# CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double-blind, Vehicle-controlled,Parallel-group Trial to Assess the Safety and Efficacy of 0.3% and 1% OPA-15406 Ointments When Administered for 4 Weeks in Pediatric Patients With Atopic Dermatitis

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Otsuka Pharmaceutical Co., Ltd

Investigational Medicinal Product

OPA- 15406

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Protocol No. 271-102-00002
(Translated Version)
CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase: 2

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| Sponsor: | Otsuka Pharmaceutical Co., Ltd<br>2-9 Kanda-Tsukasamachi, Chiyoda-ku,<br>Tokyo 101-8535, Japan |
| Immediately Reportable Event | Pharmacovigilance Operation Office,<br>Pharmacovigilance Department, Otsuka Pharmaceutical Co., Ltd.<br>3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka 540-0021, Japan<br>IRE_271-102-00002@otsuka.jp |
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# Protocol Synopsis

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| Name of Sponsor: Otsuka Pharmaceutical Co., Ltd<br>Name of Investigational Medicinal Product: Trade, Generic (OPA-15406) | Protocol No.: 271-102-00002 |
| Protocol Title: | A Multicenter, Randomized, Double-blind, Vehicle-controlled, Parallel-group Trial to Assess the Safety and Efficacy of 0.3% and 1% OPA-15406 Ointments When Administered for 4 Weeks in Pediatric Patients With Atopic Dermatitis |
| Clinical Phase/Trial Type: | Phase: 2<br>Type of Trial: Pediatric dose-finding trial |
| Treatment Indication: | Atopic dermatitis (AD ) |
| Objective(s): | Primary Objective: To evaluate the safety of 0.3% and 1% OPA-15406 when applied twice daily for 4 weeks in pediatric patients with AD<br>Secondary Objective: To evaluate the efficacy (dose response) and pharmacokinetics of 0.3% and 1% OPA-15406 when applied twice daily for 4 weeks in pediatric patients with AD |
| Trial Design: | Multicenter, randomized, double-blind, vehicle-controlled, parallel-group |
| Subject Population: | Pediatric subjects with AD with an baseline Investigator's Global Assessment (IGA) score of 2 (mild) or 3 (moderate)<br>60 subjects in total (at least 8 subjects of age 2 to 6) |
| Inclusion/Exclusion Criteria: | Major inclusion Criteria:<br>• Age: 2 to 14 years, inclusive (at time of obtaining informed consent)<br>• Diagnosis of AD based on the criteria of Hanifin and Rajka[1] (Appendix 1)<br>• Subjects whose legal guardian is able to provide informed consent prior to participation in the trial<br>• AD affecting ≥5% to ≤40% of body surface area (BSA)<br>• IGA score of 2 (mild) or 3 (moderate)<br><br>Major exclusion Criteria:<br>• Subjects who are judged by the investigator or subinvestigator to be problematic in withdrawing blood |

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| | • Subjects who are unable to stop using topical corticosteroids, topical immunomodulators, topical retinoids and topical antihistamine from 7 days prior to the baseline examination until the Week 4 assessment. Low or medium potency corticosteroids in the Guidelines for Management of Atopic Dermatitis may be used until 4 days prior to the baseline examination in the judgment of the investigator or subinvestigator for the gradual decrease in the screening period before stopping.<br>• Subjects who are unable to stop using systemic corticosteroids, systemic immunomodulators, systemic antimetabolites, systemic retinoids, and biologics from 28 days prior to the baseline examination until the Week 4 assessment. Intra-ocular, intra-nasal and intra-auricular or inhaled corticosteroids may be considered if, in the opinion of the investigator or subinvestigator, their use will not impact assessment of the affected area<br>• Subjects who are unable to stop treatment with ultraviolet A, narrowband ultraviolet B, and ultraviolet B from 28 days prior to the baseline examination until the Week 4 assessment<br>• Subjects who are unable to continue in the trial without changing the dosage and administration of systemic antihistamines, sodium cromoglicate, tranilast, or suplatast tosilate from 7 days prior to baseline examination until the Week 4 assessment. Intra-ocular, intra-nasal, or inhalant formulations may be considered if, in the opinion of the investigator or subinvestigator, their use will not impact assessment of the affected area |
| Trial Sites: | Approximately 8 sites in Japan |
| Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration: | Test Product: 0.3% and 1% OPA-15406 Ointment or vehicle<br>Twice daily repeated administration for 4 weeks |
| Trial Assessments: | Safety Endpoints: Adverse events (AEs), physical examination, vital signs (including body weight), clinical laboratory values, 12-lead ECG (as much as possible for children aged 2 - 6 years old)<br>Efficacy Endpoints: IGA, Eczema Area and Severity Index |

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| | (EASI), Visual Analogue Scale (VAS) for pruritus (only for 7 - 14 years of age), Verbal Rating Scale (VRS) for pruritus (only for 7 - 14 years of age), Patient-Oriented Eczema Measure (POEM), affected BSA<br><br>Pharmacokinetics: Blood sampling for plasma concentration of OPA-15406<br><br>Screening/others: Medical history, medication history, pregnancy test |
| Criteria for Evaluation | **Primary Endpoint:** Primary Endpoint: The number and percentage of subjects experiencing AEs<br><br>**Secondary Endpoints:** Incidence of success in IGA at Week 4, change from baseline in EASI, VAS for pruritus, VRS for pruritus, POEM, affected BSA at Week 4, and plasma concentration of OPA-15406 (trough concentration at Week 1 and Week 4) |
| Statistical Methods: | Primary Endpoint:<br><br>• The number and percentage of subjects experiencing AEs will be calculated for each treatment group<br><br>Secondary Endpoints:<br><br>• For incidence of success in IGA at Week 4, incidence of success of each treatment group and its 95% confidence interval will be calculated. The difference between vehicle group and each treatment group in the success rate and its 95% confidence interval will be calculated. Incidence of success is defined as the number of subjects whose IGA score is 0 (clear) or 1 (almost clear) and improved by at least 2 grades from baseline. Based on the Cochran-Mantel-haenszel method, the difference in success rate adjusted by the severity of IGA at baseline and its confidence interval will be calculated as primary analysis.<br><br>• For change from baseline in IGA at Week 1,Week 2 and Week 4, mixed-model repeated measures (MMRM) analysis with factors of treatment (0.3% or 1% OPA-15406 groups, vehicle group), timepoint, baseline IGA (mild or moderate), and interaction between treatment and timepoint will be applied with an unstructured variance covariance structure to the change from baseline up to Week 4 based on OC dataset. Kenward-Roger will be used for the calculation of standard error of fixed effects and degree of freedom. The least square mean of each treatment group will be calculated by timepoint. Also, the |

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| | difference in the least square means between the vehicle group and each OPA-15406 group, and the two-sided 95% confidence interval will be calculated at Week 1, Week 2 and Week 4.<br>• For other secondary endpoints, analysis will be performed in the same way as for change from baseline in IGA. However, change from baseline until Day 7 of IMP administration in VRS for pruritus will be calculated.<br>• Descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) of plasma concentration of OPA-15406 by treatment group and by timepoint will be calculated.<br>• Descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) of plasma concentration of OPA-15406 by treatment group and by timepoint adjusted by affected area (%) per total BSA at baseline examination will be calculated.<br>• Descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) of plasma concentration of OPA-15406 by treatment group, by timepoint, and by affected area (%) per total BSA at baseline examination (5% to <10%, ≥10% to <30%, ≥30%).<br>• Descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) of age, affected area at baseline (%), and amount applied (g) by affected area will be calculated. |
| Trial Duration: | Duration of the trial: Dec 2016 to Aug 2017<br>Screening period: 2-30 days<br>Assessment period: 4 weeks<br>Follow up period: 2 weeks |

# Table of Contents

# List of In-text Tables

# List of In-text Figures

# List of Appendices

# List of Abbreviations and Definitions of Terms

## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BSA | Body Surface Area |
| cAMP | Cyclic adenosine 3', 5'-monophosphate |
| CNS | Central nervous system |
| EASI | Eczema Area and Severity Index |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonization |
| IGA | Investigator's Global Assessment |
| IRB | Institutional review board |
| IRE | Immediately reportable event |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OC | Observed Cases |
| PDE | Phosphodiesterase |
| POEM | Patient-Oriented Eczema Measure |
| PQC | Product Quality Complaint |
| SAE | Serious adverse event |
| TEAE | Treatment-emergent adverse event |
| US | United States |
| VAS | Visual Analogue Scale |
| VRS | Verbal Rating Scale |

**Definitions of Terms**

| Term | Definition |
|---|---|
| Screen failure | A screen failure is a subject whose legal guardian has provided written informed consent, but to whom an investigational medicinal product will not be allocated. |
| Individual subject trial start date | The day of obtaining written informed consent from the subject's legal guardian. |
| Individual subject trial discontinuation date | The day of individual subject withdrawal from the trial before the Week 4 examination is the examination day 2 weeks after the last IMP administration. For those who have missed the examination 2 weeks after the last IMP administration, the day of withdrawal is the day the investigator or subinvestigator determined that the subject was to be withdrawn from the trial. |
| Individual subject trial completion date | For subjects who have undergone the Week 4 examination, the day of trial completion is the day of the examination 2 weeks after the last IMP administration. |
| Individual subject trial period | Period from the day of obtaining informed consent from the subject's legal guardian to the day of trial discontinuation or completion. Does not include the follow-up period. |

**List of Pharmacokinetic Parameters**

| Abbreviation and Term | Unit | Expansion or Definition |
|---|---|---|
| AUC | ng•h/mL | Area under the plasma concentration-time curve |
| $AUC_{8h}$ | ng•h/mL | Area under the plasma concentration-time curve from time zero to 8 hours |
| $AUC_{\infty}$ | ng•h/mL | Area under the plasma concentration-time curve from time zero to infinity |
| $C_{max}$ | ng/mL | Maximum plasma concentration of the drug |

# 1 Introduction

Atopic dermatitis (AD) is defined as "a disease with repeated exacerbations/remissions of which the main lesion is eczema with pruritus, and most patients have atopic predisposition. Atopic predisposition means (1) having a family history/medical history (one or more diseases of bronchial asthma, allergic rhinitis/conjunctivitis, or AD) or (2) predisposition to producing IgE antibody."[2] In some patients, atopic dermatitis that occurred in infancy may spontaneously resolve with age. Some patients experience the onset or recurrence of the disease in adulthood, namely, refractory AD in adults.

Diagnostic criteria for the disease were established by Hanifin and Rajka in 1980[1] and in Japan, Guidelines for Management of Atopic Dermatitis was published by the Japanese Dermatological Association.[2] The therapeutic strategies of AD are common in the world. The universally accepted concept of the disease is that AD is chronic eczema accompanied by physiological dysfunction of the skin and inflammation caused by multiple nonspecific stimuli or specific allergens.

Topical agents such as steroids and calcineurin inhibitors (immunosuppressors) are used for the treatment of inflammation, topical moisturizers and protective agents for skin care to treat abnormal physiological functions, and oral antihistamines and antiallergic agents for pruritus as adjuvant treatment. Elimination of as many aggravating factors as possible has been established by current consensus as a basic therapy for AD. Inflammation can generally be suppressed by topical steroids. However, long-term use of steroids may induce adverse drug reactions (eg, skin atrophy, hairiness); therefore, drugs with long-term safety have been anticipated.

Phosphodiesterase (PDE) 4 is an enzyme that hydrolyzes cyclic adenosine 3', 5'-monophosphate (cAMP) and exists in inflammatory cells, such as macrophages, lymphocytes, and neutrophils. In AD patients, elevated PDE activity in peripheral blood leukocytes and reduced intracellular cAMP levels are observed.[3] PDE4 inhibitors exert their antiinflammatory activity by increasing intracellular cAMP levels and suppressing production of inflammatory cytokines and chemical mediators. Therefore, PDE4 inhibitors have been considered effective for treatment of AD.

OPA-15406 is a PDE4 inhibitor synthesized by Otsuka Pharmaceutical Co., Ltd. In a mouse chronic contact hypersensitivity model, OPA-15406 ointment demonstrated its efficacy on dermatitis by improving the symptoms. Therefore, development of OPA-15406 ointment was started with the expectation of efficacy for AD.

Clinical development of OPA-15406 has preceded outside Japan, and the phase 2 trial in AD patients (aged 10 - 70 years old) has been completed. In Japan, the phase 1 trial in healthy adult male subjects has been completed, and the phase 2 trial in adult AD patients (aged 15 - 70 years old) is ongoing. In healthy adult subjects and AD patients (phase 1 and phase 2 trials outside Japan), OPA-15406 ointment showed no clinical relevant safety issues but good tolerability. Also, in the phase 2 trial outside Japan, 1% OPA-15406 ointment demonstrated the efficacy on AD.

As AD is common in children[4] and based on the above clinical trial results, the present trial is designed to evaluate the safety, efficacy, and pharmacokinetics of OPA-15406 ointment in pediatric AD patients (aged 2 - 14 years old).

## 1.1 Nonclinical Study Results

OPA-15406 had potent and selective PDE4 inhibitory actions, especially against PDE4B, and its 50% inhibitory concentration against PDE4B was 0.0112 μM.

Using a mouse chronic contact hypersensitivity model as an animal model of AD, the dose-dependent efficacy of the OPA-15406 ointment (0.03% to 3%) for chronic allergic dermatitis was assessed. Four weeks of topical administration of the OPA-15406 ointment showed dose-dependent efficacy in improving skin thickening at 0.03% to 3%. The effect was inferior to that of betamethasone valerate, a strong steroid, and superior to that of tacrolimus ointment, a calcineurin inhibitor. Four weeks of multiple administrations of 3% OPA-15406 ointment significantly suppressed infiltration of inflammatory cells, such as CD3 positive cells, eosinophils, and neutrophils, in skin lesions.

Using a mouse scratching-induced chronic dermatitis model, the efficacy of OPA-15406 (1% and 3%) dissolved in a solvent (1:1 mixture of acetone and methanol) was assessed. Six weeks of topical administration of OPA-15406 (1% or 3%) significantly improved the skin symptoms, though no particular effect was observed on the frequency of scratching. The efficacy was superior to those of betamethasone valerate (0.1%) and tacrolimus (0.1%) dissolved in the solvent.

The efficacy of OPA-15406 ointment (3%) was assessed in a mouse acute contact hypersensitivity model. Single administration of the OPA-15406 ointment (3%) significantly suppressed edema. The efficacy was equivalent to betamethasone valerate (Rinderon®-V ointment 0.12%) and tacrolimus ointment (Protopic® ointment 0.1%).

OPA-15406 ointment (0.1%, 0.3%, 1%, and 3%) was administered percutaneously to rats at 0.3, 0.9, 3, or 9 mg/kg as a single-dose. $C_{max}$ and AUC of OPA-15406 increased dose-dependently at 0.3 to 3 mg/kg, and reached a plateau at 3 to 9 mg/kg. Single percutaneous administration of the OPA-15406 1% ointment at 3 mg/kg was performed for abraded skin of male rats. The $C_{max}$ and $AUC_{\infty}$ of OPA-15406 in the male rats with abraded skin were 2.0 and 1.6 times that in male rats with intact skin.

With percutaneous administration of $^{14}$C-OPA-15406 1% ointment in rats, the amount of detected OPA-15406 on the skin of the administration site was the largest, and the metabolites of MAP-15484, MAP-15485, and MAP-15497 were also detected. OPA-15406, MAP-15484, and MAP-15485 were detected in the plasma of the rats treated percutaneously and subcutaneously with $^{14}$C-OPA-15406 1% ointment.

