CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double-blind, Vehicle-controlled, Parallel-group Comparison Trial to Demonstrate the Superiority of 0.3% and 1% OPA-15406 Ointment to the Vehicle in Pediatric Patients with Atopic Dermatitis (Phase 3 Trial)

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

OPA-15406

CLINICAL PROTOCOL

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Protocol No. 271-102-00008
(Translated Version)

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event	Pharmacovigilance Operation Office, Pharmacovigilance Department, Otsuka Pharmaceutical Co., Ltd. 3-2-27, Otedori, Chuo-ku, Osaka-shi, Osaka 540-0021, Japan IRE_271-102-00008@otsuka.jp
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: OPA-15406	Protocol No.: 271-102-00008
Protocol Title:	A Multicenter, Randomized, Double-blind, Vehicle controlled, Parallel-group Comparison Trial to Demonstrate the Superiority of 0.3% and 1% OPA-15406 Ointment to the Vehicle in Pediatric Patients with Atopic Dermatitis (Phase 3 Trial)
Clinical Phase/Trial Type:	Phase: 3 Type of trial: Confirmatory trial
Treatment Indication:	Atopic dermatitis (AD)
Objective(s):	Primary Objective: To demonstrate the superiority of the investigational medicinal product (IMP; 0.3% OPA-15406 ointment, 1% OPA-15406 ointment, or vehicle) to the vehicle when administered twice daily for 4 weeks using success rate in Investigator's Global Assessment (IGA) at Week 4 as the primary endpoint in pediatric patients with AD. Secondary Objective: To evaluate the efficacy (secondary endpoint) and safety of the IMP (0.3% OPA-15406 ointment, 1% OPA-15406 ointment, or vehicle) when administered twice daily for 4 weeks in pediatric patients with AD and to confirm the dose-response relationship.
Trial Design:	Multicenter, randomized, double-blind, vehicle-controlled, parallel-group comparison trial
Subject Population:	Pediatric patients with AD and IGA score of 2 or 3 240 subjects in total (the target inclusion ratio for "2 - 6 years" to "7 - 14 years" of age is 1:1)
Inclusion/Exclusion Criteria:	Main inclusion criteria • Age: 2 to 14 years, inclusive (at time of obtaining informed consent) • Able to obtain written informed consent from the subject's legal guardian. • Diagnosis of AD based on the Japanese Dermatological Association's criteria (refer to Appendix 1) • Atopic dermatitis affecting ≥5% to ≤40% of body surface area (BSA, excluding scalp) at the screening and baseline examinations

