(3) Assessment of efficacy</td>
</tr>
<tr>
<td>1) Taking photographs of lesions</td>
</tr>
<tr>
<td>2) Improvements in angiofibroma</td>
</tr>
<tr>
<td>3) Improvements in the size of angiofibroma</td>
</tr>
<tr>
<td>4) Improvements in the color of angiofibroma</td>
</tr>
<tr>
<td>5) Improvements in hypomelanotic macule and plaque on the head (if the subject has these diseases as complications)</td>
</tr>
</tbody>
</table>
6) DLQI/CDLQI
(4) Checking of the status of application of the investigational product and the descriptions in the patient diary
(5) Checking of concomitant medication/therapy
(6) Checking of the presence or absence of adverse events

12.2.6 At the time of the Fifth visit (at 12 weeks after the start of administration: completion of administration)
At 12 weeks (allowable range, 11 to 13 weeks) after the first application of the investigational product, the investigator will perform the following tests and observations and enter the result into the electronic CRF:

(1) Inspection
(2) Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate)
(3) Body weight
(4) Laboratory tests (hematologic tests, biochemical tests)
(5) Urinalysis
(6) Pregnancy tests (for women of childbearing potential only)
(7) Assessment of efficacy
   1) Taking photographs of lesions
   2) Improvements in angiofibroma
   3) Improvements in the size of angiofibroma
   4) Improvements in the color of angiofibroma
   5) Improvements in hypomelanotic macule and plaque on the head (if the subject has these diseases as complications)
   6) DLQI/CDLQI
(8) Measurement of blood sirolimus concentration
(9) Checking of the date of completion of application, the status of application of the investigational product, the date and time of the last application of the investigational product, and the descriptions in the patient diary
(10) Checking of concomitant medication/therapy
(11) Checking of the presence or absence of adverse events

12.2.7 At the time of the Sixth Visit (4 weeks after the completion of administration: follow up)
At 4 weeks (allowable range: 3 to 5 weeks) after the date of completion of application of the investigational product, the investigator will perform the following tests and observations and enter the result into the electronic CRF:

(1) Inspection
(2) Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate)
(3) Assessment of efficacy
   1) Taking photographs of lesions
   2) Improvements in angiofibroma
3) Improvements in the size of angiofibroma
4) Improvements in the color of angiofibroma
5) Improvements in hypomelanotic macule and plaque on the head (if the subject has these
diseases as complications)
6) DLQI/CDLQI

(4) Checking of concomitant medication/therapy
(5) Checking of the presence or absence of adverse events

12.2.8 Time of Withdrawal

When the application of the investigational product to a subject was discontinued, the investigator will
perform the following tests and observations and enter the result into the electronic CRF within 1 week
after the date of discontinuation. If the investigator is informed by a subject or the subject's legally
acceptable representative of his or her willingness to discontinue the trial, the investigator will instruct the
subject or the representative to visit the study institution and perform likewise the following tests and
observations and enter the result into the electronic CRF within 1 week after the date of discontinuation.

For each subject who was withdrawn from the trial, the investigator will promptly enter the fact of
withdrawal, the date of withdrawal, and the reasons for withdrawal into the electronic CRF.

(1) Inspection
(2) Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate)
(3) Body weight
(4) Laboratory tests (hematologic tests, biochemical tests)
(5) Urinalysis
(6) Pregnancy tests (for women of childbearing potential only)
(7) Efficacy assessment (to be performed if possible when the subject was withdrawn at a prescribed
visit)
   1) Taking photographs of lesions
   2) Improvements in angiofibroma
   3) Improvements in the size of angiofibroma
   4) Improvements in the color of angiofibroma
   5) Improvements in hypomelanotic macule and plaque on the head (if the subject has these
diseases as complications)
   6) DLQI/CDLQI
(8) Measurement of blood sirolimus concentration (to be performed if possible)
(9) Checking of the status of application of the investigational product, the date and time of the last
application of the investigational product, and the descriptions in the patient diary
(10) Checking of concomitant medication/therapy
(11) Checking of the presence or absence of adverse events
(12) Date of withdrawal, reasons for withdrawal, comments

12.2.9 At 4 Weeks after Withdrawal (Follow Up after Withdrawal)

At 4 weeks (allowable range, 3 to 6 weeks) after the date of withdrawal from the trial, the investigator
will perform the following tests and observations and enter the result into the electronic CRF. If a visit to
the study institution is impossible, the subject will be followed up by telephone etc., and the measurement of vital signs will not be required.

| (1) Inspection |
| (2) Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate): Only at the times of visits |
| (3) Checking of concomitant medication/therapy |
| (4) Checking of the presence or absence of adverse events |

12.3 Methods of Tests and Observations

12.3.1 Inspection
At each prescribed visit, the presence or absence of abnormal findings was ascertained by physical findings, history taking, inspection, palpation, and auscultation/percussion. Abnormal findings will be entered into the electronic CRF as adverse events.

12.3.2 Vital signs
At each prescribed visit, blood pressure (systolic, diastolic) and pulse rate will be measured. Abnormal findings will be entered into the electronic CRF as adverse events. If no measurement was taken for unavoidable reasons such as noncompliance with an instruction to remain still, the reasons will be recorded. (The absence of measurement will not be regarded as a deviation)

12.3.3 Laboratory Tests, Urinalysis, Pregnancy Test
The following tests will be performed at the first, second, third, and 5th visit and at withdrawal.
A pregnancy test will be performed only for female patients of childbearing potential and will not be required to be performed for female patients considered incapable of childbearing for such reasons as menopause (the absence of menstruation for 12 months or more without any medical reason), total hysterectomy, and the absence of menarche.

| Hematologic tests | Red blood cell count, white blood cell count, differential white blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count, hemoglobin content, hematocrit |
| Biochemical tests | Total protein, albumin, AST (GOT), ALT (GPT), γ-GTP, Al-P, LDH, CK (CPK), total bilirubin, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride (TG), BUN, creatinine, blood glucose, Ca, Na, K, P, Cl |
| Urinalysis | Occult blood in urine, protein, glucose, urobilinogen |
| Pregnancy test | Urinary hCG or serum hCG |

13 Assessment of Efficacy
In order to ensure the reliability of the efficacy assessment, the assessment will be performed by an investigator with adequate education in assessment methods. The assessment of one subject will be performed by one evaluator throughout the period from baseline to the follow-up period (or to the time of...
withdrawal if the subject was withdrawn). In addition, the photographs of each lesion, together with a color sample (Casmatch®) with a scale bar, will be taken at each assessment time point and retained in accordance with a separately specified procedure. These photographs will be taken by a photographer (one photographer at each study institution if possible) with adequate education in how to take these photographs.

13.1 Primary Outcome Measures

The primary efficacy outcome measure will be improvements in angiofibroma assessed using photographs by the IRC at 12 weeks after the start of administration. In addition, improvements in angiofibroma assessed using photographs by the IRC at 4 and 8 weeks after the start of administration and 4 weeks after the completion of administration will be used as the secondary outcome measure.

13.1.1 Improvements in Angiofibroma

Improvements in angiofibroma will be assessed in terms of the size and color (reddishness) of tumors in accordance with the following criteria, regardless of whether the assessment is performed by the IRC or the investigator. In the assessment, see the Instructions on Complying with a Uniform Set of Standards for Assessments, which is separately defined.

<table>
<thead>
<tr>
<th>Score</th>
<th>Improvements</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Markedly Improved</td>
<td>Overall shrinkage, flattening, or disappearance of tumors is observed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A nearly overall large decrease in the intensity of reddishness or a nearly overall change in reddishness to the level equal to that of the normal region.</td>
</tr>
<tr>
<td>2</td>
<td>Improved</td>
<td>Nearly overall shrinkage or flattening of tumors and a nearly overall decrease in the intensity of reddishness are observed. Or, partial disappearance of tumors and a partial large decrease in the intensity of reddishness are observed.</td>
</tr>
<tr>
<td>1</td>
<td>Slightly improved</td>
<td>Partial shrinkage or flattening of tumors and a partial decrease in the intensity of reddishness are observed. Or, a nearly overall slight decrease in the intensity of reddishness is observed.</td>
</tr>
<tr>
<td>0</td>
<td>Unchanged</td>
<td>There is no definite change in the size or the reddishness of tumors.</td>
</tr>
<tr>
<td>-1</td>
<td>Slightly exacerbated</td>
<td>Partial enlargement or new formation of tumors and a partial increase in the intensity of reddishness are observed. Or, a nearly overall slight increase in the intensity of reddishness is observed.</td>
</tr>
<tr>
<td>-2</td>
<td>Exacerbated</td>
<td>A nearly overall enlargement or new formation of tumors or a partial huge enlargement of tumors and a partial increase in the intensity of reddishness are observed. Or, more severe exacerbation is observed.</td>
</tr>
</tbody>
</table>

[Glossary]

Overall : Not less than about 75% of the extent of the lesion at baseline
Nearly overall : About 50% to 75% of the extent of the lesion at baseline
Partial : About 25% to 50% of the extent of the lesion at baseline
(The intensity of the color is) greatly decreased : Changes of 3 levels or more in reddishness in terms of the Pantone® color sample
(The intensity of the color is) greatly decreased : Changes of 2 levels or more in reddishness in terms of the Pantone®
decreased/increased. color sample
(The intensity of the color is) Changes of 1 level in reddishness in terms of the Pantone® color
slightly decreased/increased. sample

### Status of reddishness in terms of the Pantone® color sample

<table>
<thead>
<tr>
<th>Level</th>
<th>Status of Reddishness</th>
<th>Pantone® Color Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>As dark as or paler than Pantone® 489C</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>As dark as or paler than Pantone® 486C</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>As dark as or paler than Pantone® 7416C</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>As dark as or paler than Pantone® 485C</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>As dark as or paler than Pantone® 704C</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Darker than Pantone® 704C</td>
<td></td>
</tr>
</tbody>
</table>

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

#### 13.1.2 Taking Photographs of Lesions

The photographs of each lesion, i.e., angiofibroma and hypomelanotic macule and plaque on the head, together with a color sample (Casmatch®) with a scale bar, will be taken at each efficacy assessment time point and retained in accordance with a separately specified procedure. As the photographic equipment (camera), the equipment specified by the sponsor will be used. These photographs will be taken by a photographer (one photographer at each study institution if possible) with adequate education in how to take these photographs.

#### 13.2 Secondary Outcome Measures

The following 7 items are the secondary efficacy outcome measures. The timing of the assessment is at baseline plus the following: 4 and 8 weeks after the start of administration and 4 weeks after the completion of administration for item 1; and 4, 8, and 12 weeks after the start of administration and 4 weeks after the completion of administration for items 2 to 7.