In a 4-week repeated-dose percutaneous toxicity study in rats, white petrolatum, OPA-15406 ointment 0% (vehicle), 0.1% (1.06 mg/kg for male, 1.25 mg/kg for female), 0.3% (3.27 mg/kg for male, 3.78 mg/kg for female), 1% (11.02 mg/kg for male, 12.74 mg/kg for female), or 3% (33.56 mg/kg for male, 38.56 mg/kg for female) was administered to intact skin (open cutaneous) approximately equivalent to 10% of total body surface area (BSA) once daily. No changes associated with the test substance were observed at the administration sites in any treatment groups. Body weight and/or food consumption were reduced in the male rats treated with 1% and 3% ointments, and in female rats treated with 0.1%, 0.3%, and 1% ointments. These changes were reversible or likely to be reversible during the 4-week recovery period. In a 13-week repeated-dose percutaneous toxicity study in rats, white petrolatum, OPA-15406 ointment 0% (vehicle), 0.1% (0.31 mg/kg for male, 0.38 mg/kg for female), 0.3% (0.92 mg/kg for male, 1.13 mg/kg for female), 1% (3.08 mg/kg for male, 3.75 mg/kg for female), or 3% (9.39 mg/kg for male, 11.47 mg/kg for female) was administered to intact skin (open cutaneous) approximately equivalent to 3% of total BSA once daily. No changes associated with the test substance were observed at the administration sites in any treatment groups. Increase in body weight was suppressed in the male and female rats treated with the 3% ointment. The no observed adverse effect dose level of systemic toxicity was estimated to be 1% ointment (3.08 mg/kg) for males and 1% ointment (3.75 mg/kg) for females.

In a 4-week repeated-dose percutaneous toxicity study in rabbits, white petrolatum, OPA-15406 ointment 0% (vehicle), 0.1%, 0.3%, 1%, or 3% was administered to intact skin (open cutaneous) approximately equivalent to 10% of total BSA once daily. The OPA-

15406 ointment was classified as weak skin irritation at all concentrations according to the Draize scale for skin irritation.

In an 8-week repeated-dose percutaneous toxicity study in juvenile rats (25 days old at the start of administration), white petrolatum 0% (vehicle), OPA-15406 ointment 0.3% (male: 3.76 mg/kg, female: 4.23 mg/kg), 1% (male: 12.56 mg/kg, female: 14.32 mg/kg), or 3% (male: 38.52 mg/kg, female: 43.83 mg/kg) was administered once daily to intact skin (open cutaneous) approximately equivalent to 10% of total BSA. As a result, no changes associated with the test substance were observed on the administration sites in any of the treatment groups. Although suppressed weight increase and reductions in food intake and grip strength were observed in female rats with 1% or 3% ointment, these changes were not developmental toxicity and they resolved with washout. Also, there was no difference in the toxicity threshold between adult and juvenile rats. As the profile of OPA-15406 is such that it reaches the central nervous system (CNS)and the brain is known to develop after birth, a 10-week repeated-dose percutaneous toxicity study was conducted in neonatal rats (4 days old at the start of administration) with a focus on CNS development, but no influence of OPA-15406 on the function or structure of the CNS was found.

## 1.2 Clinical Study Results

Clinical development of OPA-15406 has preceded outside Japan, and the phase 2 trial in AD patients has been completed. In Japan, the phase 1 trial in healthy adult male subjects has been completed.

### 1.2.1 Phase 1 Trial in Healthy Adult Subjects in the United States (271-11-202)

In the phase 1 trial in healthy adult subjects (aged 18 - 64 years old) in the United States (US), side-by-side comparison was performed on the back of the subject using the vehicle of OPA-15406 ointment (placebo) as the control. The dose was escalated from 0.1% to 0.3%, 1%, and 3% (8 subjects for each group). The amount of administration was 0.5 g, and the treatment area was 10 $cm^2$ in single or 2-week once daily multiple administration. The plasma concentrations of OPA-15406 and its metabolites were all below the lower limit of quantification (0.2 ng/mL) at all doses. No serious adverse events were reported, and no subjects were withdrawn from the trial due to adverse events.

### 1.2.2 Phase 1 Trial in Healthy Adult Male Subjects in Japan (271-14-001)

In the phase 1 trial in healthy adult male subjects (aged 20 - 40 years old) in Japan, a single administration or 2-week twice-daily multiple administrations of OPA-15406 ointment 0.3%, 1%, or 3% formulation (8 subjects for each group) were given to a 1,000 $cm^2$ area (about 5% of BSA) on the back of the subject at 5 g per dose, using the vehicle of OPA-15406 ointment (placebo) as the control, to investigate the safety and pharmacokinetics in Japanese subjects. In the 0.3%, 1%, and 3% OPA-15406 groups, the mean $C_{max}$ was 0.508, 0.838, and 1.61 ng/mL, respectively, after the single-dose, and it was 0.506, 0.795, and 1.65 ng/mL, respectively, after the multiple doses. The $C_{max}$ increased with dose after both the single and multiple administrations; however, the level of increase was lower than the dose ratio, and no dose-proportional increase was observed. In all multiple-dose groups, the plasma concentrations of OPA-15406 and all metabolites in plasma are considered to have reached an almost steady state on Day 7. In both the OPA-15406 group and the vehicle group, no adverse events were reported, and no subjects were withdrawn from the trial. In physical findings and subjective symptoms, vital signs, skin findings, standard 12-lead ECG, and clinical laboratory tests, no clinically relevant variations or changes were observed. Also, no particular concerns were reported regarding the safety of OPA-15406 ointment up to concentrations of 3%.

### 1.2.3 Phase 1 Trial in Atopic Dermatitis Patients in the United States (271-12-204)

In the phase 1 trial in AD patients (aged 18 - 64 years old) in the US, 1 g of the 0.3%, 1%, or 3% formulation of OPA-15406 ointment (15 subjects for each group) was administered to 5% of BSA (about 1,000 $cm^2$) as 4-week twice daily multiple administrations, using the vehicle of OPA-15406 ointment (placebo) as the control. Then, OPA-15406 ointment 1% formulation (7 subjects), OPA-15406 ointment 3% formulation (8 subjects), or 0.1% tacrolimus ointment (15 subjects) was administered to 10% or more of affected BSA at 1 g per 5% of BSA as 4-week twice daily multiple administrations.

The mean $C_{max}$ of the plasma OPA-15406 concentration after administration of OPA-15406 ointment 1% and 3% formulations to 10% or more of affected BSA as 4-week twice daily multiple administrations was 12.9 and 22.3 ng/mL, respectively, and the mean $AUC_{8h}$ was 73.5 and 115 ng•h/mL, respectively.

For safety, 1 case of the serious adverse event of cholelithiasis occurred in the 1% OPA-15406 group, but its causal relationship with the investigational medicinal product (IMP)

was ruled out. Two subjects discontinued treatment with the IMP due to adverse events; one of the subjects was in the 3% OPA-15406 group (name of adverse event: hypersensitivity), and the other was in the 0.1% tacrolimus group (name of adverse event: dermatitis allergic). Both events were judged to be IMP-related.

For efficacy, the rate of subjects whose Investigator's Global Assessment (IGA) score improved to 0 or 1 at Week 4 after twice daily administrations of IMP to 5% of BSA was 53.3%, 66.7%, 40.0%, and 26.7% in the 0.3%, 1%, and 3% OPA-15406 groups and the vehicle group, respectively. Also, the rate of subjects whose IGA score improved to 0 or 1 at Week 4 after twice daily administrations of IMP to 10% or more of BSA was 57.1%, 14.3%, and 57.1% in the 1% and 3% OPA-15406 groups and the 0.1% tacrolimus group, respectively. Among all subjects, the rate of an Investigator's Global Assessment (IGA) score that improved to 0 or 1 at Week 4 was 53.3%, 63.6%, 31.8%, 26.7%, and 53.3% in the 0.3%, 1%, and 3% OPA-15406 groups, the vehicle group, and the 0.1% tacrolimus group, respectively, which suggested the efficacy of the OPA-15406 ointment 0.3% and 1% formulations for AD. The reason why the efficacy of the 3% formulation of OPA-15406 ointment was not demonstrated has not been clarified.

### 1.2.4 Phase 2 Trial in Atopic Dermatitis Patients Outside Japan (271-12-205)

In the phase 2 trial in AD patients (aged 10 - 70 years old) outside Japan, the efficacy, safety, and pharmacokinetics of an 8-week twice-daily multiple administrations of OPA-15406 ointment were investigated by selecting 0.3% and 1% formulations (40 subjects for each group) for which the efficacy was suggested in the phase 1 trial in the US, using the vehicle of OPA-15406 ointment (placebo) as the control. The primary efficacy endpoint was established as the incidence of success in IGA (rate of subjects with an IGA score of 0 or 1 with an improvement by at least 2 grades) at Week 4. The incidence of success in IGA was 14.63%, 20.93%, and 2.70% in the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group, respectively. The 0.3% OPA-15406 group showed a higher incidence of success in IGA than the vehicle group; however, no significant difference was observed between the groups ($p = 0.0690$, CMH test). In the 1% OPA-15406 group, a significant difference was observed in the incidence of success in IGA compared to the vehicle group ($p = 0.0165$, CMH test). Discontinuations due to adverse events occurred with 4 subjects (9.8%), 3 subjects (7.0%), and 7 subjects (18.9%) in the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group, respectively. In the 0.3% OPA-15406 group, erythema and pruritus that occurred in 1 subject were judged as IMP-related, and cellulitis, dermatitis atopic, and multiple

sclerosis that occurred in 1 subject each were judged as not IMP-related. In the 1% OPA-15406 group, dermatitis atopic in 2 subjects and giardiasis in 1 subject were reported; however, all of these events were judged as not IMP-related. In the vehicle group, dermatitis atopic and application site irritation in 1 subject each were judged as IMP-related, and dermatitis atopic in 2 subjects and pruritus, papule, and excoriation in 1 subject each were judged as not IMP-related. Serious adverse events were reported as liver function test abnormal and multiple sclerosis in 1 subject each in the 0.3% OPA-15406 group and giardiasis and depression in 1 subject each in the 1% OPA-15406 group; however, all of these events were determined as not IMP-related. In the results of clinical laboratory tests, vital signs, and 12-lead ECG, no marked difference was observed among the 3 groups. The plasma OPA-15406 concentrations at 4 hours post-administration at Week 4 were 0.236 to 7.26 ng/mL in 5 subjects in the 0.3% OPA-15406 group and 0.469 to 1.22 ng/mL in 4 subjects in the 1% OPA-15406 group.

### 1.2.5 Trial for Phototoxicity in Healthy Adult Subjects in the United States (271-12-212)

In the trial for phototoxicity in 40 healthy adult subjects in the US, the phototoxicity was evaluated by a single administration of 0.3%, 1%, or 3% formulation of OPA-15406 ointment or the corresponding vehicle (placebo) on the back of the subject. At the treatment area, no adverse events were observed. Also, no serious adverse events were reported, and no subjects were withdrawn from the trial due to adverse events.

### 1.2.6 Trial for Photoallergy in Healthy Adult Subjects in the United States (271-12-213)

In the trial for photoallergy in 62 healthy adult subjects in the US, photoallergy was evaluated by multiple administrations of 0.3%, 1%, or 3% formulation of OPA-15406 ointment or the corresponding vehicle (placebo) on the back of the subject by establishing a 19-day sensitization period and a 5-day induction period. At the treatment area, erythema was observed in 1 subject as an adverse event, which was moderate in severity and determined as IMP-related. No serious adverse events were reported. One subject discontinued the trial due to the onset of an adverse event, pneumonia; however, a causal relationship with the IMP was ruled out.

## 1.3 Known and Potential Risks and Benefits

In the phase 1 trial in healthy adults in the US (271-11-202), the trial for phototoxicity in the US (271-12-212), the trial for photoallergy in the US (271-12-213), the phase 1 trial in healthy adult male subjects in Japan (271-14-001), the phase 1 trial in AD patients in

the US (271-12-204), and the phase 2 trial outside Japan (271-12-205), OPA-15406 was administered to 174 healthy adult subjects and 144 AD patients (including 16 patients aged 10 - 17 years old). The longest duration of dosing was 8 weeks.

Commonly reported adverse events in healthy adult subjects receiving OPA-15406 for 4 weeks were application site dermatitis in 26 subjects (14.9%), application site erosion in 13 subjects (7.5%), pruritus in 8 subjects (4.6%), erythema in 7 subjects (4.0%), application site pruritus in 6 subjects (3.4%), application site erythema in 4 subjects (2.3%), headache in 4 subjects (2.3%), abdominal pain in 2 subjects (1.1%), and nausea in 2 subjects (1.1%).

Commonly reported adverse events in AD patients receiving OPA-15406 for 4 or 8 weeks were dermatitis atopic in 19 subjects (13.2%), headache in 7 subjects (4.9%), upper respiratory tract infection in 6 subjects (4.2%), nasopharyngitis in 4 subjects (2.8%), diarrhoea in 3 subjects (2.1%), application site pain in 3 subjects (2.1%), urinary tract infection in 3 subjects (2.1%), pruritus in 3 subjects (2.1%), vomiting in 2 subjects (1.4%), chest discomfort in 2 subjects (1.4%), impetigo in 2 subjects (1.4%), sinusitis in 2 subjects (1.4%), and post inflammatory pigmentation change in 2 subjects (1.4%).

In 271-12-204, application site pain was reported using terms of “application site stinging (mild)” in 1 subject in the OPA-15406 3% group and “application site burning sensation (mild)” in 1 subject in the OPA-15406 1% group. In 271-12-205, application site pain was reported using the term “mild burning sensation after IMP administration (mild)” in 1 subject in the OPA-15406 0.3% group. Regardless of these symptoms, the subjects continued the treatment with OPA-15406 for 8 weeks which was the longest duration of treatment.

In AD patients treated with OPA-15406, 5 serious adverse events (cholelithiasis, giardiasis, liver function test abnormal, multiple sclerosis, and depression) were reported; however, all of these events were judged as not IMP-related by the investigator or the sponsor.

Of the adverse events judged as possibly related or definitely related to OPA-15406 in the overall trials, commonly reported events (in order of incidence) were dermatitis atopic (dermatitis atopic aggravated) (2.8%) and application site pain (2.1%). Other adverse events judged as possibly related or definitely related to OPA-15406 were 1 event (0.7%) each of erythema, pruritus, application site oedema, dry mouth, hypersensitivity, vulvovaginal mycotic infection, and sinusitis. All of these events were mild in severity. Due to the small number of subjects who were enrolled in this trial and included in the

analysis, further evaluation will be required for events that occurred only once and were judged as possibly related to IMP. Therefore, these events should be monitored in detail. The Investigator's Brochure includes other detailed information.

The benefits of participating in the trial include the fact that AD symptoms may improve, and that the subjects could receive more detailed tests and examinations by physicians than they could have with just general examinations. At present, no PDE4 inhibitors to indicate AD have been approved in and outside Japan.

# 2 Trial Rationale and Objectives

## 2.1 Trial Rationale

Based on preclinical study results, OPA-15406 is expected to be useful for the treatment of AD; therefore, Otsuka Pharmaceutical Co., Ltd. started development of OPA-15406 ointment from 2011 in the US aiming to obtain approval for the indication of "AD." After completion of the phase 1 trial in healthy adults in the US (271-11-202), the phase 1 trial in AD patients aged 18 to 64 years old was performed in the US (271-12-204) as a proof-of-concept trial. Then, the phase 2 trial in AD patients aged 10 to 70 years old was completed outside Japan (271-12-205) as a dose-finding trial. Currently, a pharmacokinetic trial in AD patients aged 2 to 9 years old has been planned in the US. In Japan, development started from 2014, and the phase 1 trial was performed in healthy adults in Japan (271-14-001). After safety had been demonstrated in healthy Japanese adult subjects, the phase 2 trial in adult AD patients aged 15 to 70 years old to evaluate the safety, efficacy, and pharmacokinetics (271-15-001), and this trial in pediatric AD patients aged 2 to 14 years old to evaluate the safety, efficacy, and pharmacokinetics have both been planned.

In both pediatric and adult patients with AD, abnormalities in the skin barrier function are observed, such as an increased loss of transepidermal water, a decreased content of natural moisturizing factors in the stratum corneum, and a decreased filaggrin content in the stratum corneum.[2,5,6] Also, in both pediatric and adult patients, AD is diagnosed based on symptoms of "pruritus," "characteristic rash and its distribution," and "chronic and repeated courses," with no particular difference being found in the pathological nature between pediatric and adult patients with AD.[7] Due to the reduced skin barrier function, AD patients have increased skin irritability against nonspecific stimulants than healthy people, which causes the development of inflammation.[2] Skin inflammation

results in a vicious cycle of further exacerbation of eczema by reduced skin barrier function, increased irritability, and stimulation by scratching. It has been reported that, within a year of birth, infants develop a similar skin barrier function to that of adults.[8,9,10,11] However, infants younger than 2 years old have an incomplete barrier function compared to adults due to physiological differences, such as transepidermal water loss and pH[12] and are likely to develop skin inflammation.[4]

As described above, the pathological conditions of AD do not generally differ depending on age, but infants are still likely to develop skin inflammation. According to the International Conference on Harmonisation (ICH)-E11 (Guidance on Clinical Investigation of Medicinal Products in the Pediatric Population), babies up to 23 months after birth are defined as infants and toddlers, and those aged 2 to 11 years old are defined as children.[13] Therefore, the lower age limit is established as 2 years old in this trial. In the package insert in Japan, children are usually defined as being of an age less than 15 years old. Therefore, in the phase 2 trial (271-15-001) in adult AD patients, the lower age limit was set as 15 years old, and in this trial in pediatric AD patients, the upper age limit has been set as 14 years old.