- IGA score of 2 or 3 at the screening and baseline examinations

Main exclusion criteria

- Subjects who have an AD or contact dermatitis flare-up defined as a rapid intensification of AD, within 28 days prior to the baseline examination.
- Subjects who are unable to stop using ultraviolet light A (UVA) therapy, narrowband ultraviolet B (NB-UVB) therapy, or ultraviolet light B (UVB) from 28 days prior to the baseline examination until the Week 4 examination.
- Subjects who are unable to stop using systemic corticosteroids, systemic immunosuppressants, systemic antimetabolites, systemic retinoids and biologics from 28 days prior to the baseline examination until the Week 4 examination.
- Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as very strong or higher potency in the "Guidelines for Management of Atopic Dermatitis" from 21 days prior to the baseline examination until the Week 4 examination.
- Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as strong potency in the "Guidelines for Management of Atopic Dermatitis," topical corticosteroids other than those for skin, topical immunosuppressants, topical retinoids, topical antihistamine, and topical non-steroidal anti-inflammatory drugs (excluding for scalp) from 7 days prior to the baseline examination until the Week 4 examination. However, intra-ocular, intra-nasal, intra-auricular, and inhaled corticosteroids and intra-ocular, intra-nasal, and inhaled corticosteroids antihistamines may be considered if the investigator or subinvestigator judges that their use will not impact assessment of the affected area.
- Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as low or medium potency in the "Guidelines for Management of Atopic Dermatitis" from 4 days prior to the baseline examination until the Week 4 examination.
- 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 the baseline examination until the Week 4 examination
Trial Sites:	Approximately 30 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 Twice daily administration for 4 weeks
Trial Assessments:	Efficacy: IGA, Eczema Area and Severity Index (EASI), Verbal Rating Scale (VRS) for pruritus, Patient-Oriented Eczema Measure (POEM), affected BSA Safety: Adverse events, physical examination, vital signs, body weight, and clinical laboratory values Screening/Other: Medical history, previous medications and pregnancy test
Criteria for Evaluation:	Primary Endpoint: Success rate in IGA at Week 4: Percentage of subjects in whom IGA score is 0 or 1 and improved at least 2 grades from baseline. Secondary Endpoints: Success rate in IGA at Week 4: Percentage of subjects in whom IGA score improves to 0 or 1, success rates in EASI 75 (improvement ≥75% in EASI), EASI 90 (improvement ≥90% in EASI), and EASI 50 (improvement ≥50% in EASI) at Week 4, changes from baseline in each parameter (IGA, EASI, VRS for pruritus [7 - 14 years of age only], POEM, affected BSA) at Week 4, and change in VRS for pruritus from baseline to Day 7. Criteria for Safety Evaluation: Adverse events, clinical laboratory values, vital signs, and body weight.
Statistical Methods:	The superiority of the 0.3% and 1% OPA-15406 group to the vehicle group will be demonstrated based on the primary endpoint, success rate in IGA at Week 4 in the full analysis set (FAS). Overall type I errors will be controlled using a closed testing procedure. First, the 1% OPA-15406 treatment group and the vehicle group will be compared. If significant at the two-sided significance level of 5%, the 0.3% OPA-15406 treatment group and the vehicle group will then be compared at the two-sided significance level of 5%. The Cochran-Mantel-Haenszel test will be conducted for comparison using the baseline IGA (2 or 3) and age (“2 - 6 years” or “7 - 14 years”) as a stratification factor. The difference in the success rate in IGA and its two-sided 95% confidence interval (common risk difference adjusted by Mantel Haenszel method and its two-sided 95% confidence

	interval) between the vehicle group and 0.3% or the 1% OPA-15406 group will be determined. Also, the two-sided 95% confidence interval of the success rate in IGA in each treatment group (based on Clopper-Pearson method) will be calculated.
Trial Duration:	Duration of the trial: Mar 2019 to Nov 2019 Screening period: 2 to 30 days Assessment period: 4 weeks

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AD	Atopic dermatitis
AE	Adverse Event
ALT (GPT)	Alanine aminotransferase
AST (GOT)	Aspartate aminotransferase
BSA	Body surface area
cAMP	Cyclic adenosine 3', 5'-monophosphate
C_{max}	Peak (maximal) concentration of drug in plasma
CMH	Cochran Mantel Haenszel
CRF	Case report form
CYP	Cytochrome P450
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IGA	Investigator's Global Assessment
IMP	Investigational Medicinal Product
IRB	Institutional review board
IRE	Immediately reportable event
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
MMRM	mixed model repeated measure
NB-UVB	Narrow-band ultraviolet B
NOAEL	No observed adverse effect level
OC	Observed Cases
PDE	Phosphodiesterase
POEM	Patient-Oriented Eczema Measure
PQC	Product Quality Complaint
SAE	Serious adverse event
SS	Safety Set
TEAE	Treatment-emergent adverse event
US	United States
VRS	Verbal Rating Scale

List of Pharmacokinetic Parameters

Abbreviation and Term	Unit	Expansion or Definition
AUC_{8h}	ng·h/mL	Area under the concentration-time curve from time zero to 8 hours
C_{max}	ng/mL	Maximum (peak) plasma concentration of the drug
$R_{4w,ac}(C_{max}/Dose)$		Ratio of C_{max}/Dose at Week 4 of multiple administration to single administration
$R_{4w,ac}(AUC_{8h}/Dose)$		Ratio of AUC_{8h}/Dose at Week 4 of multiple administration to single administration

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 atopic dermatitis) or 2) predisposition to producing IgE antibody.”[1] In some patients, AD that occurred in infancy may spontaneously resolve with age. However, some AD that occurred or recurred in adulthood may become refractory AD.[1]

Diagnostic criteria for the disease were established by Hanifin and Rajka in 1980[2], and in Japan, Guidelines for Management of Atopic Dermatitis was published by the Japanese Dermatological Association and Japanese Society of Allergology.[1] 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.