1. Improvements in angiofibroma assessed using photographs by the IRC
2. Improvements in angiofibroma assessed by the investigator
3. Improvements in the size of angiofibroma assessed by the IRC and the investigator
4. Improvements in the color of angiofibroma assessed by the IRC and the investigator
5. Improvements in hypomelanotic macule and plaque of upper neck assessed by the IRC and the investigator
6. Proportion of subjects assessed as "improved" or a better category in the primary outcome measure and in secondary outcome measures 1 to 5 (improvement rate)
7. Change in total score from baseline for DLQI and CDLQI
13.2.1 Improvements in Angiofibroma Assessed by the Investigator

Improvements in angiofibroma will be assessed by the investigator in accordance with the procedure defined in Section 13.1.1 "Improvements in Angiofibroma." The assessment should be performed with reference to the photographs of the lesions taken before the prescribed visit and the Instructions on Complying with a Uniform Set of Standards for Assessments, which will be separately defined. The sites to which the investigational product has not been applied will not be included in the assessment.

13.2.2 Improvements in the Size of Angiofibroma

Improvements in the size of angiofibroma will be assessed in accordance with the following criteria, regardless of whether the assessment is performed by the IRC or the investigator. The assessment should be performed with reference to the photographs of the lesions taken before the prescribed visit and the Instructions on Complying with a Uniform Set of Standards for Assessments, which will be separately defined. The sites to which the investigational product has not been applied will not be included in the assessment.

<table>
<thead>
<tr>
<th>Score</th>
<th>Improvements</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Markedly Improved</td>
<td>Overall shrinkage, flattening, or disappearance of tumors is observed.</td>
</tr>
<tr>
<td>2</td>
<td>Improved</td>
<td>Nearly overall shrinkage or flattening of tumors is observed. Or, partial disappearance of tumors is observed.</td>
</tr>
<tr>
<td>1</td>
<td>Slightly improved</td>
<td>Partial shrinkage or flattening of tumors is observed.</td>
</tr>
<tr>
<td>0</td>
<td>Unchanged</td>
<td>There is no definite change in the size of tumors.</td>
</tr>
<tr>
<td>-1</td>
<td>Slightly exacerbated</td>
<td>Partial enlargement or new formation of tumors is observed.</td>
</tr>
<tr>
<td>-2</td>
<td>Exacerbated</td>
<td>A nearly overall enlargement or new formation of tumors or a partial huge enlargement of tumors is observed. Or, more severe exacerbation is observed.</td>
</tr>
</tbody>
</table>

[Glossary]

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

13.2.3 Improvements in the Color of Angiofibroma

Improvements in the color of angiofibroma will be assessed in accordance with the following criteria in terms of the tones of the Pantone® color sample, regardless of whether the assessment is performed by the IRC or the investigator. In the assessment of reddishness, the reddishness should be judged by applying the sponsor-specified sample for assessing reddishness to the lesions of angiofibroma to compare the sample with the tumors, and the photographs of the lesions taken before the prescribed visit and the Instructions on Complying with a Uniform Set of Standards for Assessments, which will be separately defined, should be used as a reference.
<table>
<thead>
<tr>
<th>Score</th>
<th>Improvements</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Markedly Improved</td>
<td>A nearly overall large decrease in the intensity of reddishness is observed. Or, a nearly overall change in reddishness to the level equal to that of the normal region.</td>
</tr>
<tr>
<td>2</td>
<td>Improved</td>
<td>A nearly overall decrease in the intensity of reddishness is observed. Or, a partial large decrease in the intensity of reddishness is observed.</td>
</tr>
<tr>
<td>1</td>
<td>Slightly improved</td>
<td>A nearly overall slight decrease in the intensity of reddishness is observed. Or, a partial decrease in the intensity of reddishness is observed.</td>
</tr>
<tr>
<td>0</td>
<td>Unchanged</td>
<td>There is no definite change in the reddishness of tumors.</td>
</tr>
<tr>
<td>-1</td>
<td>Slightly exacerbated</td>
<td>A nearly overall slight increase in the intensity of reddishness is observed. Or, a partial increase in the intensity of reddishness is observed.</td>
</tr>
<tr>
<td>-2</td>
<td>Exacerbated</td>
<td>A nearly overall decrease in the intensity of reddishness is observed. A partial large increase in the intensity of reddishness is observed. Or, more severe exacerbation is observed.</td>
</tr>
</tbody>
</table>

**[Glossary]**

- **Nearly overall**: Not less than about 50% of the extent of the lesion at baseline
- **Partial**: About 25% to 50% of the extent of the lesion at baseline
- **(The intensity of the color is) greatly decreased**: Changes of 3 levels or more in reddishness in terms of the Pantone® color sample
- **(The intensity of the color is) decreased/increased**: Changes of 2 levels in reddishness in terms of the Pantone® color sample
- **(The intensity of the color is) slightly decreased/increased**: Changes of 1 level in reddishness in terms of the Pantone® color sample

<table>
<thead>
<tr>
<th>Level</th>
<th>Status of Reddishness</th>
<th>Pantone® Color Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>As dark as or paler than Pantone® 489C</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>As dark as or paler than Pantone® 486C</td>
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<tr>
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<td>4</td>
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<td>-</td>
</tr>
<tr>
<td>5</td>
<td>As dark as or paler than Pantone® 704C</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Darker than Pantone® 704C</td>
<td>-</td>
</tr>
</tbody>
</table>

**Remark**  The colors shown in the Pantone® color sample column in the above table are not accurate reproduction of the color tones indicated by the numbers.

  In the assessment of reddishness, always use a sample for assessing reddishness.

13.2.4 Improvements in Hypomelanotic Macule on the Head

In subjects with hypomelanotic macules on the head (above the neck), improvements will be assessed by a comprehensive review of changes from baseline in color tone and the area of the lesion based on comparison in color tone between the lesion and a normal region near the lesion in accordance with the following criteria, regardless of whether the assessment is performed by the IRC or the investigator. The
assessment should be performed with reference to the photographs of the lesions (only the sites to which the investigational product was applied and which are included in the assessment) taken before the prescribed visit and the Instructions on Complying with a Uniform Set of Standards for Assessments, which will be separately defined. The sites to which the investigational product has not been applied will not be included in the assessment or photographed.

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

13.2.5 Improvements in Plaque on the Head

In subjects with plaque on the head (above the neck), improvements will be assessed in accordance with the following criteria, regardless of whether the assessment is performed by the IRC or the investigator. The assessment should be performed with reference to the photographs of the lesions (only the sites to which the investigational product was applied and which are included in the assessment) taken before the prescribed visit and the Instructions on Complying with a Uniform Set of Standards for Assessments, which will be separately defined. The sites to which the investigational product has not been applied will not be included in the assessment or photographed.

<table>
<thead>
<tr>
<th>Score</th>
<th>Improvements</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Markedly Improved</td>
<td>A shrinkage of eminence by about 75% or more.</td>
</tr>
<tr>
<td>2</td>
<td>Improved</td>
<td>A shrinkage of eminence by about 50% to 75%.</td>
</tr>
<tr>
<td>1</td>
<td>Slightly improved</td>
<td>A shrinkage of eminence by about 25% to 50%.</td>
</tr>
<tr>
<td>0</td>
<td>Unchanged</td>
<td>There is no definite change in the degree of eminence.</td>
</tr>
<tr>
<td>-1</td>
<td>Slightly exacerbated</td>
<td>An enlargement of eminence by about 25% to 50%.</td>
</tr>
<tr>
<td>-2</td>
<td>Exacerbated</td>
<td>An enlargement of eminence by about 50% or more.</td>
</tr>
</tbody>
</table>
13.2.6 Proportion of Subjects Assessed as "Improved" or a Better Category in Each Improvement Parameter (Improvement Rate)

In the assessment of improvements in angiofibroma and its size and color (reddishness) and improvements in hypomelanotic macule and plaque on the head by the IRC or the investigator, the proportion of subjects (improvement rate) who were assessed as "improved" or "markedly improved" will be calculated.

13.2.7 Change from Baseline in Total Score of DLQI and CDLQI

The QOL of patients in the past week will be assessed by the Japanese version of DLQI and CDLQI. DLQI should be used for patients aged 16 years or more, and CDLQI should be used for patients aged less than 16 years at the time of the first visit (screening). The answers will be rated in 4 grades for each item, and the total score of all 10 items will be calculated. Changes from baseline will be calculated for the total score of DLQI and CDLQI and the score of each subscale of DLQI at 4, 8, and 12 weeks after the start of administration (or at the time of withdrawal) and 4 weeks after the completion of administration. All answer sheets for DLQI and CDLQI will be collected and retained by the study institution and will not be collected by the sponsor.

### [DLQI]

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Score</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms/feelings</td>
<td>0-6</td>
<td>1 Have you felt itching or pain (sore, tingling, or throbbing) in the skin for the past week?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Have you felt embarrassed or self-conscious because of the skin condition for the past week?</td>
</tr>
<tr>
<td>Daily activities</td>
<td>0-6</td>
<td>3 Has the skin condition interfered with shopping, household chores, or house work for the past week?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 Has the skin condition affected what you chose to wear for the past week?</td>
</tr>
<tr>
<td>Leisure</td>
<td>0-6</td>
<td>5 Has the skin condition affected your social activities or the way you pass your free time for the past week?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 Has the skin condition interfered with doing spots for the past week?</td>
</tr>
<tr>
<td>Work/school</td>
<td>0-3</td>
<td>7 Was there any occasion where you were completely unable to work or study because of the skin condition for the past week?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ Question to those who answered &quot;no.&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Was there any occasion where you were less efficient in work or study because of the skin condition for the past week?</td>
</tr>
<tr>
<td>Personal relationships</td>
<td>0-6</td>
<td>8 Was there any occasion where you had difficult relationship with your husband (or wife), lover, close friends, family, or relatives because of the skin condition for the past week?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 Has the skin condition interfere with your sexual life for the past week?</td>
</tr>
<tr>
<td>Treatment</td>
<td>0-3</td>
<td>10 Have you had any problem such as cluttered house caused by treatment or care of the skin and too much required for treatment or care for the past week?</td>
</tr>
</tbody>
</table>
The answers will be scored in accordance with the following criteria, and the total and each subscale score will be calculated:

<table>
<thead>
<tr>
<th>Score</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 points</td>
<td>Very (&quot;yes&quot; in the case of Question 7 only)</td>
</tr>
<tr>
<td>2 points</td>
<td>Substantially</td>
</tr>
<tr>
<td>1 point</td>
<td>A little</td>
</tr>
<tr>
<td>0 point</td>
<td>Never. The question does not apply to me.</td>
</tr>
</tbody>
</table>