Prior to start of this trial, a toxicity study was performed using 25-day-old juvenile rats (corresponding to about 2 years old in humans).[14] White petrolatum, OPA-15406 ointment 0% (vehicle), 0.3%, 1%, or 3% was administered to intact skin (open cutaneous) approximately equivalent to 10% of total BSA once daily for 8 weeks in multiple administrations. As a result, no changes associated with the test substance were observed at the application sites in any of the treatment groups. For systemic symptoms, decreased body weight in females of the 1% group, and decreased body weight gain, reduced food consumption, reduced grip strength, and decreased thymus and spleen weights in females of the 3% group were observed; however, these changes resolved after washout. Also in adult animals, decreased body weight gain, reduced food consumption, and decreased thymus and spleen weights were observed, suggesting that these changes were not associated with developmental toxicity specific to juvenile rats. The no observed adverse effect dose level was 3.27 mg/kg/day for males and 1.25 mg/kg/day for females in adult rats (6 weeks old), and 38.52 mg/kg/day for males and 4.23 mg/kg/day for females in juvenile rats (25 days old), revealing that the threshold of toxicity did not decrease in juvenile animals.

In addition, it is known that the brain develops after birth, and that the profile of OPA-15406 is such that it reaches the CNS. Therefore, a 10-week repeated-dose percutaneous

toxicity study was conducted in neonatal rats (4 days old at the start of administration) with a focus on CNS development. No influence of OPA-15406 on the function or structure of the CNS was found.

Based on the clinical trial results obtained so far, the safety of OPA-15406 was discussed by dividing the OPA-15406 group into two age groups of adults ≥18 years old and juveniles including children from 10 to <18 years old. Table 2.1-1 shows the serious adverse events. In the adult population, serious adverse events were reported in 4 subjects in the 0.3% and 1% groups; however, its causal relationship with the IMP was ruled out. In the juvenile population, a serious adverse event was reported in 1 subject, and its causal relationship with the IMP was also ruled out. Table 2.1-2 shows the adverse events leading to treatment discontinuation. Adverse events leading to treatment discontinuation are reported in 6 subjects in the 0.3% and 1% groups in the adult population, and 2 subjects in the juvenile population. Table 2.1-3 shows adverse events occurred in at least 2 subjects in either group. The incidence of dermatitis atopic was slightly higher in juvenile subjects of the 0.3% group. Table 2.1-4 presents adverse events possibly related to the IMP. These results showed no marked difference in the incidence between the groups. Based on the above findings, none of the adverse events was specific to the juvenile subjects, and no particular concerns were raised over safety.

Also, efficacy was demonstrated in both the phase 1 trial in AD patients aged 18 to 64 years old in the US (271-12-204) and the phase 2 trial in AD patients aged 10 to 70 years old outside Japan (271-12-205).

**Table 2.1-1 Serious Adverse Events Reported in the OPA-15406 Group in the Clinical Trials in AD Patients**

| | Adult subjects (≥18 years old) | | | Juvenile subjects (10 to <18 years old) | |
|---|---|---|---|---|---|
| System organ class Preferred term | 0.3% (N=49) n (%) | 1% (N=56) n (%) | 3% (N=23) n (%) | 0.3% (N=7) n (%) | 1% (N=9) n (%) |
| Total | 2 (4.1) | 2 (3.6) | 0 (0.0) | 0 (0.0) | 1 (11.1) |
| Hepatobiliary disorders | | | | | |
| Cholelithiasis | 0 (0.0) | 1 (1.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Infections and infestations | | | | | |
| Giardiasis | 0 (0.0) | 1 (1.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Investigations | | | | | |
| Liver function test abnormal | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Nervous system disorders | | | | | |
| Multiple sclerosis[a] | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Psychiatric disorders | | | | | |
| Depression[b] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (11.1) |

The trial results of 271-12-204 and 271-12-205 are combined.
[a]Reported as newly developed multiple sclerosis.
[b]Reported as aggravation of depression.

**Table 2.1-2 Adverse Events Leading to Treatment Discontinuation in the OPA-15406 Group in the Clinical Trials in AD Patients**

| | Adult subjects (≥18 years old) | | | Juvenile subjects (10 to <18 years old) | |
|---|---|---|---|---|---|
| System organ class Preferred term | 0.3% (N=49) n (%) | 1% (N=56) n (%) | 3% (N=23) n (%) | 0.3% (N=7) n (%) | 1% (N=9) n (%) |
| Total | 3 (6.1) | 3 (5.4) | 1 (4.3) | 1 (14.3) | 1 (11.1) |
| Immune system disorders | | | | | |
| Hypersensitivity | 0 (0.0) | 0 (0.0) | 1 (4.3) | 0 (0.0) | 0 (0.0) |
| Infections and infestations | | | | | |
| Cellulitis | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Giardiasis | 0 (0.0) | 1 (1.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Nervous system disorders | | | | | |
| Multiple sclerosis[a] | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Psychiatric disorders | | | | | |
| Depression[b] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (11.1) |
| Skin and subcutaneous tissue disorders | | | | | |
| Dermatitis atopic | 0 (0.0) | 2 (3.6) | 0 (0.0) | 1 (14.3) | 0 (0.0) |
| Erythema | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pruritus | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

The trial results of 271-12-204 and 271-12-205 are combined.
[a]Reported as newly developed multiple sclerosis.
[b]Reported as aggravation of depression.

**Table 2.1-3 Adverse Events Occurred in at Least 2 Subjects in the Clinical Trials in AD Patients**

| | Adult subjects (≥18 years old) | | | Juvenile subjects (10 to <18 years old) | |
|---|---|---|---|---|---|
| System organ class<br>Preferred term | 0.3%<br>(N=49)<br>n (%) | 1%<br>(N=56)<br>n (%) | 3%<br>(N=23)<br>n (%) | 0.3%<br>(N=7)<br>n (%) | 1%<br>(N=9)<br>n (%) |
| Gastrointestinal disorders | | | | | |
| Dental caries | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Diarrhoea | 1 (2.0) | 2 (3.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Toothache | 0 (0.0) | 1 (1.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Vomiting | 0 (0.0) | 2 (3.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| General disorders and administration site conditions | | | | | |
| Application site pain | 1 (2.0)[a] | 1 (1.8)[b] | 1 (4.3)[c] | 0 (0.0) | 0 (0.0) |
| Chest discomfort | 0 (0.0) | 2 (3.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Infections and infestations | | | | | |
| Cellulitis | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Impetigo | 0 (0.0) | 2 (3.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Nasopharyngitis | 2 (4.1) | 1 (1.8) | 0 (0.0) | 1 (14.3) | 0 (0.0) |
| Sinusitis | 1 (2.0) | 1 (1.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Upper respiratory tract infection | 3 (6.1) | 1 (1.8) | 0 (0.0) | 2 (28.6) | 0 (0.0) |
| Urinary tract infection | 2 (4.1) | 0 (0.0) | 1 (4.3) | 0 (0.0) | 0 (0.0) |
| Nervous system disorders | | | | | |
| Headache | 2 (4.1) | 2 (3.6) | 1 (4.3) | 1 (14.3) | 1 (11.1) |
| Skin and subcutaneous tissue disorders | | | | | |
| Dermatitis atopic | 8 (16.3) | 6 (10.7) | 1 (4.3) | 3 (42.9) | 1 (11.1) |
| Erythema | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Post inflammatory pigmentation change | 1 (2.0) | 1 (1.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pruritus | 3 (6.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

The trial results of 271-12-204 and 271-12-205 are combined. Adverse events occurring in at least 2 subjects in the OPA-15406 group, or adverse events occurring in 1 subject in the OPA-15406 group and in at least 2 subjects in a combined group of the tacrolimus group or vehicle group are shown.

[a]Term used by the reporter: Mild burning sensation after IMP administration (mild)

[b]Term used by the reporter: Application site burning sensation (mild)

[c]Term used by the reporter: Application site stinging (mild)

**Table 2.1-4 Adverse Events Possibly Related to the Trial Treatment in the OPA-15406 Group in the Completed Trials of OPA-15406 in AD Patients**

| | Adult subjects (≥18 years old) | | | Juvenile subjects (10 to <18 years old) | |
|---|---|---|---|---|---|
| System organ class Preferred term | 0.3% (N=49) n (%) | 1% (N=56) n (%) | 3% (N=23) n (%) | 0.3% (N=7) n (%) | 1% (N=9) n (%) |
| Total | 4 (8.2) | 3 (5.4) | 4 (17.4) | 2 (28.6) | 0 (0.0) |
| Gastrointestinal disorders | | | | | |
| Dry mouth | 0 (0.0) | 0 (0.0) | 1 (4.3) | 0 (0.0) | 0 (0.0) |
| General disorders and administration site conditions | | | | | |
| Application site oedema | 0 (0.0) | 1 (1.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Application site pain | 1 (2.0)[a] | 1 (1.8)[b] | 1 (4.3)[c] | 0 (0.0) | 0 (0.0) |
| Immune system disorders | | | | | |
| Hypersensitivity | 0 (0.0) | 0 (0.0) | 1 (4.3) | 0 (0.0) | 0 (0.0) |
| Infections and infestations | | | | | |
| Sinusitis | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Vulvovaginal mycotic infection | 0 (0.0) | 1 (1.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Skin and subcutaneous tissue disorders | | | | | |
| Dermatitis atopic | 1 (2.0) | 0 (0.0) | 1 (4.3) | 2 (28.6) | 0 (0.0) |
| Erythema | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pruritus | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

The trial results of 271-12-204 and 271-12-205 are combined.
[a]Term used by the reporter: Mild burning sensation after IMP administration (mild)
[b]Term used by the reporter: Application site burning sensation (mild)
[c]Term used by the reporter: Application site stinging (mild)

Based on the above findings, it was judged scientifically and ethically appropriate to conduct this trial in order to evaluate the safety, efficacy, and pharmacokinetics of OPA-15406 in children aged 2 to 14 years old, in consideration of the standard age classification in ICH-E11 and the package insert, and that no particular concerns over safety in juvenile animals corresponding to newborns to 2-year-old human infants in the nonclinical studies, and no marked concerns over safety and suggested efficacy in the clinical trials in AD patients aged 10 to <18 years old including children were observed.

## 2.2 Dosing Rationale

Skin preparations are always exposed to opportunities of being removed after administration to the skin, such opportunities as washing the face, bathing, adhesion to clothing, or sweating resulting in dilution. To be sure that effective concentration on the

skin is maintained, it is desirable that the IMP be administered multiple times a day. In consideration of the fact that people generally wash their face and hands after getting up and when bathing at night, twice-daily administration is considered highly convenient for patients, and it may contribute to achieving the best adherence. Therefore, twice-daily administration is employed.

In the phase 1 trial in AD patients in the US (271-12-204), efficacy of OPA-15406 was suggested in the 0.3% and 1% formulations among the 0.3%, 1%, and 3% formulations tested. In the phase 2 trial in AD patients aged 10 years and older outside Japan (271-12-205), the efficacy of OPA-15406 was investigated by selecting the 0.3% and 1% formulations. The results showed that the 1% formulation had a significantly higher efficacy in the primary efficacy endpoint compared to the vehicle, and the 0.3% formulation also had a higher efficacy compared to the vehicle. Also, in adults and juveniles including children, no particular concerns were raised over safety in both the 0.3% and 1% formulations. Therefore, in the ongoing phase 2 trial in adult AD patients (aged 15 - 70 years old) in Japan, the same doses of 0.3% and 1% were selected as in the phase 2 trial outside Japan (271-12-205). Also in this trial, the same doses of 0.3% and 1% as in adults are selected in order to evaluate the safety and efficacy of OPA-15406 in pediatric AD patients (aged 2 - 14 years old) in Japan.

## 2.3 Severity Rationale

Atopic dermatitis is mainly treated with topical drugs. However, for severe patients, oral agents and ultraviolet therapy are often combined due to an inadequate response to topical drugs alone. Therefore, this trial is designed to include patients with an IGA score of 2 (mild) or 3 (moderate) whose symptoms are controllable only by topical drugs. In the phase 1 trial (271-12-204) and phase 2 trial (271-12-205) outside Japan, efficacy and safety were both demonstrated. Also in Japan, the phase 2 trial (271-15-001) is now ongoing to evaluate efficacy and safety in adult AD patients with an IGA score of 2 (mild) or 3 (moderate).

## 2.4 Trial Objectives

Primary objective: To evaluate the safety of 0.3% and 1% OPA-15406 ointments in pediatric patients with AD when administered twice daily for 4 weeks.

Secondary objective: To evaluate the efficacy (dose response) and pharmacokinetics of 0.3% and 1% OPA-15406 ointments in pediatric patients with AD when administered twice daily for 4 weeks.

# 3 Trial Design

## 3.1 Type/Design of Trial

This is a multicenter, randomized, double-blind, vehicle-controlled, parallel-group comparison trial to evaluate the safety, efficacy, and pharmacokinetics of OPA-15406 ointment in pediatric patients with AD. This trial consists of the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group. The trial design is shown in Figure 3.1-1.

(1) Screening period

After obtaining written informed consent from the subject's legal guardian (if possible, after also obtaining informed assent from the subject), the investigator or subinvestigator will perform a screening examination. The period between the day of the screening examination and the end of the baseline examination is defined as the screening period (2-30 days). The subjects who meet the inclusion criteria and do not meet any of the exclusion criteria at the baseline examination will shift to the assessment period and will be dynamically allocated to the test product (0.3% or 1% formulation of OPA-15406) or the vehicle (placebo).

(2) Assessment period (treatment period)

For subjects meeting the inclusion criteria and not meeting any of the exclusion criteria at the baseline examination, the period between the day of the starting baseline examination and the day of the Week 4 examination (or the day of discontinuation) is defined as the assessment period. The IMP will be administered to the treatment area from the day of the baseline examination twice daily for 4 weeks. After the baseline examination, the examination will be performed at Weeks 1, 2, and 4.

If a subject discontinues the IMP administration between the day of the baseline examination and the Week 4 examination, a withdrawal examination will be performed for that subject.

(3) Post-treatment observation period

The period from completion of the Week 4 examination to the day of the examination 2 weeks after the last IMP administration is defined as the post-treatment observation period. Examinations will be performed at 2 weeks after the last IMP administration. If any adverse event remained not recovered at the examination 2 weeks after the last IMP administration (or by the day of the last examination if the examination 2 weeks after the last IMP administration was not performed), it should be followed up according to the specifications.

(4) Trial period

The trial period for individual subjects is from the day of obtaining informed consent from the subject's legal guardian to the day of trial discontinuation or completion and does not include the follow-up period.