The basic therapy for AD are topical agents such as steroids and calcineurin inhibitors (immunosuppressors) for 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 is the 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). Topical agents of calcineurin inhibitors are also used to control inflammation, but a burning sensation may occur after administration. In addition, although the situations of AD patients are different from those of transplantation patients with continuously elevated blood concentrations of calcineurin, the daily amount of topical drugs is limited considering the possibility of systemic side effects which may be observed in the transplanted areas. Under these circumstances, 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 neutrophi. In AD patients, elevated PDE activity in peripheral blood leukocytes and reduced intracellular cAMP levels have been reported. PDE4 inhibitors have been shown to exert their antiinflammatory activity by increasing intracellular cAMP levels and suppressing production of chemical mediators such as inflammatory cytokines. Therefore, PDE4 inhibitors have been considered effective for treatment of AD.[3] In the United States (US), the Food and Drug Administration approved Eucrisa®

ointment 2% (generic name: Crisaborole) as a topical agent for pediatric (aged 2 years and older) and adult patients with mild to moderate AD in 2016.

OPA-15406 is a PDE4 inhibitor synthesized by Otsuka Pharmaceutical Co., Ltd. In a mouse chronic contact hypersensitivity model[4], 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 OPA-15406 was first initiated outside Japan, and the phase 2 trial in AD patients (aged 10 - 70 years old) and the pharmacokinetic trial in AD patients (aged
2 - 17 years) have been completed outside Japan. In Japan, the phase 1 trial in healthy adult male subjects, and the subsequent phase 2 trial in adult AD patients (aged 15 - 70 years old) and the phase 2 trial in pediatric patients with AD (aged 2 - 14 years old) have been completed. In healthy adult subjects (phase 1 trials in Japan and US), OPA-15406 ointment showed no clinical relevant safety issues but good tolerability. In AD patients (phase 1 trials in US and phase 2 trials in Japan), 1% OPA 15406 ointments showed efficacy on adult AD, and 0.3% and 1% OPA-15406 ointments showed efficacy on pediatric AD. Based on results of the above-mentioned clinical trials, this trial is designed to demonstrate the superiority of 0.3% and 1% OPA-15406 ointments to the vehicle 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 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% - 3%) for chronic allergic dermatitis was assessed. Four weeks of topical administration of the OPA-15406 ointment showed dose-dependent efficacy in improving dermatitis 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 that 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%).

When OPA-15406 ointment was administered to rats and miniature pigs, the dermal absorption of OPA-15406 was low. When ^{14}C-labeled OPA-15406 ointment (^{14}C-OPA-15406) was administered percutaneously in rats, the absorbed radioactivity was distributed through various tissues of the body, but the level of radioactivity in the central nervous system (cerebrum and cerebellum) was lower than that in plasma. Several metabolites were identified in human plasma and urine collected in the phase 1 trial in Japan (Trial 271-14-001), but it was judged that there are no human-specific metabolites since all metabolites were detected in animal plasma. The main excretion route of radioactivity was biliary excretion and fecal elimination. The in vitro protein binding rates of ^{14}C-OPA-15406 in human and animal serum were high (>99%). OPA-15406 (and its metabolites) did not readily bind to melanin.

Cytochrome P450 (CYP) 1A2 and CYP3A4 were involved in the metabolism of OPA-15406. OPA-15406 directly inhibited CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 (K_i: 1.284 - 8.833 mol/L) and showed metabolism-dependent inhibition of CYP2B6 and CYP3A4. The pharmacokinetic interaction risk of OPA-15406 is considered to be low since K_i values were much higher than the plasma exposure in the clinical trial. On the other hand, OPA 15406 showed an inducing effect on CYP1A2, CYP2B6 and CYP3A4.