### [CDLQI]

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 How itchy, scratchy, sore, or painful was your skin for the past week?</td>
</tr>
<tr>
<td>2 How embarrassed, self-conscious, disturbed, or sad were you because of the skin for the past week?</td>
</tr>
<tr>
<td>3 How did the skin condition affect your relationship with your friends for the past week?</td>
</tr>
<tr>
<td>4 How often did you use or change to unordinary, special clothes or shoes because of the skin for the past week?</td>
</tr>
<tr>
<td>5 How often did the skin problem affect your going out, playing, or hobbies for the past week?</td>
</tr>
<tr>
<td>6 How often did you cancel swimming or exercise because of the skin problem for the past week?</td>
</tr>
<tr>
<td>7 Did you have school last week? Or did you have a break from school?</td>
</tr>
<tr>
<td>→ How did the skin problem affect your school work for the past week?</td>
</tr>
<tr>
<td>If you had a break from school</td>
</tr>
<tr>
<td>→ How did the skin problem ruin your holiday pleasure for the past week?</td>
</tr>
<tr>
<td>8 How often did you experience unpleasant events, such as being called by weird names, made fun of, teased, questioned, or avoided, because of the skin problem for the past week?</td>
</tr>
<tr>
<td>9 How often were you unable to sleep because of the skin problem for the past week?</td>
</tr>
<tr>
<td>10 How hard was the skin treatment for the past week?</td>
</tr>
</tbody>
</table>

### [Relationship between the questions in CDLQI and those in the subscales]

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Question Number</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms/feelings</td>
<td>1, 2</td>
<td>0-6</td>
</tr>
<tr>
<td>Leisure</td>
<td>4, 5, 6</td>
<td>0-9</td>
</tr>
<tr>
<td>School/break</td>
<td>7</td>
<td>0-3</td>
</tr>
<tr>
<td>Personal relationships</td>
<td>3, 8</td>
<td>0-6</td>
</tr>
<tr>
<td>Sleep</td>
<td>9</td>
<td>0-3</td>
</tr>
<tr>
<td>Treatment</td>
<td>10</td>
<td>0-3</td>
</tr>
</tbody>
</table>

The answers will be scored in accordance with the following criteria, and the total and each subscale score will be calculated:

<table>
<thead>
<tr>
<th>Score</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 points</td>
<td>Very (including Question 7 &quot;Unable to go to school&quot;)</td>
</tr>
<tr>
<td>2 points</td>
<td>Substantially</td>
</tr>
<tr>
<td>----------</td>
<td>---------------</td>
</tr>
<tr>
<td>1 point</td>
<td>A little</td>
</tr>
<tr>
<td>0 point</td>
<td>Never</td>
</tr>
</tbody>
</table>

13.3 Assessment by the IRC

13.3.1 Members of the IRC

Separately from the assessment of improvements by the investigator, the members of the IRC assess and judge improvements in angiofibroma and the size and color (reddishness) and in hypomelanotic macule and plaque on the head on the basis of the photographs of the skin lesions of individual subjects collected from the study institutions while the members were blinded to the assignment information. The members of the IRC will consist of dermatologists who are independent from persons involved in the sponsorship or the conduct of the study, such as the investigator, subinvestigators, 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. Selection of the members of the IRC and the details of their duties will be separately specified in the written procedure for the IRC.

13.3.2 Transmission, Control, Compensation, and Checking of Image Files

In accordance with separately prepared written procedures, the investigator or study collaborators will take the photographs of each lesion, 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.

13.3.3 IRC

The sponsor, the CRO in charge of the control and compensation 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.

13.4 Rationale for Setting Efficacy Outcome Measures

13.4.1 Rationale for Setting Primary Outcome Measures

The size of a tumor is considered a direct indicator of the severity of angiofibroma in the clinical evaluation of angiofibroma, and shrinkage of the size is an important therapeutic goal. The reddishness of a tumor is an indicator of the degree of vasodilation or vascularity, and both the size of reddishness of a tumor are considered clinically important therapeutic indicators for angiofibroma.

On the other hand, angiofibroma can present with various symptoms, and there is currently no standard for its severity or clinical evaluation for which any sort of consensus has been achieved. For these reasons,
in order to prevent inter-rater variation in a multicenter study and to assess the various symptoms of the disease as objectively as possible, it was considered appropriate at the present stage to define criteria based on the size and color of tumor and perform assessment using images (photographs) at the IRC.

13.4.2 Rationale for Setting Secondary Outcome Measures

Of the 7 outcome measures described in Section 13.2 "Secondary Outcome Measures," outcome 1 was included because the improvements in angiofibroma at time points other than 12 weeks after the start of administration, which is the time point of the primary outcome measure, are also considered clinically significant information.

Outcome measure 2 was included in order to enable comparison of the judgment by the investigator and the result of assessment by the IRC and to collect as much information as possible about the efficacy of the present drug, because the judgment by the investigator, who directly observe subjects in practice, is clinically significant.

Outcome measures 3 and 4 were included because the size of tumor and the reddishness of tumor are each an important therapeutic indicator for angiofibroma, and improvements from each viewpoint are also considered clinically significant information.

Outcome measure 5 was included because we thought that for the present drug to be used in clinical settings, the efficacy and safety of the present drug should be investigated in patients with skin lesions on the head other than angiofibroma in a precontrolled trial setting. Furthermore, we thought that assessment should be limited to lesions of the head in this trial for the following reasons: Lesions of the head cannot readily be concealed by clothes etc. and are considered to cause the most severe psychologic distress in patients from the cosmetic viewpoint; and lesions other than those in the head, such as shagreen patch, may have some effects on the result of assessment as a verification study because the area of such lesions varies greatly from patient to patient and, thus, in some patients, the upper limit of the amount of application cannot be defined appropriately, or the adequate amount of the drug cannot be applied even if the upper limit can be defined. As the lesions to be assessed, 2 symptoms, hypomelanotic macule and plaque, were selected from skin lesions that are listed as a major manifestation or a minor manifestation in the diagnostic criteria for tuberous sclerosis complex and are likely to be treatable with the present drug and that occur on the head.

Outcome measure 6 was included because we thought it is clinically important to define the rate of improvement by the treatment with the present drug for angiofibroma, the size and color thereof, and hypomelanotic macule and plaque on the head and to assess the rate.

Outcome measure 7 was included because we thought that it is important to assess how the present drug changes the effects of skin lesions associated with tuberous sclerosis complex on the QOL (quality of life) of patients on the basis of subjective evaluation by patients. While many papers point out that angiofibroma has great effects on the QOL of patients with tuberous sclerosis complex from the cosmetic viewpoint, no rating scale has been developed that assesses its severity in a disease-specific manner, or there is no report of assessments performed by a scale that would enable comparison with other skin lesions. DLQI and CDLQI are scales of QOL that are specific to skin diseases and are simple patient questionnaires consisting of a total of 10 questions. A Japanese version is available for each questionnaire, and both scales have been shown to be reliable and valid and have actually been used in Japanese trials in patients with skin diseases. By using these scales, measurement and comparison of the QOL of patients with various skin diseases are considered possible, and we judged that these scales can be satisfactorily applied to angiofibroma and can
be used as the QOL scales in this trial, after discussion with Dr. Andrew Finlay, who developed these scales.

For each secondary outcome measure, we decided to add assessment at 4 weeks after the completion of administration because we thought that assessment after completion of administration enables evaluation and discussion of the presence or absence of rebound, recurrence, etc. after the completion of administration of the present drug.

14 Assessment of Safety

14.1 Safety Outcome Measures

(1) Incidence of adverse events and adverse drug reactions
(2) Serious adverse events and adverse drug reactions
(3) Significant adverse events and adverse drug reactions
(4) Laboratory findings and vital signs
(5) Sirolimus blood concentration

14.2 Adverse Events and Adverse Drug Reactions

14.2.1 Definition of an Adverse Event

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal change in laboratory finding), symptom, or disease in subjects who received an investigational product, whether or not causally related to the investigational product.

14.2.2 Definition of an Adverse Drug Reaction

The phrase "adverse drug reaction" means that a causal relationship between an investigational product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

14.2.3 Severity of Adverse Events

The severity of an adverse event will be determined in accordance with a classification in 3 levels in reference with the following criteria and "Standards for Classification of Seriousness of Adverse Drug Reactions by Drugs etc." (Appendix 2). Among grades defined in the Standards for Classification of Seriousness, grade 1 will be used as a criterion for "mild," grade 2 for "moderate," and grade 3 for "severe."

1) Mild: The symptoms are mild can be easily tolerable.
2) Moderate: The symptoms cause discomfort that hinders the activities of daily living and require a treatment.
3) Severe: The symptoms cause a severe hindrance in the activities of daily living.

14.2.4 Serious Adverse Events

The adverse events corresponding to the following criteria will be treated as serious adverse events. With respect to hospitalization and prolongation of hospitalization, the following are not treated as serious adverse events: hospitalization for the purpose of predetermined surgeries or examinations, educational
hospitalization, hospitalization or prolongation of hospitalization for reasons on the part of home caregivers, hospitalization for the purpose of disease control, and hospitalization for health care (medical checkup).

1) Deaths
2) Events that may lead to death*1
3) Events that require hospitalization or prolongation of hospitalization in a hospital or a clinic
4) Hindrances
5) Events that may lead to a hindrance
6) Events that are serious in accordance with 1) to 5)*2
7) Congenital diseases or abnormalities in later generations

*1: "An event that may lead to death" is an adverse event for which a patient may die immediately at the onset of the event, and no inference can be made that a more severe event leads to death.

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

14.2.5 Significant Adverse Events

Adverse events that are not serious adverse events and that are judged to be of special interest because of clinical importance. Adverse events that meet any of the following criteria will be treated as significant adverse events:

1) Adverse events leading to discontinuation of the investigational product
2) Skin irritation symptoms (such as erythema, papules, blisters, erosion, and edema)

14.2.6 Causal Relationship with the Investigational Products

The causal relationship of an adverse event and the investigational product will be determined in accordance with the following 2 levels, and an event corresponding to level 2) will be treated as an adverse drug reaction:

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

14.2.7 Observation of Adverse Events

During the period from the first administration of the investigational product through the 6th visit (through the follow up after withdrawal in the case of withdrawal), the investigator will carefully observe the subject for the occurrence of adverse events by means of interview, inspection, etc. If an adverse event
occurs, the investigator will take appropriate measures if necessary and perform follow-up observation as long as possible until the adverse event disappears or resolves. If the investigator discontinued follow-up observation on the basis of judgment that further follow-up observation is unnecessary or if the subject rejected follow-up observation, the investigator will enter the reasons therefor into the electronic CRF.

For each adverse event that occurred, the investigator will enter in detail such information as the name of the event, the date of onset (or the date and time when the event was found), severity, seriousness category (serious/nonserious), the presence or absence of intervention (if any intervention was present, the detail thereof), outcome, the date of outcome (if the event disappeared, the date of disappearance), and the causal relationship with the investigational product into the electronic CRF. For adverse events in the skin, the investigator will also record whether or not the lesion is in the area where the investigational product has been applied and thoroughly examine any adverse event suggesting skin photosensitization.

14.2.8 Pregnancy

If a subject was found to be pregnant, or pregnancy is suspected, the investigator will immediately discontinue administration of the investigational product and report prescribed information (at least subject identification code, the date of onset, the date of the first administration of the investigational product, and the date of discontinuation of administration) to the sponsor. The investigator may also request the sponsor to open the emergency key, if necessary. Pregnancy will not be treated as an adverse event but will be followed up until the outcome (delivery) is ascertained.