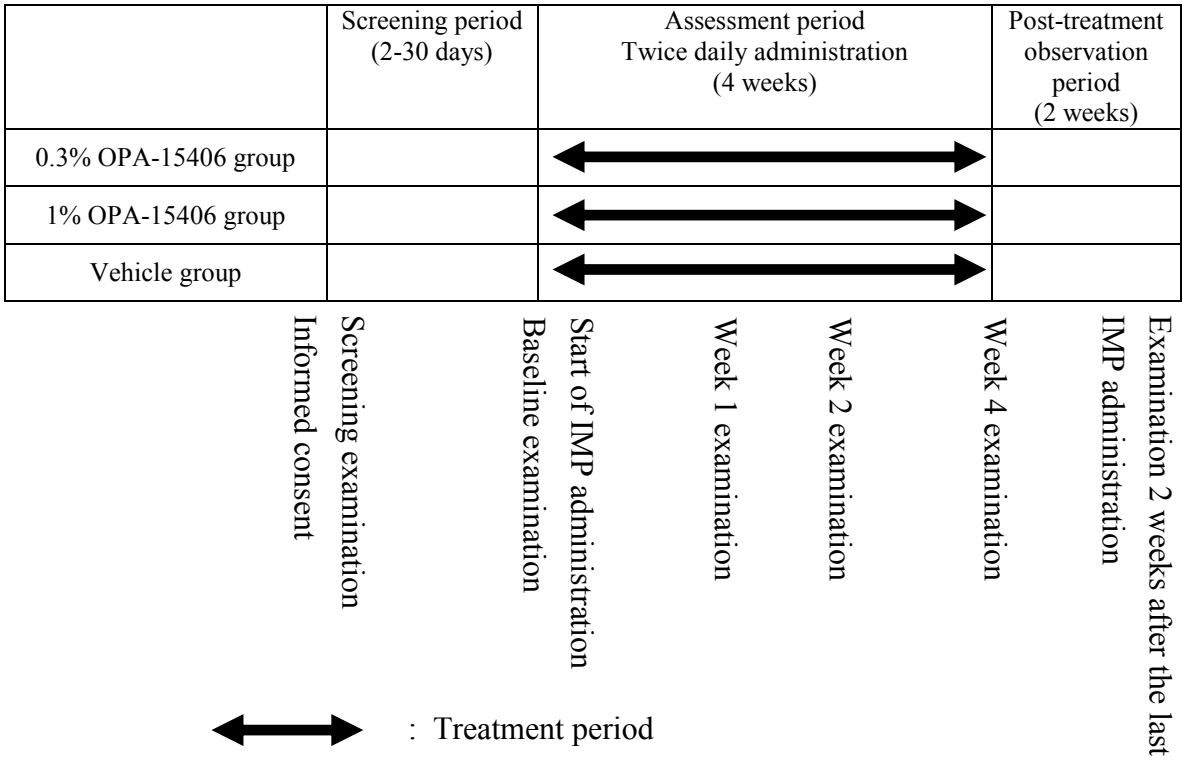


**Figure 3.1-1 Trial Design Schematic**

## 3.2 Methods of Administration

### 3.2.1 Dose, Regimen, and Treatment Period

The 0.3% or 1% formulation or the vehicle of OPA-15406 ointment will be administered twice daily (approximately 12 hours apart between morning and night administration) for 4 weeks. The amount of IMP (g) per dose is calculated as follows.

1) The subject's BSA ($m^2$) will be calculated based on height and body weight at the screening examination, using the following equation.

$$BSA\ (m^2) = \sqrt{\frac{Ht\ (cm) \times Wt\ (kg)}{3600}}$$

BSA = body surface area;
Ht = height; Wt = body weight

(Mosteller 1987)[15]

2) The treatment area will be specified (see "3.2.2 Treatment Area").
3) The amount of IMP (g) per dose will be calculated as "subject's BSA ($m^2$)" × "treatment area (%)" × "10 g/$m^2$."
   Example: In case of a BSA of 0.7 $m^2$ and an affected BSA of 32%: 0.7 $m^2$ × 0.32 × 10 g/$m^2$ = 2.24 g

[Rationale for treatment period]

The Guidelines for Management of Atopic Dermatitis specify that "Patients should be evaluated for treatment effects about once every 1 to 2 weeks, especially to maximize the drug effects and to minimize any adverse drug reaction, and if necessary, the drugs and treatment methods should be adjusted. If no particular improvements are observed, or if any abnormal change is detected in the symptoms during about a month of remission induction therapy, referral of the patient to a more specialized institution may be considered."[4] In consideration of this standard AD treatment policy, the treatment period of this trial is established as 4 weeks. In the phase 2 trial outside Japan (271-12-205), while no significant difference was observed the incidence of success in IGA (rate of subjects with an IGA score of 0 or 1 with an improvement by at least 2 grades) at Week 4, which was the primary efficacy endpoint between the 0.3% OPA-15406 group and the vehicle group ($p = 0.0690$, CMH test), the 1% OPA-15406 group showed a significantly higher incidence of success in IGA compared to the vehicle group ($p = 0.0165$, CMH test), and no particular concerns were raised over safety up to Week 8.

### 3.2.2 Treatment Area

The treatment area with the IMP is defined as follows.

- The treatment area selected at baseline examination will be affected area determined at baseline examination (see "3.7.4.6 Affected BSA").
- After the baseline examination, when the affected area has expanded or a new affected area is detected, the expanded or newly affected area will also be included in the treatment area.
- Even when the affected area is relieved, the IMP administration should be continued there as the treatment area.

The investigator or subinvestigator will instruct the subject regarding the method of administration by specifying the treatment area (%) and the amount of administration (g) for each treatment area using the human body drawing (Appendix 4 for children aged 8 to 14 years old and Appendix 5 for children aged 2 to 7 years old), and will give the human body drawing (copy) to the subject or the subject's legal guardian. The investigator or subinvestigator will record the treatment area (%) of the 4 body regions (face, neck, and head; upper limbs; trunk; and lower limbs) in the source document and case report form (CRF).

The method of IMP administration is specified in the separate procedure for IMP administration.

## 3.3 Trial Population

### 3.3.1 Number of Subjects and Description of Population

The target population of this trial is pediatric patients with AD with an IGA score of 2 (mild) or 3 (moderate). Subjects will be included in the trial to reach the target number of 60 subjects for IMP administration (at least 8 subjects aged 2 to 6 years old). Any withdrawals will not be supplemented.

### 3.3.2 Subject Selection and Numbering

For the subjects whose legal guardians have provided informed consent, the investigator or subinvestigator will assign the subject identification code and subject number (3 digit number of site ID + S + 5 digit serial number starting from 00001).

## 3.4 Eligibility Criteria

### 3.4.1 Informed Consent

Freely given written informed consent will be obtained from the subjects' legal guardians (guardians or legal representatives, as applicable by law) instead of the subjects. If possible, assent (consent not bound by the legal restrictions obtained from pediatric subjects) will be obtained from the subjects participating in the trial. A signed informed consent form will be retained as a document, and a signed assent form will also be retained as a document. The explanatory document, informed consent form, and assent form will be approved by the same institutional review board (IRB) responsible for approval of this protocol.

Each explanatory document and informed consent form should include the elements required by the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP)[16] and local regulatory requirements.

The investigator or subinvestigator may discuss the availability of the trial and the possibility for entry with a potential subject and subject's legal guardian before obtaining consent. However, written informed consent must be obtained from the subject's legal guardian prior to the initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medications.

The potential subject and subject's legal guardian can refuse to participate in or withdraw from the trial at any time without any justifiable reason. The refusal or withdrawal by the potential subject and subject's legal guardian will not affect any future treatments.

Once the appropriate essential information and a full explanation in layman's language appropriate for the potential subject's age have been provided by the investigator or subinvestigator, the IRB-approved informed consent form will be personally signed and dated by the subject's legal guardian and the person obtaining informed consent (investigator or subinvestigator). When assent is also obtained from the subject, the assent form will be personally signed and dated by the subject (if possible) and the person obtaining informed consent (investigator or subinvestigator), in the same manner. When a supplemental explanation is given by a clinical trial associate, the clinical trial associate will also sign and date the form. The subject's legal guardian will be given the explanatory document and copies of the signed informed consent form and assent form, and the originals will be kept by the investigator or subinvestigator.

If an amendment to the protocol substantially increases or alters the trial procedures, the subject's legal guardian may be asked for an additional consent and to again sign the form.

### 3.4.2 Inclusion Criteria

Subjects are required to meet the following inclusion criteria #1 through #5 in Table 3.4.2-1 at the screening examination, and #6 and #7 at the screening examination and the baseline examination.

| **Table 3.4.2-1 Inclusion Criteria** | |
|---|---|
| 1 | Sex: Either male or female |
| 2 | Hospitalization status: Outpatient |
| 3 | Age: 2 to 14 years, inclusive (at time of obtaining informed consent) |
| 4 | Diagnosis of AD based on the criteria of Hanifin and Rajka[1] (Appendix 1) |
| 5 | Subjects whose legal guardian is able to provide informed consent prior to participation in the trial |
| 6 | AD affecting ≥5% to ≤40% of BSA |
| 7 | IGA score of 2 (mild) or 3 (moderate) |

[Rationale for Inclusion Criteria]

1) AD occurs in both males and females.
2) Most patients to be included in this trial are outpatients.
3) The objective of this study is to evaluate the safety and efficacy of the OPA-15406 ointment in pediatric patients. In consideration of the standard age classification in ICH-E11 and the package insert, children aged 2 to 14 years old are selected. In the toxicity study in juvenile animals, suppressed weight increase and reductions in food intake and grip strength were observed in female rats with 1% or 3% ointment. However, these changes were not developmental toxicity specific to juvenile rats, and there was no difference in the toxicity threshold between adult and juvenile rats. In the phase 1 trial in Japanese healthy adult subjects (271-14-001) and in the phase 2 trial in patients aged 10 years and older outside Japan (271-12-205), no particular safety concerns were raised.
4) The criteria of Hanifin and Rajka have been most commonly used worldwide and have the same major diagnostic criteria as those of the Japanese Dermatological Association; therefore, the criteria can be used also in Japan without problems.
5) In consideration of ethical issues concerning patients who are minors.

6), 7) To appropriately evaluate the efficacy of the IMP on the target disease.

### 3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1 at the screening examination and the baseline examination.

| **Table 3.4.3-1** | **Exclusion Criteria** |
|---|---|
| 1 | Subjects who have an AD or contact dermatitis flare-up defined as a sudden intensification of AD, within 28 days prior to the baseline examination |
| 2 | Subjects who have a concurrent or history of skin disease other than AD (eg, acne, psoriasis, Netherton's syndrome, ichthyosis, graft versus host disease, etc) and who are judged inappropriate for assessment of AD in the present trial |
| 3 | Subjects who have an active viral skin infection (eg, herpes simplex, herpes zoster, chicken pox) or a clinical sign of any of these |
| 4 | Subjects who have a concurrent or history of malignancy |
| 5 | Subjects with a history of recurrent bacterial infection resulting in hospitalization or requiring intravenous antibiotic treatment |
| 6 | Subjects with a clinically significant complication or history of any of the following disorders that the investigator or subinvestigator judges would prevent safe conduct of the trial or impact efficacy assessments:<br>• Cardiac disease (eg, rheumatic fever or heart valve replacement)<br>• Endocrinologic disease (eg, severe or uncontrolled diabetes)<br>• Pulmonary disease<br>• Neurologic disease<br>• Psychiatric disease<br>• Hepatic disease (eg, hepatitis B, hepatitis C)<br>• Renal disease<br>• Hematologic disease<br>• Immunologic or immunocompromised disease (eg, lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome, carriers of human immunodeficiency virus [HIV] antibodies)<br>• Other major disease (eg, systemic fungal infection) or other severe uncontrolled condition (eg, drug or alcohol abuse) judged by the investigator or subinvestigator to pose a health risk to the subject or to have the potential to impact trial assessment |
| 7 | Based on the laboratory test results at the screening examination, subjects for whom it is deemed by the investigator or subinvestigator that the trial cannot be conducted safely. |
| 8 | Subjects who are judged by the investigator or subinvestigator to have a clinically significant electrocardiogram (ECG) findings at the screening examination. (For children aged 2 - 6 years old, a 12-lead ECG will be recorded, |

| Table 3.4.3-1 Exclusion Criteria | |
|---|---|
| | as much as possible.) |
| 9 | Subjects who are judged by the investigator or subinvestigator to have a clinically abnormal blood pressure or pulse rate at the screening examination |
| 10 | Subjects who are judged by the investigator or subinvestigator to be problematic in withdrawing blood |
| 11 | Subjects who are unable to stop using topical corticosteroids, topical immunomodulators, topical retinoids and topical antihistamine from 7 days prior to the baseline examination until the Week 4 examination. Low or medium potency corticosteroids in the Guidelines for Management of Atopic Dermatitis[2] may be used until 4 days prior to the baseline examination in the judgment of the investigator or subinvestigator for the gradual decrease in the screening period before stopping. |
| 12 | Subjects who are unable to stop using systemic corticosteroids, systemic immunomodulators, systemic antimetabolites, systemic retinoids, and biologics from 28 days prior to the baseline examination until the Week 4 examination. Intra-ocular, intra-nasal and intra-auricular or inhaled corticosteroids may be considered if, in the opinion of the investigator or subinvestigator, their use will not impact assessment of the affected area. |
| 13 | Subjects who are unable to stop treatment with ultraviolet A , narrowband ultraviolet B, and ultraviolet B from 28 days prior to the baseline examination until the Week 4 examination |
| 14 | Subjects who are unable to continue in the trial without changing the dosage and administration of systemic antihistamines, sodium cromogicate, tranilast, or suplatast tosilate from 7 days prior to the baseline examination until the Week 4 examination. Intra-ocular, intra-nasal, or inhalant formulations may be considered if, in the opinion of the investigator or subinvestigator, their use will not impact the assessment of the affected area. |
| 15 | Subjects with known hypersensitivity (including history) to any drugs (prescription, OTC, etc) or any ingredient of OPA-15406 ointment (eg, white petrolatum, mineral oil, paraffin, white wax, or propylene carbonate) |
| 16 | Subjects with known plans to receive any of the prohibited concomitant drugs or therapies during the trial period |
| 17 | Subjects who have used any other investigational drug within 4 months prior to the baseline examination or who are scheduled to participate in any other clinical trial during the trial period |
| 18 | Subjects who have never been treated with a prescription medication for AD or who are satisfied with their current AD treatment regimen |
| 19 | Female subjects aged 7 to 14 years old who are pregnant or suspected of being pregnant, or who cannot agree to abstain from any actions that have the possibility of resulting in pregnancy |
| 20 | Subjects who are judged by the investigator or subinvestigator to be inappropriate to participate in the trial for any other reason |

[Rationale for Exclusion Criteria]

1), 11)-13) Due to a possible impact on the efficacy evaluation of the IMP.

2), 6), and 16) Due to a possible impact on the safety and efficacy evaluation of the IMP.

3)-5) In consideration of safety.

7)-10) In consideration of safety.

14) Due to a possible impact on the efficacy evaluation of the IMP and in consideration of safety.

15) In consideration of safety.

17) In reference to the "Criteria for Period to Avoid Participation in Clinical Studies" of the Japan Association of Contract Institutes for Clinical Pharmacology.

18) To exclude patients who are not in need of treatment and to prevent registering patients who are satisfied with their current treatment, because trials have aspects of research.

19) To prevent unknown consequences of the IMP in pregnant women, fetuses, or infants, and in consideration of safety.

20) To allow the investigator or subinvestigator to judge in consideration of other factors.

## 3.5 Endpoints

### 3.5.1 Primary Endpoint

The number and percentage of subjects experiencing AEs

[Rationale]

To properly evaluate the safety of OPA-15406.

### 3.5.2 Secondary Endpoints

IGA, Eczema Area and Severity Index (EASI), Visual Analogue Scale (VAS) for pruritus (only for patients aged 7 - 14 years old), Visual Rating Scale (VRS) for pruritus (only for patients aged 7 - 14 years old), Patient-Oriented Eczema Measure (POEM), and affected BSA

[Rationale]

IGA is selected because it is one of the reliable indicators to assess the severity of AD symptoms and to determine the efficacy of IMP. IGA is evaluated based on the severity of overall symptoms (eg, erythema, infiltration, papules, effusion, and scab formation) at administration sites and does not include other factors (eg, excoriation, lichenification, severity at each part, subjective symptoms, and affected BSA). For this reason, EASI, VAS for pruritus, VRS for pruritus, POEM, and affected BSA are also established to evaluate the efficacy from multiple points of view.

Plasma concentration of OPA-15406 (the trough concentration at Week 1 and Week 4)

[Rationale]

To determine the internal exposure to OPA-15406 in pediatric AD patients.

## 3.6 Measures to Minimize/Avoid Bias

This trial is a randomized, double-blind trial.

The IMP allocation manager will prepare a master "random allocation table" hereinafter, "randomization table") and conduct IMP coding according to the operating procedures for randomization. Also, the IMP allocation manager will prepare an emergency code list for use in emergencies such as the occurrence of a serious adverse event.

The investigator, subinvestigator, and subjects are blind to the IMP randomization code. Except for some designated personnel, the sponsor's trial staff, including the personnel of contract research organizations, are also unable to access the IMP randomization code during the trial period.

Prior to the trial start and unblinding, the IMP allocation manager will confirm that the IMPs are indistinguishable. The randomization table is sealed by the IMP allocation manager just after completion of IMP randomization and it is kept under strict control until unblinding after fixation of all CRFs and the database.