In the 4, 13 and 26-week repeated-dose percutaneous toxicity studies in rats, OPA-15406 ointment was administered to intact skin (open cutaneous) once daily. As a result, no changes associated with the test substance were observed at the administration sites in any OPA-15406 ointment (vehicle, 0.1%, 0.3%, 1% and 3%) groups. Although suppressed weight increase was observed, it was not exacerbated in a prolonged treatment period. The no observed adverse effect level (NOAEL) for systemic toxicity in the 26 week repeated-dose percutaneous toxicity study was estimated to be 2.95 mg/kg (1% ointment) in the male rats and 1.07 mg/kg (0.3% ointment) in the female rats.

In the 4, 13 and 39-week repeated-dose percutaneous toxicity studies in miniature pigs, OPA-15406 ointment was administered to intact or abraded skin (open cutaneous) once daily. As a result, no changes associated with the test substance were observed in any

OPA-15406 ointment (vehicle, 0.3%, 1% and 3%) groups. The NOAEL for systemic toxicity in the 39 week repeated-dose percutaneous toxicity study was estimated to be 8.1 mg/kg (3% ointment) in the male rats and 8.3 mg/kg (3% ointment) in the female rats.

In a 4-week repeated-dose percutaneous toxicity study in rabbits, OPA-15406 ointment was administered to intact skin. The OPA-15406 ointment (vehicle, 0.1%, 0.3%, 1% and 3%) was classified as weak skin irritation at all concentrations according to the Draize scale for skin irritation.

For further information, refer to the Investigator's Brochure.

1.2 Clinical Study Results

Phase 2 trials in AD patients have been completed both in Japan and outside Japan.

For further information, refer to the Investigator's Brochure.

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

In the phase 1 trial in healthy adult subjects (aged 18 - 64 years old) in the 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 (SAEs) were reported and no subjects were withdrawn from the trial due to adverse events (AEs).

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

In the phase 1 trial in healthy adult male subjects (aged 20 - 40 years old) in Japan, a single-dose or 2-week twice-daily multiple doses of the 0.3%, 1%, or 3% OPA-15406 ointment (8 subjects for each group) or the vehicle of OPA-15406 ointment (placebo) as the control were administered to a 1000 cm^2 area (about 5% of body surface area [BSA]) on the back of the subject at 5 g per dose to assess the safety and pharmacokinetics of the OPA-15406 ointment in Japanese subjects. In the 0.3%, 1%, and 3% OPA-15406 groups, the mean maximum plasma concentration (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 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 AEs were reported, and no subjects were withdrawn from the trial. In physical findings and subjective symptoms, vital signs, skin findings, standard 12-lead electrocardiogram (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 Trial for Phototoxicity in Healthy Adult Subjects in the United States (Trial 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 AEs were observed. Also, no SAEs were reported, and no subjects were withdrawn from the trial due to AEs.

1.2.4 Trial for Photoallergy in Healthy Adult Subjects in the United States (Trial 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 AE, which was moderate in severity and determined as investigational medicinal product (IMP)-related. No SAEs were reported. One subject discontinued the trial due to the onset of an AE, pneumonia; however, a causal relationship with the IMP was ruled out.

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

In the phase 1 trial in AD patients (aged 18 - 65 years old) in the US, 0.3%, 1%, or 3% formulation of OPA-15406 ointment (15 subjects for each group) or the vehicle of OPA-15406 ointment (placebo) as the control were administered to 5% of BSA (about 1000 cm^2) as 4-week, twice-daily, multiple administrations. OPA-15406 ointment 1% formulation (7 subjects) and 3% formulation (8 subjects), and 0.1% tacrolimus ointment (15 subjects) were then administered to 10% or more at about 1g per 5% twice daily as 4-week 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 SAE of cholelithiasis occurred in the 1% OPA-15406 group, but its causal relationship with the IMP was ruled out. Two subjects discontinued treatment with the IMP due to AEs; one of the subjects was in the 3% OPA-15406 group (name of AE: hypersensitivity) and the other was in the 0.1% tacrolimus group (name of AE: allergic dermatitis), and both events were judged to be IMP-related.

For efficacy assessed in 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.