14.3 Reporting Serious Adverse Events

14.3.1 Investigators

If a serious adverse event occurred during the period from the first administration of the investigational product through the 6th visit (through the follow up after withdrawal in the case of withdrawal), the investigator will give the highest priority to the safety of the subject and take necessary measures regardless of the presence or absence of a causal relationship with the investigational product, and report the event to the sponsor. The following is an outline of the procedure:

1. Within 24 hours of learning of the onset, the investigator will inform the sponsor with which the investigator is affiliated of the occurrence of the serious adverse event ("Report of Serious Adverse Events [First Report]" is to be used if possible). The investigator will also inform the head of the study institution of the occurrence of the SAE as soon as possible.
2. As early as possible within 7 days of informing the sponsor, the investigator will prepare a "Report of Serious Adverse Events" submit it to the sponsor and the head of the study institution with which the investigator is affiliated, and store a copy of the report.
3. The investigator will further try to collect detailed data and report any new information to the sponsor and the head of the study institution.
14.3.2 Sponsor

If the sponsor was informed by the investigator of the onset of a serious adverse event, the sponsor will follow the following procedure:

1. As early as possible within 7 days of being informed by the investigator, the sponsor, will obtain the "Report of Serious Adverse Events."
2. The sponsor will inspect the "Report of Serious Adverse Events" and make appropriate inquiries to the investigator about any information lacking.
3. If the report is considered to fall under the provisions of Article 273 of the Enforcement Regulations of the Pharmaceutical and Medical Device Act, the sponsor will report the event to appropriate regulatory agencies within the specified period. The sponsor will also immediately report the adverse event to each investigator and each head of the study institution in written form.

14.4 Procedure for Opening Emergency Keys

If the investigator judges that an emergency key needs to be opened because of occurrence of an adverse event, the investigator will promptly report the details of the patient using the "Report of Serious Adverse Events" to the sponsor and may request the sponsor to open the emergency key. If a subject was found to be pregnant, the investigator will also promptly report the details of the patient to the sponsor and may request the sponsor to open the emergency key. If the sponsor judges that the emergency key needs to be opened on the basis of the obtained information and after consultation with a medical expert if necessary, the allocation manager will open the top copy of the emergency key, or the Clinical Development Manager will open the duplicate copy of the emergency key.

After the emergency key is opened, data of the patient will be promptly finalized and handled in the same manner as that of patients for whom the emergency key is not opened.

15 Procedure for Discontinuing the Trial and Withdrawing Individual Subjects

15.1 Procedure for Discontinuing the Entire Trial and a Part of the Trial

1. If the sponsor obtained any information suggesting that the investigational products may be disadvantageous to subjects, the sponsor will discuss the matter with a medical expert and consider discontinuing a part or the whole of the trial.
2. If the sponsor decided to discontinue a part of the whole of the trial, the sponsor will promptly report the fact of discontinuation and the reasons therefor to all investigators, heads of the study institutions, and regulatory agencies in written form.
3. If the head of the study institution was informed by the sponsor of discontinuation of a part or the whole of the trial, the head of the study institution will promptly inform the investigator and the IRB in written form and explain the matter in detail.
4. If the trial is discontinued, the investigator will promptly inform subjects, provide appropriate medical care, and take other necessary measures.
15.2 Procedure for Withdrawing Individual Subjects from the Trial

If an event meeting the criteria described in Section 15.3 "Withdrawal Criteria" occurs, the investigator will follow the following procedure and promptly enter necessary information into the electronic CRF.

(1) The investigator will immediately discontinue administration of the investigational product to the subject and perform the tests and observations for the time of withdrawal within 1 week from the date of withdrawal (the date when withdrawal was decided).
(2) The investigator will enter the date of withdrawal and the reasons for withdrawal and, if necessary, comments into the electronic CRF.
(3) The investigator will perform the tests and observations for follow up at 4 weeks after withdrawal.
(4) If a subject discontinued the trial without visiting the study institution, the investigator will ascertain that the subject is alive and investigate the reasons for not visiting the study institution by telephone etc. as far as possible and record the result together with the date of withdrawal (the date when withdrawal was decided; the date of the final administration is also to be recorded if possible).
(5) If a subject did not visit the study institution for follow up after withdrawal, the investigator will ascertain that the subject is alive and investigate the reasons for not visiting the study institution by telephone etc. as far as possible and record the result.
(6) If the investigator judges that it is preferable not to perform the observations and tests for the time of withdrawal for safety reasons, the investigator will record the reasons.

15.3 Withdrawal Criteria

If a subject meets any of the following criteria during the period from the initial registration to before the definitive registration or the period after the definitive registration (see Section 9.3 "Subject Registration"), administration of the investigational product and the trial for the subject will be discontinued, followed by prompt explanation of the fact of discontinuation to the subject and the subject's legally acceptable representative and prompt entry of the fact of discontinuation, the date of discontinuation, and the reasons for discontinuation into the electronic CRF. For subjects who has received the investigational product, the safety of the subjects will be secured by performing the tests and observations for the time of withdrawal and performing the follow-up tests and observations at 4 weeks after withdrawal.

15.3.1 Withdrawal Criteria for the Period from the Initial Registration to before the Definitive Registration

(1) A subject or the subject's legally acceptable representative requested withdrawal (revocation of consent).
(2) It was found that a subject does no meet the inclusion criteria or fall under the exclusion criteria.
(3) A subject needs a treatment that would have a great effects on the result of this trial, such as surgical treatment for skin lesions associated with tuberous sclerosis complex.
(4) The investigator judges that it is not appropriate to continue the trial for other reasons.
15.3.2 Withdrawal Criteria for the Period after the Definitive Registration

(1) A subject or the subject's legally acceptable representative requested withdrawal (revocation of consent).

(2) The investigator judges that it is difficult to continue the trial because of occurrence of adverse events.

(3) It was found after the definitive registration that a subject at the time of the definitive registration did not meet the inclusion criteria or fell under the exclusion criteria.

(4) A subject needs a treatment that would have a great effects on the result of this trial, such as surgical treatment for skin lesions associated with tuberous sclerosis complex.

(5) A subject failed to apply the investigational product for 8 days or more consecutively.

(6) A subject is or may be pregnant.

(7) The investigator judges that it is not appropriate to continue the trial for other reasons.

16 Compliance with the Protocol and Revision Thereof

16.1 Compliance with the Protocol and Deviations Therefrom

(1) This trial will be conducted in compliance with the protocol on the basis of an agreement between the investigators and the sponsor.

(2) The investigator must not deviate from or change the protocol without a prior written agreement with the sponsor and a prior approval by the IRB, except for medically unavoidable reasons (emergency deviation), such as to avoid emergent risks.

(3) In the case of emergency deviation, the investigator will submit an emergency deviation report to the sponsor and the head of the study institution and obtain an approval by IRB, an acknowledgment by the head of the study institution, and an agreement with the sponsor.

(4) The investigator will record all protocol deviations, if any.

16.2 Protocol Amendment

(1) In the following cases, the sponsor must revise the protocol after discussion with a medical expert if necessary:
   • The sponsor learned information about the quality, efficacy, and safety of the test drug and other information that is important for appropriate conduct of the trial.
   • The sponsor makes changes to the protocol for medically unavoidable reasons.

(2) The sponsor will promptly inform each investigator of the definite changes in written form.

(3) The investigator will give full consideration to the ethical and scientific appropriateness of conducting the trial in accordance with the revised protocol.

(4) The sponsor and the investigator will discuss the revised protocol and affix the names and seals or signatures on 2 copies of the protocol or an alternative document as a proof of agreement. The investigator will also obtain approval by the IRB.

(5) If the sponsor is instructed by the IRB, the the trial office, etc. to make changes in the revision, the sponsor will have an appropriate discussion with a medical expert and report the result to the investigator.
17 Statistical Analysis

Statistical analyses will be performed in accordance with "Statistical Principles for Clinical Trials" (Iyakushin No. 1047 dated November 30, 1998). The analyses described in this section and technical details will be specified in "Statistical Analysis Plan," which will be prepared separately.

17.1 Analysis Sets

17.1.1 Efficacy Analysis Set

Patients with definitive registration, except those who have not received the investigational product and those for whom no information has been obtained on efficacy after the start of administration, will be treated as the full analysis set (FAS). In this trial, both the primary outcome measure and the secondary outcome measures will be analyzed in the FAS.

17.1.2 Safety Analysis Set

All patients who have received the investigational products will be treated as the safety population (SP).

17.2 Statistical Analyses and Analytical Methods

The details of the analyses and methods therefor will be described in the statistical analysis plan.

17.2.1 Subject Characteristics

With respect to the background factors of subjects, frequency distribution (number of patients, %) will be calculated for categorical parameters, and summary statistics (mean, standard deviation, median, minimum, maximum), as well as the frequency distribution of categorized data if necessary, will be calculated for continuous volume, followed by an investigation of intergroup bias by Fisher's exact probability test, Fisher's chi-squared test, Wilcoxon rank sum test, t test, etc. depending on the distribution or characteristics of data.

17.2.2 Primary Efficacy Outcome Measures

With respect to improvements in angiofibroma assessed using photographs by the IRC at 12 weeks after the start of administration (or at the time of withdrawal), the present drug and placebo will be compared by Wilcoxon rank sum test.

17.2.3 Secondary Efficacy Outcome Measures

17.2.3.1 Improvements in Angiofibroma and its Size and Color and in Hypomelanotic Macule and Plaque on the Head

With respect to improvements assessed by the IRC and the investigator, the present drug and placebo will be compared by Wilcoxon rank sum test in the entire FAS and the pediatric and adult subgroups at the assessment time points of 4 weeks, 8 weeks, or 12 weeks after the start of administration (or at the time of
withdrawal) and 4 weeks after the completion of administration (except analysis of the primary outcome measure).

17.2.3.2 Improvement Rate for Angiofibroma and its Size and Color and for Hypomelanotic Macule and Plaque on the Head

Improvement rate is defined as the proportion of subjects assessed as "improved" or a better category ("improved" or "markedly improved") that is calculated from improvements assessed by the IRC and the investigator. With respect to improvement rate in the entire FAS and the pediatric and adult subgroups, the present drug and placebo will be compared by Fisher's exact probability test.

17.2.3.3 DLQI/CDLQI

(1) With respect to change from baseline in the total score of DLQI or CDLQI, the present drug and placebo will be compared by Wilcoxon rank sum test in the entire FAS and the pediatric and adult subgroups at the assessment time points of 4 weeks, 8 weeks, or 12 weeks after the start of administration (or at the time of withdrawal) and 4 weeks after the completion of administration.

(2) With respect to change from baseline in the score of each subscale of DLQI, the present drug and placebo will be compared by Wilcoxon rank sum test in the entire FAS and the pediatric and adult subgroups at the assessment time points of 4 weeks, 8 weeks, or 12 weeks after the start of administration (or at the time of withdrawal) and 4 weeks after the completion of administration. Subscale score will be investigated for DLQI only because there is a difference between DLQI and CDLQI in the method for investigating subscales.