The emergency code list will be kept under strict control by the registration system until the end of the trial. If a medical emergency occurs in a subject and knowledge of his or her IMP randomization code is considered important for treatment, the emergency code will be broken according to the "5.7 Procedure for Breaking the Blind."

When IMPs are recovered by the sponsor prior to unblinding, they are to be recovered sealed by the IMP manager.

The subject will be allocated using the dynamic allocation method (minimization method). Details will be specified in a separate specification prepared in advance.

The results of drug concentration measurements will not be revealed until unblinding at the end of the trial.

## 3.7 Trial Procedures

The schedule of assessments is shown in Table 3.7-1. Items that clinical trial associates are capable of performing may be performed by the clinical trial associates under the supervision of the investigator.

**Table 3.7-1 Schedule of Assessments**

| Assessment | Screening period (2-30 days) | Assessment period (4 weeks) | | | | | Post-treatment observation period (2 weeks) |
|---|---|---|---|---|---|---|---|
| | Screening examination | Baseline examination | Week 1 examination[a] (± 2 days) | Week 2 examination[b] (± 3 days) | Week 4 examination[b] (± 3 days) Withdrawal examination[d] | Unscheduled visit | Examination 2 weeks after the last IMP administration[c] (± 7 days) |
| Informed consent | ○ | | | | | | |
| Inclusion/exclusion criteria | ○ | ○ | | | | | |
| Subject demographics | ○ | | | | | | |
| Physical findings | ○ | ○ | ○ | ○ | ○ | ○[e] | ○ |
| Vital signs (including body weight) | ○ | ○ | ○ | ○ | ○ | ○[e] | |
| 12-lead ECG[f] | ○ | | | | ○ | ○[e] | |
| Clinical laboratory tests | ○ | | | | ○ | ○[e] | |
| Pregnancy test[g] | ○ | | | | ○ | ○[e] | |
| IGA | ○ | ○ | ○ | ○ | ○ | | |
| EASI | | ○ | ○ | ○ | ○ | | |
| VAS for pruritus[h] | | ○ | ○ | ○ | ○ | | |
| VRS for pruritus[h] | | ○[i] ← | → ○ | | | | |
| POEM | | ○ | ○ | ○ | ○ | | |
| Affected BSA | ○ | ○ | ○ | ○ | ○ | ○ | |
| Treatment area | | ○ | ○ | ○ | | ○ | |
| Blood sampling for plasma drug concentration measurement | | | ○[j] | | ○[k] | | |
| Administration diary | | ○[l] ← | | | → ○ | | |
| Severity of AD | | ○ | | | | | |
| Status of IMP Administration | | | ○ | ○ | ○ | | |
| Prescription and return of IMP | | ○[m] | ○[n] | ○ | ○[o] | ○[n] | |
| IMP administration | | ○[p] ← | | | | → | |

**Table 3.7-1 Schedule of Assessments, Continued**

| Assessment | Screening period (2-30 days) | Assessment period (4 weeks) | | | | | Post-treatment observation period (2 weeks) |
|---|---|---|---|---|---|---|---|
| | Screening examination | Baseline examination | Week 1 examination[a] (± 2 days) | Week 2 examination[b] (± 3 days) | Week 4 examination[b] (± 3 days) Withdrawal examination[d] | Unscheduled visit | Examination 2 weeks after the last IMP administration[c] (± 7 days) |
| Adverse events | ← | ← | ← | ← | ← | ← | ← |
| Concomitant medications and therapies | ← | ← | ← | ← | ← | ← | |
| Patch test[q] | | ← | ← | ← | ← | ← | ← |

IGA = Investigator's Global Assessment; EASI = Eczema Area and Severity Index; VAS = Visual Analogue Scale; VRS = Verbal Rating Scale; POEM = Patient-Oriented Eczema Measure

[a]Allowable window of ± 2 days

[b]Allowable window of ± 3 days

[c]Allowable window of ± 7 days

[d]Withdrawal examination should be conducted, as much as possible.

[e]The evaluations can be conducted, as necessary.

[f]For children aged 2-6 years old, should be conducted as much as possible. If possible, it will be conducted prior to blood sampling.

[g]Only for female children aged 7 to 14 years old.

[h]Only for children aged 7 to 14 years old.

[i]Should be evaluated during the baseline examination, 4 ± 2 hours, 8 ± 2 hours (if possible), and 12 ± 2 hours (if possible) after the first IMP administration, and then twice daily from the next day (before IMP administration in the morning and at night) until the morning of the Week 1 examination (without IMP administration) (up to the morning of Day 7 at the latest).

[j]On the day of blood sampling, the first IMP application should be after blood sampling at the trial site.

[k]On the day of examination, the IMP should not be applied.

[l]Subjects should keep a diary every day from the baseline examination to the Week 4 examination (withdrawal examination).

[m]Only IMP prescription

[n]IMP will be additionally prescribed, as necessary.

[o]Only IMP collection

[p]After completing all evaluations on the day of the baseline examination, IMP administration will be started at the trial site, and date and time of the application will be recorded.

[q]If any adverse event of suspected hypersensitivity occurred at the treatment area, verbal consent should be obtained again from the subject to conduct a patch test, and the patch test should be conducted according to the procedure.

### 3.7.1 Schedule of Assessments

#### 3.7.1.1 Screening Examination (From the Day of Obtaining Informed Consent to 2 Days Prior to the Baseline Examination)

After acquisition of written informed consent from the subject's legal guardian, the investigator or subinvestigator will assign a subject identification code and subject number (3 digit number of site ID + S + 5 digit serial number starting from 00001).

The investigator or subinvestigator will perform the following examinations, observations, and evaluations and select subjects who meet the inclusion criteria and do not meet any of the exclusion criteria.

- Subject demographics
- Physical examination
- Vital signs (including body weight)
- 12-lead ECG (For children aged 2 - 6 years old, as much as possible. If possible, it will be conducted prior to blood sampling.)
- Clinical laboratory tests
- Pregnancy test (only for female children aged 7 - 14 years old)
- IGA
- Affected BSA
- Adverse events
- Concomitant medications and therapies

The investigator or subinvestigator will record the results of the eligibility of subjects on the list of screened subjects and the list of enrolled subjects.

##### 3.7.1.1.1 Subject Demographics

The investigator or subinvestigator will assess or measure the following items and record them in the source document and CRF.

- Date of informed consent
- Sex
- Date of birth
- Height (Measured as an integer value in unit of centimeter. When it is measurable to one decimal place, the value is rounded to an integer value.)
- Complications
- Date of onset of AD
- Medical history (within 6 months prior to the date of informed consent)

- In- or outpatient status (outpatient)
- Subject number
- Country where the trial is conducted (Japan)
- Race
- Ethnicity
- Possibility of pregnancy

#### 3.7.1.2 Subject Registration

The investigator or subinvestigator will register all subjects in the Interactive Web Response System (IWRS).

#### 3.7.1.3 Baseline Examination (2 - 30 Days After the Screening Examination)

The investigator or subinvestigator will perform the following examinations, observations, and evaluations, and record the results in the source document and CRF.

- Physical examination
- Vital signs (including body weight)
- IGA
- EASI
- VAS for pruritus (only for 7 - 14 years of age)
- VRS for pruritus (only for 7 - 14 years of age)
- POEM
- Affected BSA
- Severity of AD
- Adverse events
- Concomitant medications and therapies

For the clinical laboratory tests and 12-lead ECG, the results of the baseline examination will be used as data for the screening examination. The investigator or subinvestigator will select subjects who meet the inclusion criteria and do not meet any of the exclusion criteria based on results of the screening and baseline examinations. Also, the investigator or subinvestigator will record the results of the subjects' eligibility on the list of screened subjects and the list of enrolled subjects.

#### 3.7.1.4 Allocation of Investigational Medicinal Products to Subjects

The investigator or subinvestigator will enter the necessary information for subject's eligibility in the IWRS. On the day of the baseline examination, the subjects confirmed to be registered in the IWRS will be allocated to the 0.3% OPA-15406 group, the 1% OPA-15406 group, or the vehicle group. The investigator or subinvestigator will confirm the allocation result and the drug code of IMP to be prescribed for 2 weeks on the IWRS screen displaying the registration result and prescribe the IMP. The weight of the dispensed IMP will be measured (to one decimal place in unit of gram). (Hereinafter, when the weight of IMP is measured, it will be measured to one decimal place in the same manner.) After completion of all evaluations on the day of baseline examination, the first application of IMP will be given at the trial site, and date and time of the application will be recorded. The subjects will be instructed to visit the trial site without morning IMP administration on the day of the next visit.

#### 3.7.1.5 Between the Day of Baseline Examination and the Day of Week 1 Examination

The investigator or subinvestigator will instruct the subject to evaluate the following item at 4 ± 2 hours, 8 ± 2 hours (if possible), 12 ± 2 hours (if possible) after the first IMP administration on the day of baseline examination, and then twice daily from the next day (before IMP administration in the morning and at night) up to the morning of Week 1 examination (before administration) (up to the morning of Day 7 at the latest).

- VRS for pruritus (only for 7 - 14 years of age)

#### 3.7.1.6 Week 1 Examination (±2 Days)

The investigator or subinvestigator will perform the following examinations, observations, and evaluations and record the results in the source document and CRF.

- Physical examination
- Vital signs (including body weight)
- IGA
- EASI
- VAS for pruritus (only for 7 - 14 years of age)
- POEM
- Affected BSA
- Blood sampling for plasma drug concentration measurement
- Adverse events

- Concomitant medications and therapies
- Status of IMP Administration

The investigator or subinvestigator will determine the treatment area (%) and enter it in the IWRS. Also, the investigator or subinvestigator will confirm the subject's allocation status on the IWRS screen and, if necessary, prescribe additional IMP. When the IMP is additionally prescribed, the weight of the dispensed IMP will be measured.

#### 3.7.1.7 Week 2 Examination (±3 Days)

The investigator or subinvestigator will perform the following examinations, observations, and evaluations and record the results in the source document and CRF.

- Physical examination
- Vital signs (including body weight)
- IGA
- EASI
- VAS for pruritus (only for 7 - 14 years of age)
- POEM
- Affected BSA
- Adverse events
- Concomitant medications and therapies
- Status of IMP Administration

The investigator or subinvestigator will collect the IMP and measure the weight of the collected IMP. The investigator or subinvestigator will determine the treatment area (%) and enter it in the IWRS. The investigator or subinvestigator will confirm the amount of IMP to be prescribed for the next 2 weeks and prescribe it. The weight of the dispensed IMP will be measured. The subjects will be instructed to visit the trial site without morning IMP administration on the day of the next visit.

#### 3.7.1.8 Week 4 Examination (±3 Days) or Withdrawal Examination

The investigator or subinvestigator will perform the following examinations, observations, and evaluations and record the results in the source document and CRF.

- Physical examination
- Vital signs (including body weight)
- 12-lead ECG (For children aged 2 - 6 years old, as much as possible. If possible, it will be conducted prior to blood sampling.)

- Clinical laboratory tests
- Pregnancy test (only for female children aged 7 - 14 years old)
- IGA
- EASI
- VAS for pruritus (only for 7 - 14 years of age)
- POEM
- Affected BSA
- Blood sampling for plasma drug concentration measurement
- Adverse events
- Concomitant medications and therapies
- Status of IMP Administration

The investigator or subinvestigator will collect the IMP and measure the weight of the collected IMP.

#### 3.7.1.9 Examination 2 Weeks After Last IMP Administration (±7 Days)

The investigator or subinvestigator will perform the following examinations, observations, and evaluations and record the results in the source document and CRF.

- Physical examination
- Adverse events

#### 3.7.1.10 Unscheduled Visits

The investigator or subinvestigator will instruct the subjects to visit the trial site if the area of affected BSA markedly enlarges. The investigator or subinvestigator will perform the following examinations, observations, and evaluations and record the results in the source document and CRF.

- Affected BSA
- Adverse events
- Concomitant medications and therapies

The followings can be evaluated, as necessary.

- Physical examination
- Vital signs (including body weight)
- 12-lead ECG
- Clinical laboratory tests

- Pregnancy test

The investigator or subinvestigator will determine the treatment area (%) and enter it in the IWRS. Also, the investigator or subinvestigator will confirm the subject's allocation status on the IWRS screen and, if necessary, prescribe additional IMP. When the IMP is additionally prescribed, the weight of dispensed IMP will be measured.

### 3.7.2 Status of IMP Administration

Details of the administration diary will be recorded in the CRF. If the frequency of compliance with IMP administration is less than 80%, the status of IMP administration is judged as poor. The investigator and subinvestigator will confirm the status of IMP administration based on records in the administration diary and instruct the subjects, as necessary.

### 3.7.3 Severity

The investigator or subinvestigator will determine the severity[7] (mild, moderate, severe, or very severe) and record the result in the source document and CRF.

| Definition | Severity |
|---|---|
| Just mild skin eruption regardless of the area | Mild |
| Skin eruption with severe inflammation on <10% of the BSA | Moderate |
| Skin eruption with severe inflammation on ≥10% to <30% of the BSA | Severe |
| Skin eruption with severe inflammation on ≥30% of the BSA | Very severe |

Mild skin eruption: lesions mainly consisting of mild erythema, dryness, or desquamation
Skin eruption with severe inflammation: lesions consisting of erythema, papules, erosion, infiltration, or lichenification

### 3.7.4 Efficacy Assessments

#### 3.7.4.1 Investigator's Global Assessment (IGA)

The investigator or subinvestigator will assess the skin symptoms using IGA.[17] The investigator or subinvestigator will score the severity (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe/very severe) of the overall symptoms of the treatment area (erythema, infiltration, papules, effusion, and scab formation). The result will be recorded in the source document and CRF. The same subject will be evaluated by the same physician, as much as possible.

| Symptom | Severity score |
|---|---|
| No inflammatory signs of AD | 0 = Clear |
| Just perceptible erythema and just perceptible papulation/infiltration | 1 = Almost clear |
| Mild erythema and mild papulation/infiltration | 2 = Mild |

| Symptom | Severity score |
|---|---|
| Moderate erythema and moderate papulation/infiltration | 3 = Moderate |
| Severe erythema and severe papulation/infiltration with oozing/crusting | 4 = Severe/very severe |

### 3.7.4.2 Eczema Area and Severity Index (EASI)

The investigator or subinvestigator will assess the skin symptoms using EASI.[18] The investigator or subinvestigator will score the severity (0-3 points) and affected BSA (%) based on the 4 symptoms (erythema, infiltration/papules, excoriation, and lichenification) on the 4 body regions (face, neck, and head; upper limbs; trunk; and lower limbs) and record the results in the source document and CRF. As shown in the table below, the score of each region will be calculated and totalized. The maximum EASI score is 72 points. The same subject will be evaluated by the same physician, as much as possible.

| Body region | Calculation of the score for each region |
|---|---|
| Face, neck, and head | (E＋I＋Ex＋L) × score of affected BSA ×0.1 (×0.2 for children aged 2-7 years old) |
| Upper limbs | (E＋I＋Ex＋L) × score of affected BSA ×0.2 |
| Trunk | (E＋I＋Ex＋L) × score of affected BSA ×0.3 |
| Lower limbs | (E＋I＋Ex＋L) × score of affected BSA ×0.4 (×0.3 for children aged 2-7 years old ) |

E = severity score of erythema; I = severity score of infiltration/papules; Ex = severity score of excoriation; L = severity score of lichenification
Severity score: clear = 0; slight = 0.5; mild = 1; mild-moderate = 1.5; moderate = 2; severe = 2.5; very severe = 3
Score of affected BSA (for each region): clear = 0; 1% to 9% = 1; 10% to 29% = 2; 30% to 49% = 3; 50% to 69% = 4; 70% to 89% = 5; 90% to 100% = 6

### 3.7.4.3 Visual Analogue Scale (VAS) for Pruritus

The investigator or subinvestigator will evaluate the level of pruritus based on VAS.[19] The subjects aged 7 to 14 years old will mark the point of pruritus intensity during the last 24 hours on the line of a 100-mm VAS sheet (Appendix 2) between the left end (no pruritus) and the right end (very severe pruritus). The investigator or subinvestigator will record the length from the left end to the mark (integer value with mm as unit) in the medical record and CRF. The VAS sheet will be kept as the source document. For subjects aged 2 to 6 years, this will not be evaluated.

### 3.7.4.4 Verbal Rating Scale (VRS) for Pruritus

The investigator or subinvestigator will evaluate the pruritus intensity based on VRS.[19] The subjects aged 7 to 14 years old will evaluate the pruritus intensity according to the following criteria. The subjects will record the level of pruritus and the time and date of evaluation in a pruritus diary.

0: None

1: Mild

2: Moderate

3: Severe

The investigator or subinvestigator will record details of the pruritus diary in the CRF. The pruritus diary will be kept as the source document. For subjects aged 2 to 6 years, this will not be evaluated.

#### 3.7.4.5 Patient-Oriented Eczema Measure (POEM)

The investigator or subinvestigator will evaluate eczema according to the POEM (Appendix 3).[20] The subjects will answer 7 questions about their eczema. If it is difficult for subjects to answer the questions, their parents will answer them instead. The investigator or subinvestigator will record the results in the source document and CRF. The total score of POEM is 28 points at the most.

#### 3.7.4.6 Affected BSA

The investigator or subinvestigator will draw the affected BSA (range of skin eruption at the time of examination) on the human body drawing (Appendix 4 for subjects aged 8 to 14 years old, or Appendix 5 for subjects aged 2 to 7 years old) to determine the affected areas (%) on the respective 4 body regions (face, neck, and head; upper limbs; trunk; and lower limbs). The respective affected areas (%) will be recorded in the source document and CRF. One palm of the subject corresponds to 1% BSA.

### 3.7.5 Safety Assessments

#### 3.7.5.1 Adverse Events

Refer to "5 Reporting of Adverse Events. "

#### 3.7.5.2 Clinical Laboratory Tests

The investigator or subinvestigator will perform clinical laboratory tests for the following items. Date of blood and urine sampling will be recorded on the source document and CRF.

- Hematology: differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), white blood cell count, red blood cell count, hemoglobin, hematocrit, platelets

- Serum chemistry: total cholesterol, total protein, albumin, blood urea nitrogen, creatinine, total bilirubin, AST (GOT), ALT (GPT), gamma glutamyl transpeptidase, lactic dehydrogenase, alkaline phosphatase, serum electrolytes (Ca, Na, K, Cl)
- Qualitative urinalysis: glucose, protein

The tests will be performed at the central laboratory. The investigator or subinvestigator will confirm the test results from the central laboratory, put the date and his or her printed name and personal seal or signature on the report from the clinical laboratory, and retain it for each subject as the source document. The central laboratory will send the test results to the sponsor (in the form of electronic data).

The total blood volume to be drawn for the clinical laboratory tests is about 10 mL during the trial period (about 5 mL each for the screening examination and for the Week 4 examination).

For female children aged 7 to 14 years old, a pregnancy test will be performed, and the result must be obtained prior to the IMP administration.

#### 3.7.5.3 Physical Examination

The investigator or subinvestigator will assess the subject's physical condition by interview, visual examination, auscultation, or palpation.

#### 3.7.5.4 Vital Signs (Including Body Weight)

After the subject has rested for 3 minutes or more in principle, body temperature (measured by 0.1°C in the armpit), blood pressure (systolic/diastolic), pulse rate, and body weight (measured to one decimal place in unit of kilogram) will be measured, and the results of measurement will be recorded in the source document and CRF.

#### 3.7.5.5 12-Lead ECG

After the subject has rested for 10 minutes or more in a supine position, 12-lead ECG will be recorded prior to blood sampling, as much as possible. Also, for subjects aged 2 to 6 years old, it will be conducted before blood sampling, if possible. For the ECG measurement, heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval will be measured, using a 12-lead electrocardiograph obtained from the central ECG reading facility. The measurement results will be analyzed at the central ECG reading facility. The investigator or subinvestigator will confirm the "12-lead ECG analysis report" from the central ECG reading facility, assess whether the ECG results are normal or abnormal, and record the time and date of the measurement, assessment result, and findings in the source document and CRF. Then, the investigator

or subinvestigator will put the confirmation date and his or her printed name and personal seal or signature on the "12-lead ECG analysis report" from the central ECG reading facility and retain it for each subject as the source document.

If IMP randomization is necessary before the results from the central ECG reading facility are available, the automated analysis results of the 12-lead electrocardiograph at baseline (same as the ECG data to be sent to the central ECG reading facility) may be used for judgment of subject's eligibility. In that case, the investigator or subinvestigator will put the confirmation date and his or her printed name, and personal seal or signature on the automated analysis results of the 12-lead electrocardiograph and retain it as the source document.

The central ECG reading facility will send the 12-lead ECG analysis results (in electronic data format) to the sponsor.

#### 3.7.5.6 Other Safety Assessments

Other safety assessments than the above have not been established.

### 3.7.6 Pharmacokinetic Assessments

The plasma concentration of OPA-15406 will be measured. For the vehicle group, it will not be measured. On the day of measurement, the subjects will visit the trial site without morning IMP administration.

#### 3.7.6.1 Blood Sampling Timepoints and the Rationale

Trough concentration at Week 1 and Week 4

It has been expected that AD patients with inflammation and a reduced skin barrier function will have higher absorption of the applied OPA-15406 through the skin into the blood than in those with healthy skin. Therefore, it is necessary to assess the internal exposure to OPA-15406 in pediatric AD patients. Assuming that skin inflammation improves during the course of IMP administration in relation to the number of days elapsed from the start of IMP administration, it is considered appropriate to determine the plasma OPA-15406 concentration at Week 1 when the subjects are expected to be exposed to OPA-15406 at the highest level during the trial observation period and at Week 4 to confirm the long-term exposure. In the phase 1 trial of OPA-15406 in healthy subjects (271-14-001), the plasma OPA-15406 concentrations reached an almost steady state on Day 7 after multiple administrations of OPA-15406.

#### 3.7.6.2 Methods of Blood Sampling and Processing

Sufficient caution should be taken for the parts of sterilization and site of blood sampling to avoid the blood samples from contamination with any IMP remnant on the skin surface. Approximately 2 mL of blood will be collected per dose from arm vein using vacuum blood collection tube (with heparin Na contained) and sufficiently mixed. The sample will be mixed by inversion and cooled in ice-water. Within 30 minutes of collection, the sample will be centrifuged at approximately 3000 rpm for 10 minutes. Then, the plasma will be promptly transferred to a polypropylene tube and stored frozen at –15°C or less. When a refrigerated centrifuge is available, the sample will be centrifuged at 4°C. For each subject, the time and date of the latest IMP administration and blood sampling will be recorded on the source document and CRF.

The total blood volume to be drawn for the pharmacokinetic evaluation is about 4 mL during the trial period (2 mL each at the Week 1 examination and the Week 4 examination).

#### 3.7.6.3 Sending Plasma Samples

The contract research organization for clinical laboratory tests will send the frozen samples packed in dry ice to the bioanalytical laboratory.

The plasma concentration of OPA-15406 will be determined at the bioanalytical laboratory by using the liquid chromatography with tandem mass spectrometry.
The bioanalytical laboratory will measure samples of the OPA-15406 group according to the randomization table. Residual plasma samples after measurement will be stored at −70°C or less by the bioanalytical laboratory until the sponsor allows their disposal. The sponsor will report the completion of measurement to the bioanalytical laboratory. The bioanalytical laboratory will submit the report on results of drug concentration measurement (copy) and the measurement results (electronic data) to the sponsor.

### 3.7.7 End of Trial

The “End of Trial” is defined as the Completion or Discontinuation Date entered in the Completion Status Form of the CRF for the last subject completing or withdrawing from the trial.

## 3.8 Stopping Rules, Withdrawal Criteria, and Procedures

### 3.8.1 Termination or Interruption of the Entire Trial

1) When the entire trial is to be terminated or interrupted by the sponsor, the sponsor will promptly provide the heads of all trial sites involved in the trial and the regulatory authority with written notification and a detailed written explanation of the reason for the termination or interruption of the trial.
2) When the investigator has received notification of termination or interruption of the entire trial by the sponsor from the head of the trial site, the investigator will obtain a detailed written explanation of the termination or interruption of the trial from the head of the trial site, promptly notify the trial subjects currently receiving IMP administration, and take necessary measures such as switching to appropriate alternative treatment(s).
3) When development of the IMP is terminated by the sponsor, the sponsor will promptly provide the heads and the investigators of all trial sites involved in the trial and the regulatory authority with written notification and a detailed written explanation of the reason for the termination of development.

### 3.8.2 Termination or Interruption of the Trial at Individual Trial Sites

1) In the event of termination or interruption of the trial, the investigator will promptly provide the head of the trial site with written notification and a written explanation of the details of the termination or interruption of the trial.
2) When the sponsor is informed by the head of a trial site that the investigator has terminated or interrupted the trial, the sponsor will obtain a detailed written explanation of the termination or interruption of the trial from the head of the trial site.

### 3.8.3 Individual Subject Discontinuation

Any subject may discontinue participation in the trial at any time without any medical disadvantage. The investigator or subinvestigator may withdraw a subject from the trial at any time if it is considered necessary for medical treatment of that subject.

#### 3.8.3.1 Treatment Discontinuation

After the start of IMP administration, the investigator or subinvestigator may discontinue IMP administration for many reasons. These reasons for discontinuation include a request from the subject who is not satisfied with IMP administration or occurrence of an adverse event, a condition requiring medication(s) or treatment(s) that has not been permitted, or some other condition that requires treatment to be discontinued at the discretion of the investigator or subinvestigator. Under all circumstances, each

investigator or subinvestigator must confirm details of such circumstances and provides the subject with all possible choices to continue with the IMP administration according to "3.8.3.4 Procedures to Encourage Continued Trial Participation."

In any of the events listed below, the investigator or subinvestigator will discontinue IMP administration, perform the tests to be performed at withdrawal stipulated and promptly inform the sponsor of the withdrawal. The investigator or subinvestigator will record the date and reason for withdrawal in the CRF.

If withdrawal is necessitated by problems with safety, such as the occurrence of an adverse event or aggravation of an underlying disease, the investigator or subinvestigator will promptly take appropriate measures and perform follow-up if necessary.

1) Request from the subject or subject's legal guardian to discontinue participation in the trial
2) Discovery that the subject was included in the trial despite violation of the inclusion or exclusion criteria
3) Occurrence of any adverse event that makes it difficult for the subject to continue administration of IMP (including a suspected treatment-related adverse event of skin hypersensitivity on the treatment area)
4) Increase in the total treatment area to more than 40% of BSA
5) Discovery that the subject is pregnant or suspected to be pregnant
6) Judgment by the investigator or subinvestigator that it is necessary to withdraw the subject from the trial

### 3.8.3.2 Documenting Reasons for Treatment Discontinuation

The subjects may discontinue IMP administration due to the reasons shown below.

- Reasons related to adverse events:
  - Request from the subject due to distress or discomfort associated with a non-serious adverse event that does not place the subject at excessive risk in normal cases
  - Decision by the investigator or subinvestigator that continuing with IMP administration places the subject at excessive risk (eg, cases with IMP-related safety concerns, including hypersensitivity at the administration site)
    - Serious adverse event (SAE)
    - Other safety concerns or adverse events possibly related to IMP
- Death
- Reasons not related to medical conditions (the details will be documented, and the history of adverse events for the subject will be confirmed.)

- Withdrawal of consent (complete documented withdrawal of consent)
- Lost to follow-up
- Pregnancy (see "5.6 Pregnancy")
- Entire or partial discontinuation of the trial by the sponsor

If the subject discontinued the IMP administration due to an adverse event, the investigator, subinvestigator, or other clinical trial associates will follow the adverse event until it resolves or stabilizes, as much as possible, according to the procedures specified in "3.8.3.1 Treatment Discontinuation."

### 3.8.3.3 Withdrawal of Consent

All subjects and subjects' legal guardians have the right to withdraw their consent of trial participation at any time without any disadvantages. The subjects and the subjects' legal guardians can only withdraw their consent for future trial participation, but they cannot withdraw consent for the use of data that has already been collected as part of the trial. The investigator or subinvestigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject's legal guardian withdraws consent in written form, or unless the investigator or subinvestigator prepares a document which confirms the verbal consent for complete withdrawal from the trial by the subject or subject's legal guardian, the subject will undergo as many of the evaluations specified in the protocol as possible.

Complete withdrawal of consent means that the subject or the subject's legal guardian refuses all of the following follow-up procedures.

- All follow-up procedures specified in the protocol (in any form such as the subject visiting the trial site, by telephone, or visiting the subject's home)
- Part of the follow-up procedures specified in the protocol (among part of the follow-up procedures refused by the subject or the subject's legal guardian, those agreed between the subject's legal guardian and the clinical trial associate)
- Contact with the subject or the subject's legal guardian by the clinical trial associate to assess the subject's current condition or to obtain the necessary medical or laboratory information related to the trial objectives (including contact by phone alone)
- Contact with persons other than the subject who can be determined by the source document and can also talk about the subject's condition (eg, family members, legally acceptable representatives, friends, neighbors, and physicians) (including contact only by phone, mail, or e-mail)
- Access to other medical information sources (eg, medical records of other hospitals or clinics, notes of a physician from whom the subject was referred, public records,

information on registration to dialysis, transplants, population dynamics, or social media)

Withdrawal of consent is a significant event for these trials. Therefore, care should be taken regarding the procedures in the same manner as when obtaining the initial informed consent. To ensure the subjects' rights and the integrity of the trial, the reasons for consent withdrawal by the subject and the subject's legal guardian should be completely understood, documented, and managed. The subject and the subject's legal guardian may at first ask for an interruption or to withdraw from IMP administration. This request does not equal the will of complete withdrawal of consent for continued participation in the trial, but it may indicate that the subject and the subject's legal guardian have felt some burden of continued participation in the trial regarding their work or social activities. Therefore, in reference to "3.8.3.2 Documenting Reasons for Treatment Discontinuation," the investigator or subinvestigator will confirm the reasons for withdrawal from IMP administration and determine whether continued participation in the trial is possible by adjusting the schedule of administration or evaluations. Complete withdrawal of consent for trial participation is established only for those subjects and subjects' legal guardians who have refused all of the above follow-up procedures.

#### 3.8.3.4 Procedures to Encourage Continued Trial Participation

If discontinuation of IMP administration or withdrawal of consent is expected, the investigator or subinvestigator will discuss with the subject and the subject's legal guardian about the possible options for them to continue participating in the trial. With full respect for the subjects' rights, the investigator or subinvestigator will take appropriate steps to confirm the reason(s) for withdrawal of consent. When the reason(s) has been confirmed, it will be documented.

## 3.9 Screen Failures

A screen failure subject is a subject from whom consent for trial participation has been obtained and whose legal guardian signed the informed consent form, but to whom an IMP was not allocated on the day of the baseline examination.

If a subject is a screen failure, the following information should be recorded in the source document and CRF for screen failure subjects.

Subject number, date of screening examination, date of informed consent, date of birth, sex, reason for screen failure, country where the trial was conducted (Japan), race, ethnicity, possibility of pregnancy

## 3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary, secondary, and/or exploratory endpoints, irrespective of whether the subject actually administered all doses of IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as completed subjects. Based on the trial objectives, subjects who complete the examinations at Week 4 and 2 weeks after the last IMP administration are defined as completed subjects.

## 3.11 Follow-up of Subjects who Have Stopped Visiting the Trial Site

If a subject has stopped visiting the trial site for an unknown reason, the investigator or subinvestigator will promptly contact (by telephone, etc.) the subject or relevant party such as family members to confirm any adverse events and encourage the subject to visit the trial site. If the subject does not visit the trial site, the follow-up result will be recorded for the following items:

1) Date of follow-up
2) Method of follow-up
3) Whether or not the subject has been contacted
4) Reason why the subject has not (or has not been able to) visited the site
5) Details on status of IMP administration
6) Whether or not an adverse event(s) has occurred: if yes, the name of adverse event(s), dates of onset/recovery, severity, relationship with IMP, measures taken for IMP administration, treatment for the adverse event(s), and outcome
7) If lost to follow-up, the reason why

## 3.12 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on and before the examination 2 weeks after the last IMP administration during the treatment period, and subjects whose survival is unknown on the trial completion day will be classified as lost to follow-up as the reason for discontinuation. The subject's survival can be judged by various information sources by

obtaining the proper documents which indicate death (ie, death certificate, medical record, public record, or statement by a family member or their doctor in charge) or those which indicate survival (ie, meeting record with the subject, medical record, contact record with the subject by phone, statement by a family member or their doctor in charge, or public record).