17.2.3.4 Others

(1) For various outcome measures, descriptive statistics (number of patients assessed, mean, SD, minimum, maximum, 95% confidence interval) will be calculated by population, treatment group, and time of assessment, as appropriate. Figures and tables will be prepared if necessary.

(2) If a bias is detected in any background factor (P<0.15), a separate analysis adjusted for the bias will be performed if necessary, and the result will be discussed. In addition, exploratory analyses will be performed if necessary.

17.2.4 Assessment of Safety

(1) Adverse events

Adverse events (adverse drug reactions) will be coded by system organ classes (SOCs) and preferred terms (PTs) using the MedDRA and tabulated and analyzed as follows:

For adverse events (adverse drug reactions) by SOC and PT, the number of patients with any event and the incidence will be calculated by population (whole, children, adults), treatment group, time of onset, severity, etc., as appropriate.

(2) Serious adverse events

For each patient with any event, the circumstances of the onset of the event, development, outcome, causal relationship with the investigational product will be described.

(3) Significant adverse events
With respect to adverse events leading to discontinuation of administration and skin irritation symptoms (see Section 14.2.5 "Significant Adverse Events"), the number of patients with any event and the incidence will be calculated by population (whole, children, adults), treatment group, time of onset, severity, etc.

(4) Laboratory findings and vital signs
For each test parameter, summary statistics (number of patients assessed, mean, SD, minimum, maximum, 95% confidence interval) will be calculated by population (whole, children, adults), treatment group, time of measurement, etc., as appropriate. In addition, cross tables showing changes or distributions of data or data before and after administration will be prepared.

(5) Sirolimus blood concentration
For all measured concentrations, summary statistics (number of patients assessed, mean, SD, minimum, maximum, 95% confidence interval) will be calculated by population (whole, children, adults), treatment group, time of measurement, etc., as appropriate.

(6) In addition, exploratory analyses will be performed if necessary. Figures and tables will be prepared if necessary.

17.2.5 Interval Estimation and Significance Level
The significance level $\alpha$ for the test of the outcome measures of efficacy and safety will be two-sided 5%. The confidence coefficient (1-$\alpha$) for interval estimation will be two-sided 95%. In addition, in the test of the intergroup difference in the bias in background factors, $p$ value will be used as a reference indicator, and the significance level $\alpha$ will be two-sided 15%.

17.3 Handling of Missing and Inappropriate Data
Handling of missing data and inappropriate data obtained outside the allowable range of the time points of assessment and observation will be determined by the sponsor after obtaining advice from a medical expert if necessary.

17.4 Preparation of, Additions to, and Changes in the Statistical Analysis Plan
The details of the analytical method for each outcome measure will be described in the statistical analysis plan. The preparation of the statistical analysis plan shall be completed before data finalization, and analyses and analytical methods may be added, if necessary, until then. If any change was made in the analytical plan described in the protocol or if the statistical analysis plan was revised, such fact shall be described in the statistical analysis plan.

18 Target number of subjects
Thirty patients per group, 60 patients in total (as the number of patients with definitive registration).
Both groups in total should include at least 20 children and 25 adults and at least the following number of subjects in each age category:
<table>
<thead>
<tr>
<th>Age Category</th>
<th>Standard Body Surface Area</th>
<th>Minimum Number of Subjects to Be Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to 5 years</td>
<td>Less than 0.8 m²</td>
<td>3</td>
</tr>
<tr>
<td>6 to 11 years</td>
<td>Not less than 0.8 m² and less than 1.3 m²</td>
<td>6</td>
</tr>
<tr>
<td>12 to 18 years</td>
<td>1.3 m² or more</td>
<td>6</td>
</tr>
<tr>
<td>19 years or older</td>
<td></td>
<td>25</td>
</tr>
</tbody>
</table>

[Rationale for Setting]

Since angiofibroma associated with tuberous sclerosis complex affects a large number of pediatric patients, we thought that the number of patients in this trial should be such that the efficacy and safety of the present drug can be investigated separately in adults (aged 19 years or more) and in children (aged 18 years or less) by subgroup analyses.

Thus, in order to ascertain the amplitude of the effects of the present drug by photographic assessment, Dr. Kaneda, the principal investigator of the study, performed simulated photographic assessment to evaluate improvements as a posterior analysis, using the photographs of the lesions of 36 subjects who participated in the I/II study (active drug group, 24 patients; placebo group, 12 patients) at baseline and at 12 weeks after the start of administration. Using the result of the evaluation as reference, a distribution of improvements was prepared as shown in Table 18-1.

Table 18-1: Distribution of Improvements in Angiofibroma Assessed using Photographs

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Markedly Improved</th>
<th>Improved</th>
<th>Slightly Improved</th>
<th>Unchanged</th>
<th>Slightly Aggravated</th>
<th>Aggravated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>Active drug</td>
<td>12</td>
<td>33%</td>
<td>42%</td>
<td>14%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6</td>
<td>0%</td>
<td>0%</td>
<td>21%</td>
<td>29%</td>
<td>50%</td>
</tr>
<tr>
<td>Adults</td>
<td>Active drug</td>
<td>12</td>
<td>0%</td>
<td>42%</td>
<td>47%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6</td>
<td>0%</td>
<td>0%</td>
<td>21%</td>
<td>62%</td>
<td>17%</td>
</tr>
</tbody>
</table>

On the basis of this distribution, the number of children and adults were calculated using the ratio of the number of patients for the active drug and for placebo of 1:1, $\alpha$ of two-sided 0.05, and ordinal scale as hypotheses. As a result, the number of patients that would achieve a power $(1 - \beta) = 0.8$ in children and adults at the same time in subgroup analysis was 17 and 21, respectively and a power = 0.95 in children and adults at the same time in subgroup analysis was 25 and 30, respectively, considering withdrawals/dropouts, at least 60 patients in total were considered necessary.

With this target number of patients, the power in all patients (children and adults combined), which is the primary outcome measure, is not less than 0.99.
19 Trial Period

Time of start of trial: November 2015
Time of final subject registration (definitive registration): June 2016
Time of completion of trial: October 2016 (time of completion of the follow-up of the final subject)

20 Electronic CRFs Etc.

20.1 Entry into Electronic CRFs and Reporting

Electronic CRFs will be used as the case report forms and will be prepared by the investigator and study collaborators by making entries into the electronic data capture (EDC) system specified by the sponsor on the basis of source documents. Entry by study collaborators will be permitted only for the transcription of data described in source documents. Entries, changes, and revisions for the electronic CRFs will be made in accordance with "Electronic CRF Entry Manual," which will be provided separately by the sponsor. The subinvestigator or study collaborators who make entries into the electronic CRFs must be those listed in "List of Subinvestigator and Study Collaborators."

20.2 Checking of Electronic CRFs by the Investigator

The information entered by the subinvestigator or study collaborators will be checked by the investigator at every entry or before finalization.

The investigator will inspect the information entered into the EDC system, confirm that all entries (including audit trail and responses to queries) are accurate and complete, and affix an electronic signature.

If any data that have been entered into the EDC system is in contradiction to the source documents, the investigator will prepare a record that explains the reasons, store appropriately, and promptly submit a copy of the record to the sponsor.

Before or after checking by the investigator, if the sponsor and the data manager or monitors of the CRO found inconsistency, questionable matters, etc. in data entered, by data cleaning or SDV, they will issue queries and request reconfirmation, additions, changes, and revisions in data entered.

20.3 Finalization of Electronic CRFs and Cancellation Thereof

After the completion of data cleaning of the electronic CRFs by the sponsor and the CRO and after the completion of electronic signature by the investigator to prove that all entries into the electronic CRFs have been checked, the data manager will perform finalization in accordance with the data management procedure manual. After data finalization, no addition, change, or correction may be made. If a need arose to make corrections after finalization, the data manager will perform cancellation of finalization by a request by the investigator and inform the investigator. After cancellation of finalization, the above-listed operations are possible.
20.4 Preparation of Patient Diary and Reporting

The patient diary will be written every day by the subject or the subject's legally acceptable representative about the status of application of the investigational product, the site of application, reasons for any missed application, and the number of opened tubes.

The investigator will recover the patient diary at each prescribed visit, check the descriptions, and make inquiries to the subject or the subject's legally acceptable representative if necessary. If the investigator found any deficiency, the investigator will instruct the patient to make appropriate additions/corrections. The investigator will instruct the subject to use double lines for making corrections to the description so that the original description is readable. If the investigator makes corrections, the investigator will affix a signature or a seal with the date and describe the reasons. The investigator will recover all patient diaries from the subject or the subject's legally acceptable representative by the time of completion of the trial (or by the time of withdrawal) and store them. The sponsor will not recover the patient diaries.

21 Source Documents

Source documents are records needed to reproduce and evaluate the development of events in the trial and are the documents, data, and records on which the electronic CRFs are based. To be specific, the following will be treated as source documents in this trial. Any agreement on source documents at individual study institutions will be in a written form, and source documents will be stored with other trial-related documents.

- Medical records, test data, nurse's records
- Informed consent documents, assent documents
- Screening list
- Investigational products control record
- Patient diary
- DLQI and CDLQI questionnaires
- SD cards storing image files

21.1 Direct Access to Source Documents Etc.

On the basis of the trial contract etc., the investigator, the study institution, etc. will allow the sponsor, the monitors and auditors of the CRO, the IRB, and regulatory agencies direct access to records that must be stored by the investigator, the study institution, etc., such as source documents and trial-related documents for inspection and checking.

21.2 Information for Which Electronic CRFs are Treated as the Source Documents

If source documents do not contain descriptions on the following information, information entered directly into the electronic CRFs will be treated as the source documents:

1. Checking of the inclusion criteria and the exclusion criteria
2. Determination of an abnormal change in laboratory data and related detailed descriptions
3. Determination of the severity and seriousness of adverse events, causal relationship with the investigational products, and related detailed descriptions
4. Date and time of application immediately before the measurement of blood concentration
(5) Detailed descriptions on the follow up of withdrawals (dropouts)
(6) Comments

22 Quality Control and Quality Assurance

The sponsor will control and assure quality in accordance with the SOP in order to verify if the quality of the trial has been secured.

22.1 Quality Control

The sponsor will check if the following major operations are being performed appropriately in accordance with the respective procedure manuals.

(1) In order to standardize the methods used in the trial, the sponsor will explain the methods for selecting, registering, testing, and assessing subjects to those involved in the conduct of the trial, including the investigator, before the start of the trial.

(2) Monitors will perform periodic monitoring during the trial in order to check written consent by subjects, the conduct of the trial in compliance with the protocol, etc.

(3) Monitors will collect information about adverse events during monitoring.

(4) Monitors will check the entries in the electronic CRFs on the basis of source documents such as medical records.