If the subject cannot be contacted even after calling 3 times (the phone calls should be documented), the investigator, subinvestigator, or designated person will try to get in contact with the subject by sending a letter via registered mail or by other substitute methods. If these efforts are not successful, the subject is judged as "lost to follow-up."

## 3.13 Subject and Subject's Legal Guardian Compliance

- To avoid using drugs that are not permitted by the investigator or subinvestigator.
- To thoroughly understand the details of the administration guidance and follow it.
- To keep an administration diary every day.
- Subjects aged 7 to 14 years old should keep a pruritus diary until the morning of the Week 1 examination (Day 7 at the latest).
- When bathing or taking a shower, to administer the IMP afterwards.
- To visit the trial site on the specified visit days during the trial period.
- To visit the trial site without morning IMP administration on the day of drug concentration measurement.
- To bring the IMP, administration diary, and pruritus diary as instructed.
- To avoid excessive exercises, getting a suntan, and excessive drinking and eating and to keep regular hours to prevent possible effects on safety.
- Information obtained during participation in this trial must not be disclosed to any third party.

## 3.14 Deviations From the Trial Protocol

1) The investigator or subinvestigator should not deviate from the protocol or change it without prior written agreement between the investigator and the sponsor and the written approval of the IRB of the trial site based on prior review.
2) In unavoidable medical circumstances such as the need to avoid emergent risk to a subject, the investigator or subinvestigator may deviate from the protocol or change the protocol without prior written agreement from the sponsor and prior approval of the IRB. In such an event, the investigator will promptly submit a document providing the details of and reason for the deviation or change to the sponsor and the head of the trial site and obtain approval from the IRB. In

addition, the investigator will obtain written approval from the head of the trial site and the written agreement of the sponsor by way of the head of the trial site.

3) The investigator or subinvestigator will record all deviations from the protocol.

# 4 Restrictions

## 4.1 Prohibited Concomitant Drugs and Therapies

1) From 28 days prior to the baseline examination until the Week 4 examination, use of the following drugs and therapies is prohibited
   - Systemic corticosteroids, systemic immunomodulators, systemic antimetabolites, systemic retinoids, biologics
     Intra-ocular, intra-nasal, intra-auricular or inhaled corticosteroids may be considered if, in the opinion of the investigator or subinvestigator, their use will not impact evaluations of the affected area.
   - Ultraviolet light A, narrowband ultraviolet B, ultraviolet light B
2) From 7 days prior to the baseline examination until the Week 4 examination, use of the following drugs and therapies is prohibited.
   - Topical corticosteroids, topical immunomodulators, topical retinoids, and topical antihistamine.
     Low or medium potency corticosteroids in the Guidelines for Management of Atopic Dermatitis[2] may be used until 4 days prior to the baseline examination in the judgment of the investigator or subinvestigator for the gradual decrease in the screening period before stopping
3) From 7 days prior to baseline examination until the Week 4 examination, change in the dose and frequency of use for the following drugs is prohibited.
   - Systemic antihistamines, sodium cromoglicate, tranilast, suplatast tosilate
     Intra-ocular, intra-nasal, or inhalant formulations may be considered if, in the opinion of the investigator or subinvestigator, their use will not impact evaluations of the affected area.
4) From the baseline examination until the Week 4 examination, use of the following drugs and products on the treatment area is prohibited.
   - All topical drugs (including ethical drugs, over-the-counter products, herbal medicine, quasi-drugs, and cosmetic products)
     Continuous use of cosmetics used in the face, neck, and head area if any had been used before obtaining informed consent is permitted unless the type of cosmetics and frequency of use are maintained the same.

All other drugs and therapies not specified in the prohibited concomitant drugs and therapies are allowed to be used; however, any regimen or dose change or use of a new drug or therapy should be avoided as much as possible between the screening

examination and the Week 4 examination. If any drug other than the IMP (excluding cosmetics) is used between 30 days before the screening examination and the Week 4 examination, the name of the drug, purpose of use, daily dose, dose frequency, route of administration, and dates of start and end of administration will be recorded in the source document and CRF, regardless of it being prohibited or allowed for concomitant use. If any concomitant therapy is given between 30 days before the screening examination and the Week 4 examination, regardless of it being prohibited or allowed for concomitant use, the name of the therapy, purpose of use, and the dates of the start and end of the therapy will be recorded in the source document and CRF.

# 5 Reporting of Adverse Events

## 5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs would not include information recorded as medical history at screening for pre planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of Investigational New Drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IMP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.

  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

**Nonserious adverse events** are all AEs that do not meet the criteria for a "serious" AE.

**Immediately Reportable Event (IRE):**

- Any SAE.
- Any AE related to occupational exposure.
- Potential Drug Induced Liver Injury (DILI) case (see Section 5.4).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE section of CRF if there is an abnormality or complication.

**Clinical Laboratory Test Value Changes:** It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

**Severity:** Adverse events will be graded on a 3-point scale and reported as indicated on the CRF. Skin and subcutaneous tissue disorders will be graded according to the Common Terminology Criteria for Adverse Events v4.0 Japanese JCOG edition.

**1 = Mild:** Discomfort noticed, but no disruption to daily activity.

**2 = Moderate:** Discomfort sufficient to reduce or affect normal daily activity.

**3 = Severe:** Inability to work or perform normal daily activity.

**IMP Causality:** Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related: There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.

Not Related: There is no temporal or causal relationship between the IMP and the AE.

## 5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and CRFs provided by the sponsor. If an AE has occurred on the application site, it will also be recorded. Eliciting SAEs will be started after the subject's legal guardian has signed an informed consent form.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. If an AE has occurred on the application site, it will also be recorded. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier or not expected based on the course of the condition.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 5.3 Immediately Reportable Events (IRE). Special attention should be paid to recording hospitalization and concomitant medications.

## 5.3 Immediately Reportable Events (IRE)

After either the investigator, subinvestigator, or designated person becomes aware of any SAE or any AE related to occupational exposure in healthcare professionals, potential drug-induced liver injury, or confirmed pregnancy, the investigator or subinvestigator must immediately report the event to the sponsor (within 24 hours in principle) by e-mail

(IRE_271-102-00002@otsuka.jp) or by facsimile (FAX: 06-6942-3692) if e-mail is not available (see cover page of this protocol for contact information). An immediately reportable event (IRE) form must be completed and sent by e-mail or facsimile to the sponsor. (Please note that the IRE form is NOT the AE section of CRF.)

Subjects experiencing SAEs should be followed until the events are resolved or clinically stabilized, or until the subjects are lost to follow-up. Recovery is defined as the subject's health returning to baseline status, and stabilization is a condition determined by the investigator or subinvestigator that no further improvement or worsening is likely. The investigator or subinvestigator should provide the subjects with appropriate treatments and the sponsor with prompt updates on the subjects' status.

## 5.4 Potential Drug-Induced Liver Injury

For a subject who experiences an elevation in AST or ALT that is ≥3 times the upper limit of the normal range, a total bilirubin level should also be evaluated. If the total bilirubin level is ≥2 times the upper limit of the normal range, the investigator or subinvestigator should promptly (within 24 hours in principle) complete an IRE form with all values listed and send it to the sponsor by e-mail or facsimile, and report as an AE on the CRF.

## 5.5 Implementation of Patch Test

If any adverse event suspected of hypersensitivity occurs in the treatment area, the subject will be withdrawn from the trial and given appropriate treatments. According to the following procedures, a patch test will be performed. After obtaining verbal consent to patch test from the subject's legal guardian, the consent will be recorded in the source document and CRF. Prior to conducting the patch test, the recovery of symptom(s) should be confirmed. To avoid any drugs used in the treatment affecting the patch test result, an appropriate washout period will be provided. In principle, the patch test will be performed after a 2-week washout period for those receiving oral steroids or after a 1-week washout period for those receiving topical steroids or topical/oral antihistamines. Test substances for the patch test are to consist of the IMP that the subject had received, vehicle, and white petrolatum. After 48 hours from application, the patch test unit will be removed. The first reading will be made about 1.5 to 2 hours after the tape removal, the time at which the removal-associated irritant reaction disappears. Then, subsequent

readings will be made at 72 or 96 hours after the application and at 1 week after the application (allowable window of 5-7 days after the application). The time and date of the reading and the reading result will be recorded in the source document and CRF.

Reading criteria for skin reaction are shown in Table 5.5-1 (refer to the Guidelines for Management of Contact Dermatitis[21] issued by the Japanese Dermatological Association for procedures of the patch test).

**Table 5.5-1 Reading Criteria**

| ICDRG criteria | Reaction |
|---|---|
| − | No reaction |
| +? | Erythema only |
| + | Erythema + infiltration, papules |
| ++ | Erythema + infiltration + papules + small blisters |
| +++ | Large blisters |
| IR | Irritant reaction |
| NT | Not tested |

## 5.6 Pregnancy

Before enrolling female children aged 7 to 14 years old, the investigator or subinvestigator must review the trial participation guidelines for female children aged 7 to 14 years old. The topics should generally include:

- Informed consent form
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, female (candidate) subjects aged 7 to 14 years old and subjects' legal guardians must be advised of the importance of avoiding pregnancy during their trial participation and the potential risk factors of an unintentional pregnancy. The subject's legal guardian must sign an informed consent form stating that the above-mentioned risk factors and consequences were discussed with him or her.

At the screening examination, female children aged 7 to 14 years old will undergo a urine or serum pregnancy test (human chorionic gonadotropin test). If a positive urine test result is obtained, the investigator or subinvestigator will follow up with a confirmation serum test.

During the trial, all female subjects and subjects' legal guardians should be instructed to contact the investigator or subinvestigator immediately if they suspect they might be pregnant.

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial.

The investigator or subinvestigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and promptly forward it to the sponsor (within 24 hours in principle). The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator or subinvestigator must report to the sponsor, on appropriate Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

## 5.7 Procedure for Breaking the Blind

If a medical emergency occurs in a subject, such as an SAE, and his or her IMP randomization code is considered important for treatment by the investigator or subinvestigator, the emergency code will be broken according to the "Procedure for Emergency Code Breaking." If the blind is broken, the investigator or subinvestigator must notify the sponsor within 24 hours of opening the code, prepare a record of the reasons and the courses of blind-breakage, and submit it to the sponsor.

## 5.8 Follow-up of Adverse Events

In this trial, information on adverse events (AEs) will be followed up as described below.

### 5.8.1 Follow-up of Non-serious Adverse Events

Non-serious AEs that are identified during the trial must be recorded on the AE section of CRF with the current status noted. Any subject with an AE or who has not recovered from an AE at the examination 2 weeks after the last IMP administration will be followed up once in at least 4 weeks after the end of the trial until the AE either resolves or clinically stabilizes, or until the subject is lost to follow-up. All non-serious AEs that are ongoing at the examination 2 weeks after the last IMP administration will be recorded as "ongoing" on the CRF. For evaluation of AEs that occurred during the trial, additional relevant medical history information may be requested to further ascertain causality (including but not limited to, information such as risk-related behavior, family history, and occupation). Follow-up information obtained after the examination 2 weeks after the last IMP administration will be recorded in medical records.

### 5.8.2 Follow-up of Serious Adverse Events

In this trial, subjects will be actively observed for occurrence of any SAEs between the completion day of IMP administration and the day of the examination 2 weeks after the last IMP administration.

Serious AEs that are identified or ongoing at the day of trial completion (final observation day) must be recorded on the AE section of CRF and reported to the sponsor according to the procedures outlined in "5.3 Immediately Reportable Events (IRE)." All SAEs persisting on the day of trial completion (final observation day) will recorded in the CRF as "ongoing." This may include unresolved previously reported SAEs or new SAEs. The investigator or subinvestigator must follow any SAEs until the events are either resolved or clinically stabilized, or the subject is lost to follow-up. The investigator or subinvestigator should report important follow-up information of SAEs to the sponsor using the IRE form until the events are either resolved or clinically stabilized, or the subject is lost to follow-up.

### 5.8.3 Follow-up and Reporting of Serious Adverse Events Occurring After Day of Trial Completion (Final Observation Day)

Any new SAEs reported by the subject to the investigator or subinvestigator after the day of trial completion (final observation day), and are determined by the investigator or subinvestigator to be IMP-related should be reported to the sponsor. This may include SAEs that are captured on follow-up telephone contact or at any other timepoint after the defined trial period (day of trial completion). The investigator or subinvestigator should follow any SAEs identified after the day of trial completion (final observation day) until

the events are either resolved or clinically stabilized, or the subject is lost to follow-up. The investigator or subinvestigator should report any significant follow-up information to the sponsor using the IRE form until the event has been resolved or clinically stabilized, or the subject is lost to follow-up.

# 6 Pharmacokinetic Analysis

The plasma concentration of OPA-15406 (trough concentration at Week 1 and Week 4) will be measured.

# 7 Statistical Analysis

## 7.1 Sample Size

60 subjects

The sample size of 20 subjects for each group, a total of 60 subjects, has been established in consideration of the feasibility of the trial and the number of subjects needed to evaluate efficacy and safety. Assuming that the probabilities of success in IGA for each group are the same as those in the phase 2 trial outside Japan (271-12-205), the expected incidence of success in the 1% OPA-15406 group, the 0.3% OPA-15406 group, and the vehicle group is 20.93%, 14.63%, and 2.7%, respectively. In that case, the probability of the 1% group > the vehicle group, the 0.3% group > the vehicle group, and the 1% group minus the vehicle group > 10% in the point estimate of incidence of success is 96.2%, 88.3%, and 71.5%, respectively. Also, the probability of the 1% group > the 0.3% group ≥ the vehicle group in point estimate of incidence of success is 60.6%.

## 7.2 Datasets for Analysis

### 7.2.1 Safety Analysis Set

The safety analysis set consists of all subjects who have received the IMP at least once.

### 7.2.2 Efficacy Analysis Set

The efficacy analysis set consists of all subjects who have received the IMP at least once and whose efficacy data has been obtained after the start of IMP administration.

### 7.2.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set consists of all subjects whose plasma drug concentration has been measured.

## 7.3 Handling of Missing Data

In this trial, no data imputation will be made for missing pharmacokinetic data. For the efficacy variable of IGA, missing value in IGA will be handled as follows.

1) Primary analysis for incidence of success in IGA
   - Subjects with an IGA score of 0 (clear) or 1 (almost clear) with an improvement by at least 2 grades from baseline are defined as responders. Subjects with missing IGA data at the time of evaluation will be handled as non-responders.
2) Sensitivity analysis
   - Subjects with an IGA score of 0 (clear) or 1 (almost clear) with an improvement by at least 2 grades from baseline are defined as responders. For subjects with missing IGA data at the time of evaluation, the last observation carried forward (LOCF) will be used.
   - Subjects with an IGA score of 0 (clear) or 1 (almost clear) with an improvement by at least 2 grades from baseline are defined as responders. Observed cases (OC) will be used.
   - Subjects with an improvement in IGA score to 0 (clear) or 1 (almost clear) are defined as responders. Subjects with missing IGA data at the time of evaluation will be handled as non-responders.

## 7.4 Primary, Secondary, and Exploratory Endpoint Analyses

### 7.4.1 Primary Endpoint Analysis

Analysis of AEs is described in Section 7.6.1.

### 7.4.2 Secondary Endpoint Analysis

1) For the incidence of success in IGA at Week 4, the incidence of success of each treatment group and its 95% confidence interval will be calculated. The difference between the vehicle group and each treatment group in the incidence of success and its 95% confidence interval will be calculated. Incidence of success in IGA is defined as the rate of subjects whose IGA score is 0 (clear) or 1 (almost clear) and has improved by at least 2 grades (responders) from baseline. Based on the Cochran-Mantel-Haenszel method, the difference in incidence of success adjusted by the severity of IGA at baseline and its confidence interval will be calculated as the primary analysis. For reference, the Cochran-Mantel-Haenszel

method will be performed using baseline IGA (mild or moderate) as a stratification factor, and the p-value will be calculated. A multiplicity adjustment will not be conducted.