(5) The data manager and persons in charge of data management will check the entries in the electronic CRFs.

(6) If deficiency was found or questions arose in the above (4) and (5), the sponsor will issue queries and request the investigator or the study collaborators to recheck the entry data and make additions, changes, or corrections as appropriate. If the subinvestigator or study collaborators have made additions, changes, or corrections, the investigator will perform the final check.

(7) If necessary, the sponsor will hold a clinical conference, check the entries and appropriateness of the electronic CRFs, and investigate the treatment of subjects.

(8) The data manager and persons in charge of data management will perform data processing by computers and secure reliability in accordance with the SOP.

(9) The sponsor will check the descriptions when preparing documents such as a notice of protocol, a request for trial/contract, a record of the delivery/recovery of the investigational products.

22.2 Quality Assurance

The audit manager will perform auditing to ascertain if the trial is being conducted in compliance with the protocol, the SOP, and relevant laws and regulations such as the Pharmaceutical and Medical Device Act and GCP in accordance with the SOP of the sponsor. The sponsor, the CRO, and the study institutions will be audited.
23 Ethics

23.1 Compliance with GCP Etc.

This trial will be conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki (1964) and its revised version, the standards specified in Paragraph 3, Article 14 and Article 80-2 of the Pharmaceutical and Medical Device Act, relevant laws and regulations such as "Ordinance on Good Clinical Vonduct" (Ordinance No. 28 dated March 27, 1997) (hereinafter referred to as "GCP"), and this protocol.

23.2 Review by IRB

Prior to the conduct of the trial, the IRB founded by the study institution will obtain data that the IRB needs, including the protocol, the informed consent documents, and the investigator's brochure, and examine the conduct and continuation of the trial from the viewpoints of ethical, scientific, and medical appropriateness, and inform the head of the study institution of its opinions in written form.

23.3 Protection of Subject's Privacy

The investigator will give full consideration to the maintenance of the confidentiality of subjects. Subject identification codes only will be entered into the electronic CRFs, and the names etc. of subjects shown on other documents and materials that are submitted to the sponsor, if any, will be erased. In addition, when publishing the study results for academic purposes, consideration will also be given to the protection of subjects' privacy.

The sponsor and the monitors and auditors of the CRO must not disclose to third parties any personal information officially learned through the trial. The above rule will apply even after retirement.

23.4 Compensation for Health Injuries

The sponsor will take measures such as buying insurance to ensure the payment of compensation including the cost required to treat health injuries caused to subjects in relation to the trial.

23.5 Financial Payments

Financial payments related to this trial will be described separately in the agreement between the sponsor and the study institution or the contract.

24 Retention of Records

24.1 Data and Records to be Retained

24.1.1 Sponsor

The trial-related documents to be retained will be those specified in GCP and the SOP.
24.1.2 Study Institutions

The trial-related documents to be retained will be those specified in GCP and the SOP of the study institution.

24.2 Duration of Retention

24.2.1 Sponsor

The sponsor will retain the trial-related documents to be retained until the date shown in the following (1) or (2), whichever the later. When retention is no longer necessary for the trial-related documents to be retained by the head of the study institution or the founder of the IRB, the sponsor will inform the head of the study institution or the founder of the IRB of such fact.

(1) Date corresponding to 5 years after the marketing approval of the test drug. For data related to a pharmaceutical preparation that needs to receive reexamination as prescribed under Paragraph 1, Article 14-4 of the Pharmaceutical and Medical Device Act (in addition, the pharmaceutical preparation is such that the period from the date of approval to the completion of reexamination exceeds 5 years), until reexamination is completed.

(2) Date corresponding to 3 years after discontinuation or completion of the trial.

24.2.2 Study Institutions

The head of the study institution will retain the trial-related documents to be retained until the date shown in the following (1) or (2), whichever the later. If the sponsor needs a longer period of retention, the head of the study institution will discuss the duration and method of retention with the sponsor. In the retention of records, a person responsible for the retention of records will be assigned to each record.

(1) Date corresponding to 3 years from the marketing approval of the test drug (or from the date when termination of development was notified)

(2) Date corresponding to 3 years after discontinuation or completion of the trial.

24.2.3 Founder of IRB

The founder of the IRB will retain the trial-related documents to be retained until the date shown in the following (1) or (2), whichever the later. If the sponsor needs a longer period of retention, the founder of the IRB will discuss the duration and method of retention with the sponsor. In the retention of records, a person responsible for the retention of records will be assigned to each record.

(1) Date corresponding to 3 years from the marketing approval of the test drug (or from the date when termination of development was notified)

(2) Date corresponding to 3 years after discontinuation or completion of the trial.

25 Agreement on Publication

The sponsor holds the copyright of any publication that the sponsor prepared or authorized to prepare on the basis of the result of the trial that the sponsor requested. The sponsor also has the ownership of the information contained in this protocol (unpublished data, in particular). Thus, investigators willing to participate in this trial, persons involved in the conduct of the trial, study institutions, and the IRBs that
received these information from the sponsor must not publish these information to third parties without written consent from the sponsor, except for the purpose of obtaining consent from subjects. In addition, the sponsor has the ownership of the data obtained by this trial, and a prior approval by the sponsor is required before publishing a part or the whole of the result of this trial to the outside such as scientific meetings and medical journals (except disclosure to regulatory agencies).

The result of this trial may be used for publications by the sponsor and the application dossier for submission to regulatory agencies.

26 List of Appendices

Appendix 1: Diagnostic Criteria for Tuberous Sclerosis Complex (International TSC Consensus Conference 2012)
Appendix 2: Standards for Classification of Seriousness of Adverse Drug Reactions by Drugs etc.
Appendix 3: Body Surface Area Table (Fujimoto method)

27 List of Attachments

Attachment 1: Study Institutions and Investigators

28 Literature References

Statistical Analysis Plan

A Phase III Study of NPC-12G in Patients with Skin Lesions

Associated with Tuberous Sclerosis Complex

Protocol number: NPC-12G-1
Edition Number: Ver.1.1
Prepared: December 21, 2016
<table>
<thead>
<tr>
<th>Edition</th>
<th>Date of Preparation</th>
<th>Corrector</th>
<th>Main Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ver. 1.0</td>
<td>August 5, 2016</td>
<td>Tsuyoshi Mikami</td>
<td>Original</td>
</tr>
<tr>
<td>Ver. 1.1</td>
<td>December 21, 2016</td>
<td>Tsuyoshi Mikami</td>
<td>Analysis items added, clerical errors corrected</td>
</tr>
</tbody>
</table>
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1 Objectives
The statistical analysis plan (hereinafter referred to as “this plan”) is prepared to complement the section on statistical analysis in the protocol of the trial titled “a phase III study of NPC-12G in patients with skin lesions associated with tuberous sclerosis complex” (hereinafter referred to as “this trial”).

2 Study Organization
The analysis will be conducted in accordance with the Operating Procedure for Statistical Analysis.

3 Target Sample Size
30 patients per group, 60 patients in total (as the number of patients with definitive registration)
Both groups in total should include at least 20 children and 25 adults and at least the following number of subjects in each age category:

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Standard Body Surface Area</th>
<th>Minimum Number of Subjects to Be Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-5 years</td>
<td>&lt;0.8 m²</td>
<td>3</td>
</tr>
<tr>
<td>6-11 years</td>
<td>≥0.8 m² and &lt;1.3 m²</td>
<td>6</td>
</tr>
<tr>
<td>12-18 years</td>
<td>≥1.3 m²</td>
<td>6</td>
</tr>
<tr>
<td>19 or older</td>
<td></td>
<td>25</td>
</tr>
</tbody>
</table>

[Rationale for Setting]
Since angiofibroma associated with tuberous sclerosis complex affects a large number of pediatric patients, we thought that the number of patients in this trial should be such that the efficacy and safety of the present drug can be investigated separately in adults (aged 19 years or older) and in children (aged 18 years or younger) by subgroup analyses.
Thus, in order to ascertain the amplitude of the effects of the present drug by photographic assessment, Dr. Wataya-Kaneda, the principal investigator of the study, performed simulated photographic assessment to evaluate improvements as a posterior analysis, using the photographs of the lesions of 36 subjects who participated in the I/II study (active drug group, 24 patients; placebo group, 12 patients) at baseline and at 12 weeks after the start of administration. Using the result of the evaluation as a reference, a distribution of improvements was prepared as shown in Table 3.1.
Table 3.1. Distribution of Improvements in Angiofibroma Assessed using Photographs

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Markedly Improved</th>
<th>Improved</th>
<th>Slightly Improved</th>
<th>Unchanged</th>
<th>Slightly exacerbated</th>
<th>Exacerbated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>Active drug</td>
<td>12</td>
<td>33%</td>
<td>42%</td>
<td>14%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6</td>
<td>0%</td>
<td>0%</td>
<td>21%</td>
<td>29%</td>
<td>50%</td>
</tr>
<tr>
<td>Adults</td>
<td>Active drug</td>
<td>12</td>
<td>0%</td>
<td>42%</td>
<td>47%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6</td>
<td>0%</td>
<td>0%</td>
<td>21%</td>
<td>62%</td>
<td>17%</td>
</tr>
</tbody>
</table>

On the basis of this distribution, the number of children and adults were calculated using the ratio of the number of patients for the active drug and for the placebo of 1:1, α of two-sided 0.05, and ordinal scale as hypotheses. As a result, the number of patients that would achieve a power (1 - β) = 0.8 in children and adults at the same time in subgroup analysis was 17 and 21, respectively and a power = 0.95 in children and adults at the same time in subgroup analysis was 25 and 30, respectively, considering withdrawals/dropouts, at least 60 patients in total were considered necessary.

With this target number of patients, the power in all patients (children and adults combined), which is the primary outcome measure, is not less than 0.99.
4 Overall Rules for Statistical Analysis

(1) The following 6 parameters will be calculated as summary statistics: the number of patients, mean, standard deviation, minimum, median, and maximum.

(2) The number of digits to be displayed is shown in Table 4.1. Values will not be rounded off during calculation.

(3) Multiplicity will not be adjusted in this trial.

(4) Unless otherwise specified, the significance level \( \alpha \) for the test of the outcome measures of efficacy and safety will be two-sided 5%. The confidence coefficient (1-\( \alpha \)) for interval estimation will be two-sided 95%.

Table 4.1. Overall Rules for Statistical Analysis

<table>
<thead>
<tr>
<th>Item</th>
<th>Number of Digits to Be Displayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>To be displayed in integers.</td>
</tr>
<tr>
<td>Proportion</td>
<td>To be rounded off to the first decimal place.</td>
</tr>
<tr>
<td>Summary statistics</td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>To be displayed in integers.</td>
</tr>
<tr>
<td>Mean</td>
<td>To be rounded off to the first decimal place.</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>To be rounded off to the second decimal place.</td>
</tr>
<tr>
<td>Minimum</td>
<td>The entire display digits will be displayed.</td>
</tr>
<tr>
<td>Median</td>
<td>To be rounded off to the first decimal place.</td>
</tr>
<tr>
<td>Maximum</td>
<td>The entire display digits will be displayed.</td>
</tr>
<tr>
<td>CV%</td>
<td>To be displayed up to two decimal places.</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>To be rounded off to the second decimal place.</td>
</tr>
<tr>
<td>Test/estimation</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>Values less than 0.001 will be displayed as &lt;0.001. Values not less than 0.001 will be rounded off to the third decimal place.</td>
</tr>
<tr>
<td>Coefficient of concordance,</td>
<td>To be rounded off to the second decimal place.</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td></td>
</tr>
</tbody>
</table>

5 Analysis Sets

5.1 Efficacy Analysis Set

Patients with definitive registration, except those who have not received the investigational product and those for whom no information has been obtained on efficacy after the start of administration, will be treated as the full analysis set (FAS).

5.2 Safety Analysis Set

All patients who have received the investigational product will be treated as the safety population (SP).
6 Data Handling

6.1 Handling of Missingness and Abnormal Samples
- Missing data will not be imputed.

6.2 Data Handling at the Time of Withdrawal
- In the primary outcome measure, the phrase “at the time of withdrawal” as used in the phrase “at 12 weeks after the start of administration (or at the time of withdrawal)” is intended to mean that data “at the time of withdrawal” include all data obtained up to the time of withdrawal within the entire period of up to 12 weeks. In the analyses for each period, data “at the time of withdrawal” for each evaluation time point “at 4 weeks after the start of administration (or at the time of withdrawal),” “at 8 weeks after the start of administration (or at the time of withdrawal),” and “at 12 weeks after the start of administration (or at the time of withdrawal)” are defined as data obtained up to the time of withdrawal within the period from the start of administration through 4 weeks, the period from 5 weeks through 8 weeks, and the period from 9 weeks through 12 weeks, respectively.

6.3 Handling of the Quantitative Limit
- Any sirolimus blood concentration that is below the quantitative limit (BQL) will be replaced by “0” when displaying diagrams of changes of measurements over time by subject in the preparation of time plots.

6.4 Handling of Windows of Tolerance for Time Points
- Data obtained at the prescribed time points will be used in principle. Any missing value at the prescribed time point will be imputed with the value obtained at a time point nearest to the prescribed time point and within the window of tolerance for the purpose of evaluation.

7 Disposition of Subjects

7.1 Analysis Sets
- Patients with consent
- Patients with definitive registration

7.2 Analysis Items
- Disposition of subjects
- Reason for discontinuation

7.3 Analytical Method

7.3.1 Disposition of Subjects
- The number of patients withdrawn from the study or who continue the study will be tabulated for each interval and a tree diagram will be prepared.
7.3.2 Reason for Discontinuation
- The reasons for withdrawal will be tabulated.

8 Demographic and Other Baseline Characteristics
8.1 Analysis Sets
- Efficacy analysis set
- Safety population

8.2 Subject Background Factors
Among the demographic variables, summary statistics will be calculated for continuous data. The number and proportion of subjects will be calculated for categorical data. The analysis items are shown in Table 8.1, Table 8.2, and Table 8.3. The number of patients who fall under the category “present” for genetic diagnosis will be used as the denominator for the proportion of “the presence or absence of TSC1 mutation” and the proportion of “the presence or absence of TSC2 mutation.”

Table 8.1. Subject Background Factors (Continuous Data)

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit</th>
<th>Display Digits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Western style)</td>
<td>Age</td>
<td>Integer</td>
</tr>
<tr>
<td>Body height</td>
<td>cm</td>
<td>First decimal place</td>
</tr>
<tr>
<td>Body weight</td>
<td>kg</td>
<td>First decimal place</td>
</tr>
</tbody>
</table>

Table 8.2. Subject Background Factors (Categorical Data)

<table>
<thead>
<tr>
<th>Item</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Men/women</td>
</tr>
<tr>
<td>Age Category 1</td>
<td>3 to 5 years/6 to 11 years</td>
</tr>
<tr>
<td></td>
<td>/12 to 18 years/19 years or older</td>
</tr>
<tr>
<td>Age Category 2</td>
<td>Children (18 years or younger)</td>
</tr>
<tr>
<td></td>
<td>/adults (19 years or older)</td>
</tr>
<tr>
<td>Presence or absence of genetic diagnosis</td>
<td>Presence/absence</td>
</tr>
<tr>
<td>Presence or absence of TSC1 mutation</td>
<td>Presence/absence</td>
</tr>
<tr>
<td>Presence or absence of TSC2 mutation</td>
<td>Presence/absence</td>
</tr>
<tr>
<td>Complication (intellectual disability)</td>
<td>Presence/absence</td>
</tr>
<tr>
<td>Complication (epilepsy)</td>
<td>Presence/absence</td>
</tr>
<tr>
<td>Presence or absence of prior medication (mTOR inhibitor [sirolimus, everolimus, temsirolimus])</td>
<td>Presence/absence</td>
</tr>
<tr>
<td>Presence or absence of prior medication (external preparation of tacrolimus [Protopic®])</td>
<td>Presence/absence</td>
</tr>
</tbody>
</table>
Table 8.3. Items Related to Clinical Symptoms of Tuberous Sclerosis Complex (Categorical Data)

<table>
<thead>
<tr>
<th>Major manifestation</th>
<th>Item</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypochromic macules (≥3, at least 5 mm in diameter)</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Facial angiofibromas (≥3) or fibrous cephalic plaque</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Ungual fibromas (≥2)</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Shagreen patch</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Multiple retinal hamartomas</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Cortical dysplasias</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Subependymal nodules</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Subependymal Giant Cell Astrocytoma</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Cardiac rhabdomyoma</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Lymphangioleiomyomatosis (LAM)</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Angiomyolipomas (≥2)</td>
<td>Presence/absence</td>
</tr>
<tr>
<td>Minor manifestation</td>
<td>“Confetti” skin lesions</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Dental enamel pits (≥3)</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Intraoral fibromas (≥2)</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Retinal achromatic patch</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Multiple renal cysts</td>
<td>Presence/absence</td>
</tr>
<tr>
<td></td>
<td>Nonrenal hamartomas</td>
<td>Presence/absence</td>
</tr>
</tbody>
</table>

8.3 Analytical Method

For the subject background factors, frequency distribution (number of patients, %) will be tabulated for categorical data, and summary statistics will be calculated for continuous data. If necessary, continuous data will be classified into categorical data, and frequency distribution will be tabulated for the data. In order to confirm imbalances between the groups, Fisher's exact probability test will be performed for categorical data, and the t-test will be performed for continuous data.

Frequency will be tabulated by treatment group for prior medication, concomitant medication, and complication in the safety analysis set. The frequency of complication will also be tabulated for adults/children. Any medication whose administration has been completed by the time of the start of administration of the investigational product will be treated as prior medication, and other medications will be treated as concomitant medication.

9 Analysis of Efficacy Outcome Measures

9.1 Analysis Sets

- Efficacy analysis set
9.2 Outcome Measures

9.2.1 Primary Outcome Measure

“Improvements in angiofibroma assessed using photographs by the independent review committee (IRC) at 12 weeks after the start of administration”

9.2.2 Secondary Outcome Measures

The following 7 items are the secondary efficacy outcome measures.

The timing of the assessment is at baseline and 4, 8, and 12 weeks after the start of administration, and 4 weeks after the completion of administration.

(1) Improvements in angiofibroma assessed using photographs by the IRC (excepting at 12 weeks)
(2) Improvements in angiofibroma assessed by the investigator
(3) Improvements in the size of angiofibroma assessed by the IRC and the investigator
(4) Improvements in the color of angiofibroma assessed by the IRC and the investigator
(5) Improvements in hypomelanotic macule and plaque of the upper neck assessed by the IRC and the investigator
(6) Proportion of subjects assessed as “improved” or a better category in the primary outcome measure and in secondary outcome measures 1 to 5 (improvement rate)
(7) Change in the total score from baseline for DLQI and CDLQI

9.3 Analytical method

9.3.1 Analysis of the Primary Outcome Measure

With respect to improvements in angiofibroma assessed using photographs by the IRC at 12 weeks after the start of administration (or at the time of withdrawal), the present drug and placebo will be compared by the Wilcoxon rank sum test (primary analysis).

Similar assessment will be performed for the adults/children subgroups without considering multiplicity. In addition, frequency distribution and summary statistics will be calculated for improvements at each assessment time point.

9.3.2 Analysis of the Secondary Outcome Measures

(1) Improvements in angiofibroma assessed using photographs by the IRC

With respect to this parameter at the following assessment time points, the present drug and placebo will be compared by the Wilcoxon rank sum test for the adults/children subgroups: 4 weeks after the start of administration (or at the time of withdrawal), 8 weeks after the start of administration (or at the time of withdrawal), 12 weeks after the start of administration (or at the time of withdrawal), and 4 weeks after the completion of administration. Data that “cannot be assessed” for improvements will not be included in the data to be used for the Wilcoxon rank sum test. In addition, frequency distribution and summary statistics will be calculated for improvements at each assessment time point.

(2) Improvements in angiofibroma assessed by the investigator

8
The same analysis as for the improvements assessed by IRC-judgment will be performed.

(3) Improvements in the size of angiofibroma assessed by the IRC and the investigator
The same analysis as for the improvements in angiofibroma will be performed.

(4) Improvements in the color of angiofibroma assessed by the IRC and the investigator
The same analysis as for the improvements in angiofibroma will be performed.

(5) Improvements in hypomelanotic macule and plaque of the upper neck assessed by the IRC and the investigator
The same analysis as for the improvements in angiofibroma will be performed.

(6) Verification of the agreement between the IRC-judgment and the judgment by the investigator
With respect to improvements in angiofibroma (including size and color) and improvements in hypomelanotic macule and plaque of the upper neck, agreement between the judgments will be verified by preparing a cross table for the IRC’s judgment and the judgment by the investigator and evaluating the Kendall's coefficient of concordance and rank correlation coefficient for each time point.

(7) Proportion of subjects assessed as “improved” or a better category in the primary outcome measure and in secondary outcome measures 1 to 5 (improvement rate)
Improvement rate is defined as the proportion of subjects assessed as “improved” or a better category (“improved” or “markedly improved”) that is calculated from the improvements assessed by the IRC and the investigator. With respect to improvements in the FAS as a whole and in the adults/children subgroups, the present drug and placebo will be compared by Fisher's exact probability test. Data that “cannot be assessed” for improvements will be treated as “no improvement” and will be included in the data to be used for Fisher's exact probability test.

(8) Change in the total score from baseline for DLQI and CDLQI
A) With respect to change from baseline in the total score of DLQI and of CDLQI at the following time assessment points, summary statistics will be calculated, and the present drug and placebo will be compared by the Wilcoxon rank sum test in the FAS as a whole and in each of the subgroups of adults, children, those not younger than 16 years (patients with DLQI use), and those younger than 16 years (patients with CDLQI use): 4 weeks after the start of administration (or at the time of withdrawal), 8 weeks after the start of administration (or at the time of withdrawal), 12 weeks after the start of administration (or at the time of withdrawal), and 4 weeks after the completion of administration.