2) The incidence of success in IGA at Week 1 and Week 2 will be calculated, in the same manner as the incidence of success in IGA at Week 4.
3) For the change from baseline in IGA at Week 1, Week 2 and Week 4, mixed-model repeated measures (MMRM) analysis with factors of treatment (0.3% or 1% OPA-15406 groups, and vehicle group), timepoint, baseline IGA (mild or moderate), and interaction between treatment and timepoint will be applied with an unstructured variance covariance structure to the change from baseline up to Week 4 based on OC dataset. Kenward-Roger will be used to calculate the standard error of fixed effects and degree of freedom. The least square mean of each treatment group will be calculated by timepoint. Also, the difference in the least square means between the vehicle group and each OPA-15406 group, and the two-sided 95% confidence interval and p-value will be calculated at Week 1, Week 2 and Week 4. Analysis of covariance (ANCOVA) with factors of treatment (0.3% or 1% OPA-15406 groups, vehicle group), and baseline IGA (mild or moderate) will be applied to the change from baseline up to each timepoint based on OC and LOCF dataset. The least square mean of each treatment group will be calculated by timepoint. Also, the difference in the least square means between the vehicle group and each OPA-15406 group, and the two-sided 95% confidence interval and p-value will be calculated. Using the OC and LOCF data sets, the descriptive statistics will be calculated for measured values and changes from baseline by treatment group for each timepoint.
4) The change from baseline in EASI, VAS for pruritus, POEM, and affected BSA will be calculated in the same manner as the change from baseline in IGA. Except for baseline, the same MMRM and ANCOVA models as those used in the analysis of IGA will be used. For baseline, the baseline values of the respective variables will be used.
5) Change from baseline in VRS for pruritus up to Day 7 will be calculated. Using the OC and LOCF data sets up to Day 7, ANCOVA with factors of treatment (0.3% or 1% OPA-15406 groups, vehicle group), and baseline value will be applied to the change from baseline up to each timepoint based on OC and LOCF dataset. The least square mean of each treatment group will be calculated by timepoint. Also, the difference in the least square means between the vehicle group and each OPA-15406 group, and the two-sided 95% confidence interval and p-value will be calculated. Using the OC and LOCF data sets, the descriptive statistics will be calculated for measured values and changes from baseline by treatment group for each timepoint. The data will be collected at 4, 8, and 12 hours after the start of administration, 1 day after the start of administration (morning and night), and thereafter in the same manner up to Day 7 (morning).
6) For time to response in IGA and VRS for pruritus, Kaplan-Meier plots will be generated for each treatment group and vehicle group. For IGA, subjects with an IGA score is 0 (clear) or 1 (almost clear) with an improvement by at least 2 grades

from the baseline are defined as responders. For VRS for pruritus, subjects with VRS score of 0 (none) or 1 (mild) with an improvement by at least 1 grade from the baseline are defined as responders.

7) The descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) of plasma OPA-15406 concentrations will be calculated by treatment group and by timepoint.
8) The descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) of plasma OPA-15406 concentrations adjusted for affected area (%) per total BSA at baseline evaluation will be calculated by treatment group and by timepoint.
9) The descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) of plasma OPA-15406 concentrations will be calculated by treatment group, by timepoint, and by affected area per total BSA at baseline examination (5% to <10%, ≥10% to <30%, and ≥30%).
10) The descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) of age, affected area at baseline (%), and amount of administration (g) by affected area will be calculated.

### 7.4.3 Interim Analysis

In this trial, no interim analysis will be performed.

## 7.5 Analysis of Demographic and Baseline Characteristics

For sex, age, complications, medical history, previous medications (for AD or other diseases), concomitant medications, severity of AD, and baseline values of IGA, EASI, VAS for pruritus, VRS for pruritus, POEM, and affected BSA, the descriptive statistics will be calculated by treatment group depending on the characteristics of each parameter.

## 7.6 Safety Analysis

### 7.6.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The version of MedDRA will be specified in the statistical analysis plan. The number and percentage of subjects experiencing the following AEs will be calculated for treatment group.

a) TEAEs by severity

b) TEAEs potentially causally related to IMP

c) TEAEs resulting in death

d) Serious TEAEs

e) TEAEs leading to discontinuation of IMP administration

If a subject experiences the same AE multiple times in the same period, the highest severity will be used for tabulations.

### 7.6.2 Clinical Laboratory Tests

For clinical laboratory values, descriptive statistics will be calculated for measured values at baseline and each timepoint, and changes from baseline by timepoint for each treatment group. Based on the reference range, shift tables will be created for changes from baseline classified into normal, high, and low.

### 7.6.3 Vital Signs

For vital signs, descriptive statistics will be calculated for measured values at baseline and each timepoint, and changes from baseline by timepoint for each treatment group.

### 7.6.4 12-Lead ECG

For 12-lead ECG, descriptive statistics will be calculated for the measured values and changes from baseline by timepoint for each treatment group. Absolute QTc interval prolongation will be classified into >450 msec, >480 msec, and >500 msec, and the frequency distribution will be displayed. In the same manner, the change from baseline will also be classified into >30 msec and >60 msec, and the frequency distribution will be displayed.

### 7.6.5 Other Safety Data

Not applicable

# 8 Management of Investigational Medicinal Products

## 8.1 Packaging and Labeling

The IMP will be provided to the persons designated by the IMP manager, by the sponsor or designated agent. The IMP will be supplied in a packing box. Each packing box used in the treatment period will be labeled with the subject number, code name of the IMP, protocol number, name and address of the sponsor, statement that the drug is for use in a clinical trial, lot number, expiration date, storage method, drug number, and other precautions.

## 8.2 Storage

The IMP will be stored in a securely locked location. Access will be limited to the IMP manager. Neither the investigators nor any designees may provide IMP to any subject not participating in this trial.

The IMP will be stored at room temperature. The trial site staff will maintain a temperature log in the drug storage area by recording the temperature at least once each working day.

## 8.3 Accountability

The IMP manager must maintain an inventory record of IMP received, dispensed, administered, and returned.

## 8.4 Returns and Destruction

Upon completion or termination of the trial, all unused and partially used IMP must be returned to the sponsor or a designated agent.

All IMPs returned must be accompanied by appropriate documentation, such as storage records. Returned IMPs should be in the original containers (ie, subject kits). The assigned trial monitor will facilitate the return of unused and partially used IMP.

## 8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

### 8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator, subinvestigator, or designee must record all PQCs identified from the receipt of the IMP from the sponsor, or the sponsor's designee, up to final confirmation of destruction, including the treatment period. The investigator, subinvestigator, or designee must notify the sponsor (or the sponsor's designee) within 24 hours of becoming aware of the PQC by e-mail according to the procedure outlined below.

Email address for PQC reporting (PQC_271-102-00002@otsuka.jp)

Identification of a PQC by the subject should be reported to the investigator or subinvestigator, who should then follow the above reporting procedure.

### 8.5.2 Information Required for Reporting Purposes

- Description of compliant
- Reporter identification (eg, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)

- Pictures (if available)
- Availability for return

### 8.5.3 Return Process

Indicate during the PQC report if the complaint sample is available for return. If complaint sample is available for return, it should be discussed with the sponsor, and the sample should be returned.

It must be documented in the site accountability record that a complaint sample has been forwarded to the sponsor for complaint investigation.

### 8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

# 9 Records Management

## 9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigators/institutions will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

## 9.2 Data Collection

During each subject's visit to the clinic, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;

- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any significant medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of each clinician (or designee) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above. Any changes to information in the trial progress notes and other source documents will be initialed and dated on the day the change is made by a site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, wrong data  right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician. If electronic data systems are being utilized, a full audit trail of changes must be maintained.

Information from the trial progress notes and other source documents will be entered by investigative site personnel directly onto electronic CRFs in the sponsor’s electronic data capture system. Changes to the data will be captured by an automatic audit trail.

## 9.3 File Management at the Trial Site

The heads of all trial sites will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline and as required by the applicable local regulations. The trial sites must take measures to prevent accidental or premature destruction of these documents during the retention period.

## 9.4 Records Retention at the Trial Site

The trial site will retain all the trial-related documents and records for the longer of the following 2 periods. If the sponsor requires a longer period of archiving, the trial site will consult with the sponsor on the period and procedures of record retention.

- A period of at least 2 years following the date on which approval to market the drug is obtained. If IMP development is discontinued, or if it is notified that the trial results will not be attached to the application for approval, a period of at least 3 years following the date on which the development discontinuation is determined or the date on which the notification indicating that the results will not be attached to the application for approval is received.
- A period of at least 3 years following the date on which the trial is discontinued or completed

The trial site must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to collect such records. The trial site will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and the relevant regulatory authorities.

# 10 Quality Control and Quality Assurance

## 10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

## 10.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

# 11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling CRFs, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject. Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

# 12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject numbers in CRFs. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

# 13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written informed consent will be obtained from subjects' legal guardians enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

# 14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND

4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

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## Appendix 1 Diagnostic Criteria for Atopic Dermatitis (Hanifin & Rajka)

| A. Must have 3 or more basic features described below |
|---|
| 1) Pruritus<br>2) Typical morphology and distribution<br>Flexural lichenification in adults<br>Facial and extensor involvement in infants and children<br>3) Chronic or chronically-relapsing dermatitis<br>4) Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis) |
| B. Must have 3 or more following minor features: |
| 1) Xerosis<br>2) Ichthyosis, palmar hyperlinearity, keratosis pilaris<br>3) Immediate (type 1) skin test reaction<br>4) Elevated serum IgE<br>5) Early age of onset<br>6) Tendency toward cutaneous infections (especially Staph. aureus and Herpes simplex)/impaired cell-mediated immunity<br>7) Tendency toward non-specific hand or foot dermatitis<br>8) Nipple eczema<br>9) Cheilitis<br>10) Recurrent conjunctivitis<br>11) Dennie-Morgan infraorbital fold<br>12) Keratoconus<br>13) Anterior subcapsular cataracts<br>14) Orbital darkening<br>15) Facial pallor, facial erythema<br>16) Pityriasis alba<br>17) Anterior neck folds<br>18) Itch when sweating<br>19) Intolerance to wool and lipid solvents<br>20) Perifollicular accentuation<br>21) Food intolerance<br>22) Course influenced by environmental and emotional factors<br>23) White dermographism, delayed blanch |

## Appendix 2 Visual Analogue Scale (VAS) Sheet for Pruritus

No Itching Maximum Itching

0 _____ 100

## Appendix 3 Patient-Oriented Eczema Measure (POEM)

The POEM questionnaire is shown on the next page. If it is difficult for subjects to answer the questions, their parents will answer them instead.

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion

Patient Details: _____

_____

_____

_____ Date: _____

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your skin been itchy because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

2. Over the last week, on how many nights has your sleep been disturbed because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

3. Over the last week, on how many days has your skin been bleeding because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

5. Over the last week, on how many days has your skin been cracked because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

6. Over the last week, on how many days has your skin been flaking off because of your eczema?

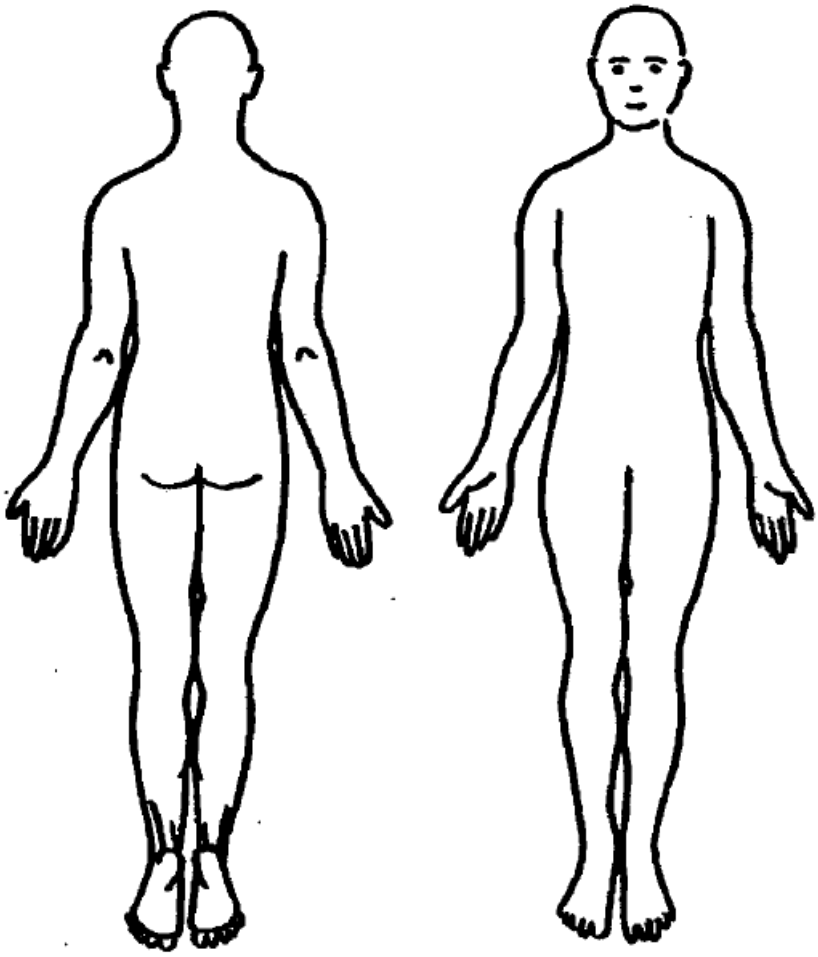
No days 1-2 days 3-4 days 5-6 days Every day

7. Over the last week, on how many days has your skin felt dry or rough because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

Total POEM Score (Maximum 28): .....

## Appendix 4 Human Body Drawing for Children Aged 8 to 14 Years Old



Total amount of administration _____ g

---

For hospital use only

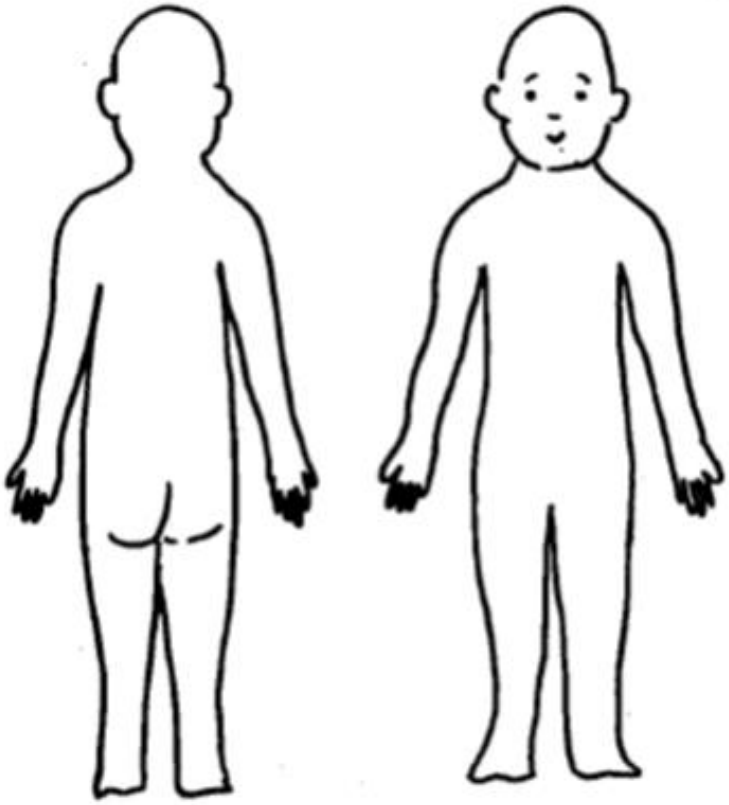
| Affected site | Affected area (%) |
|---|---|
| Face, neck, and head | % |
| Upper limbs | % |
| Trunk | % |
| Lower limbs | % |

| Administration site | Treatment area (%) |
|---|---|
| Face, neck, and head | % |
| Upper limbs | % |
| Trunk | % |
| Lower limbs | % |
| Total | % |

Signature of the investigator/subinvestigator

_____Day/_____Month/20_____

## Appendix 5 Human Body Drawing for Children Aged 2 to 7 Years Old



Total amount of administration _____ g

---

For hospital use only

| Affected site | Affected area (%) |
|---|---|
| Face, neck, and head | % |
| Upper limbs | % |
| Trunk | % |
| Lower limbs | % |

| Administration site | Treatment area (%) |
|---|---|
| Face, neck, and head | % |
| Upper limbs | % |
| Trunk | % |
| Lower limbs | % |
| Total | % |

Signature of the investigator/subinvestigator

_____Day/_____Month/20_____