B) With respect to change from baseline in each subscale score of DLQI at the following time
assessment points, summary statistics will be calculated, and the present drug and placebo will be compared by the Wilcoxon rank sum test in the FAS as a whole and in each of the subgroups of adults and children (those not younger than 16 years and not older than 18 years): 4 weeks after the start of administration (or at the time of withdrawal), 8 weeks after the start of administration (or at the time of withdrawal), 12 weeks after the start of administration (or at the time of withdrawal), and 4 weeks after the completion of administration. The subscale score will be investigated for DLQI only because there is a difference between DLQI and CDLQI in the method for investigating subscales.

10 Analysis of Drug Concentration
10.1 Analysis Sets
- Safety population

10.2 Parameters and Analytical Method
- With respect to data showing sirolimus blood concentration, summary statistics (number of patients, number and proportion of patients showing the drug concentration, mean, standard deviation, CV%, minimum, median, maximum, and 95% confidence interval) will be calculated by subgroup (adults, children), by treatment group, and by measurement time. In addition, the number of patients with values below the detection limit will be tabulated.
- A plot of blood concentration-time in the NPC-12G group and a diagram of changes of measurements over time throughout all time points will be prepared for each subject. Patients with values below the quantitative limit (BQL) at all time points will not be displayed in the diagram of changes of measurements over time.

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit</th>
<th>Display Digits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus blood concentration</td>
<td>ng/mL</td>
<td>Second decimal place (in lists, values will be displayed in the display digits for the data)</td>
</tr>
</tbody>
</table>

11 Assessment of Safety
11.1 Analysis Sets
- Safety population

11.2 Parameters and Analytical Method
11.2.1 Status of Administration of the Investigational Product
- With respect to the status of administration of the investigational product, the compliance rate in the study as a whole will be calculated for each week. The compliance rate will be calculated as follows:
Compliance rate = number of doses during each period as confirmed by the patient diary ÷ (number of
days in each period × 2) × 100 (%).
- Summary statistics will be calculated by treatment group and by group (adults/children, 3 to 5 years/6
to 11 years/12 to 18 years), with the total dose being defined as the amount obtained by subtracting the
total amount collected (g) from the total weight prescribed [total number prescribed × 13.8 g].

<table>
<thead>
<tr>
<th>Table 11.1.1. Definition of Each Period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration</strong></td>
</tr>
<tr>
<td>1 week after the start of administration</td>
</tr>
<tr>
<td>2 weeks after the start of administration</td>
</tr>
<tr>
<td>3 weeks after the start of administration</td>
</tr>
<tr>
<td>4 weeks after the start of administration</td>
</tr>
<tr>
<td>5 weeks after the start of administration</td>
</tr>
<tr>
<td>6 weeks after the start of administration</td>
</tr>
<tr>
<td>7 weeks after the start of administration</td>
</tr>
<tr>
<td>8 weeks after the start of administration</td>
</tr>
<tr>
<td>9 weeks after the start of administration</td>
</tr>
<tr>
<td>10 weeks after the start of administration</td>
</tr>
<tr>
<td>11 weeks after the start of administration</td>
</tr>
<tr>
<td>12 weeks after the start of administration</td>
</tr>
<tr>
<td>13 weeks after the start of administration</td>
</tr>
<tr>
<td>Entire period</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 11.1.2. Dose Parameters (Continuous Data)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Item</strong></td>
</tr>
<tr>
<td>Dose</td>
</tr>
</tbody>
</table>
Mean dose in the entire period | mg/day | Integer

11.2.2 Adverse Events
- With respect to adverse events, adverse drug reactions, deaths, serious adverse events, adverse events leading to discontinuation, and adverse events related to skin irritation symptoms, the number of patients with events and incidence will be determined by treatment group. The same analysis will be performed in the subgroups of adults, children, 3 to 5 years, 6 to 11 years, and 12 to 18 years.
- With respect to adverse events and adverse drug reactions by System Organ Class (hereinafter referred to as “SOC”) and by Preferred Term (hereinafter referred to as “PT”) according to MedDRA/J, the number of patients with events and incidence will be determined by subgroup (whole, adults/children, 3 to 5 years/6 to 11 years/12 to 18 years), by treatment group, by severity, by seriousness, and by whether the event occurred at the site of administration.
- With respect to adverse events leading to discontinuation by SOC and by PT, the number of patients with events and incidence will be determined by treatment group.
- With respect to adverse events and adverse drug reactions related to skin irritation symptoms by SOC and by PT, the number of patients with events and incidence will be determined by treatment group and by subgroup (whole, adults/children, 3 to 5 years/6 to 11 years/12 to 18 years).

1) Any adverse event that is judged to be casually “related” to the investigational product will be treated as an adverse drug reaction.
2) SOC and PT will be used for analyses.
3) If a subject experienced the same event multiple times within one category of term used for tabulation, the number of events for that adverse event for that subject will be counted as 1 in the tabulation of the number of patients with events. If the same situation occurs in the tabulation by severity, the most severe event will be counted as 1, and other events will not be counted in the tabulation of the number of patients.
4) Incidence (%) = (number of patients with events/number of patients in the safety analysis set) × 100. The incidence between groups is compared with use of Fisher’s exact probability tests as needed.
5) The number of events is defined as the total number of events including all events that occur in the same subject multiple times within one category of term used for tabulation.
6) The number of digits to be displayed is shown in Table 11.2.
7) The incidence is compared between
Table 11.2. Adverse Events

<table>
<thead>
<tr>
<th>Item</th>
<th>Number of Digits to Be Displayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events, number of patients with events</td>
<td>To be displayed in integers.</td>
</tr>
<tr>
<td>Incidence (percentage)</td>
<td>To be rounded off to the first decimal place.</td>
</tr>
</tbody>
</table>

11.2.3 Laboratory Tests
- For baseline, data at Visit 1 or Visit 2, whichever is the closest to the date of the first administration, will be used.
- For each test and by group (adults, children), by treatment group, and by measurement time, summary statistics (the number of patients, mean, standard deviation, minimum, median, maximum, 95% confidence interval) will be calculated for continuous quantities using the values in units shown in Table 11.3.1, and the frequencies will be calculated for categorical data. In addition, a diagram of changes in test values over time, a tabulation of abnormal values, a scattering diagram or a cross table of data before and after administration will be prepared.
- In the tabulation of abnormal values, “H/L/ abnormality present” will be treated as “abnormality present,” and the others will be treated as “normal.”

In order to confirm imbalances in baseline values between the groups, the 2-sample Wilcoxon rank sum test will be performed for categorical data, and the t-test will be performed for continuous data.
### Table 11.3.1. Unified Unit, Conversion, and Display Digits for Laboratory Findings (Continuous Data)

<table>
<thead>
<tr>
<th>Laboratory Tests</th>
<th>Unified Unit</th>
<th>Conversion Formula</th>
<th>Display Digits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red blood cell count</td>
<td>(10^4/\mu L)</td>
<td>If (10^3\times 1/10) If (10^6\times 100)</td>
<td>Integer</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>/\mu L</td>
<td>If (10^3\times 1000) If (10^2\times 100)</td>
<td>Integer</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>%</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>%</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td>Monocytes</td>
<td>%</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>%</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td>Basophils</td>
<td>%</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td>Platelet count</td>
<td>(10^4/\mu L)</td>
<td>If (10^3\times 1/10)</td>
<td>First decimal place</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>g/dL</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td>Hematocrit level</td>
<td>%</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td><strong>Biochemical tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total protein</td>
<td>g/dL</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td>Albumin</td>
<td>g/dL</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td>AST(GOT)</td>
<td>U/L</td>
<td></td>
<td>Integer</td>
</tr>
<tr>
<td>ALT(GPT)</td>
<td>U/L</td>
<td></td>
<td>Integer</td>
</tr>
<tr>
<td>(\gamma)GTP</td>
<td>U/L</td>
<td></td>
<td>Integer</td>
</tr>
<tr>
<td>ALP</td>
<td>U/L</td>
<td></td>
<td>Integer</td>
</tr>
<tr>
<td>LDH</td>
<td>U/L</td>
<td></td>
<td>Integer</td>
</tr>
<tr>
<td>CK(CPK)</td>
<td>U/L</td>
<td></td>
<td>Integer</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>mg/dL</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>mg/dL</td>
<td></td>
<td>Integer</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>mg/dL</td>
<td></td>
<td>Integer</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>mg/dL</td>
<td></td>
<td>Integer</td>
</tr>
<tr>
<td>Triglycerides (TG)</td>
<td>mg/dL</td>
<td></td>
<td>Integer</td>
</tr>
<tr>
<td>BUN</td>
<td>mg/dL</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td>Creatinine</td>
<td>mg/dL</td>
<td></td>
<td>Second decimal place</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>mg/dL</td>
<td></td>
<td>Integer</td>
</tr>
<tr>
<td>Ca</td>
<td>mg/dL</td>
<td>mmol/L: Conversion unnecessary</td>
<td>Integer</td>
</tr>
<tr>
<td>Na</td>
<td>mEq/L</td>
<td>mmol/L: Conversion unnecessary</td>
<td>Integer</td>
</tr>
<tr>
<td>K</td>
<td>mEq/L</td>
<td>mmol/L: Conversion unnecessary</td>
<td>First decimal place</td>
</tr>
<tr>
<td>P</td>
<td>mg/dL</td>
<td></td>
<td>First decimal place</td>
</tr>
<tr>
<td>Cl</td>
<td>mEq/L</td>
<td>mmol/L: Conversion unnecessary</td>
<td>Integer</td>
</tr>
</tbody>
</table>

### Table 11.3.2. Laboratory Findings (Categorical Data)

<table>
<thead>
<tr>
<th>Item</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult blood in urine</td>
<td>- / ± / 1+ / 2+ / 3+ / 4+</td>
</tr>
<tr>
<td>Protein</td>
<td>- / ± / 1+ / 2+ / 3+ / 4+</td>
</tr>
<tr>
<td>Sugar</td>
<td>- / ± / 1+ / 2+ / 3+ / 4+</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>- / ± / 1+ / 2+ / 3+ / 4+</td>
</tr>
</tbody>
</table>

### 11.2.4 Vital Signs
- For each test, summary statistics (number of patients, mean, standard deviation, minimum, median, maximum, 95% confidence interval) will be calculated by subgroup (adults, children), by treatment group,
and by measurement time. In addition, graphs showing changes over time and scatter diagrams will be prepared. The t-test of baseline values will be performed to verify bias between the groups.

Table 11.4. Vital Signs and Body Weight (Continuous Data)

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit</th>
<th>Display Digits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>mmHg</td>
<td>Integer</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>mmHg</td>
<td>Integer</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>/min</td>
<td>Integer</td>
</tr>
</tbody>
</table>