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

In the phase 2 trial in AD patients (aged 10 - 70 years old) outside Japan, the efficacy, safety, and tolerability of the 8-week twice-daily multiple doses of OPA-15406 ointment was 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 success rate in IGA (percentage of subjects with IGA score of 0 or 1 with improvement by at least 2 grades) at Week 4, and the success rate 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 success rate in IGA than in the vehicle group; however, no significant difference was observed between the groups ($p = 0.0690$, Cochran-Mantel-Haenszel [CMH] test). In the 1% OPA-15406 group, a significant difference was observed in the success rate in IGA compared to the vehicle group ($p = 0.0165$, CMH test). Discontinuations due to AEs 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. 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.

1.2.7 Pharmacokinetic Phase 2 Trial in Atopic Dermatitis Patients Outside Japan (Trial MEDI-MM 36-206)

In the pharmacokinetic phase 2 trial in pediatric AD patients (aged 2 - 17 years old) outside Japan, 1% OPA-15406 ointment was administered twice daily for 4 weeks in subjects aged 2 to 11 years old with affected BSA ≥35% and subjects aged 7 to 17 years old with affected BSA ≥25% to assess pharmacokinetics and safety. The mean C_{max} was 23.1 ng/mL on Day 1 and 16.9 ng/mL on Day 15 and accumulation was not observed. Although 9 AEs were reported, no SAEs were reported. Eight events were mild in severity and one event was moderate. Vomiting, rash, and application site burning sensation were reported as AEs for which a causal relationship with the IMP cannot be ruled out. The rash was moderate in severity, leading to the discontinuation of IMP administration. Efficacy was explored and a decrease in Eczema Area and Severity Index (EASI) score and a reduction of affected BSA were observed after administration.

1.2.8 Phase 2 Trial in Adult Atopic Dermatitis Patients in Japan (Trial 271-15-001)

In the phase 2 trial in AD patients (aged 15 - 70 years old) in Japan, the efficacy, safety, and pharmacokinetics of the 8-week twice-daily multiple doses of the 0.3% or 1% OPA-15406 ointment (60 subjects for each group) were investigated using the vehicle of OPA-15406 ointment (placebo) as the control. The primary efficacy endpoint was established as the success rate in IGA (percentage of subjects with IGA score of 0 or 1 with improvement by at least 2 grades) at Week 4, and the success rate in IGA was 14.93%, 22.39%, and 9.09% 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 success rate in IGA than the vehicle group; however, no significant difference was observed between the treatment groups ($p = 0.3004$, CMH test). In the 1% OPA 15406 group, a significant difference was observed in the success rate in IGA compared to the vehicle group ($p = 0.0328$, CMH test). No SAEs were observed in either group. Discontinuations due to AEs occurred with 15 subjects (22.4%), 7 subjects (10.4%), and 15 subjects (22.7%) in the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group, respectively. In the 0.3% OPA-15406 group, AEs were reported as dermatitis atopic in 10 subjects, pruritus in 4 subjects, and pruritus and application site pain in 1 subject. Of these, 4 of the subjects with dermatitis atopic, 2 of the subjects with

pruritus and the 1 subject with application site pain were judged to be IMP-related. In the 1% OPA-15406 group, AEs were reported as dermatitis atopic in 6 subjects and pruritus in 1 subject. Of these, 4 of the subjects with dermatitis atopic were judged to be IMP-related. In the vehicle group, AEs were reported as dermatitis atopic in 11 subjects, pruritus in 4 subjects, and dermatitis atopic and pruritus in 1 subject. Of these, 6 of the subjects with dermatitis atopic were judged to be 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 mean plasma trough concentration of OPA-15406 (median treatment area: 16.5% to 19.5%) was 1.74 ng/mL (Week 1), 1.71 ng/mL (Week 4) and 1.51 ng/mL (Week 8) in the 0.3% OPA-15406 group and 4.96 ng/mL (Week 1), 5.22 ng/mL (Week 4) and 5.22 ng/mL (Week 8) in the 1% OPA-15406 group. The plasma trough concentrations of OPA-15406 adjusted for amount of administration were similar at Week 1, Week 4 and Week 8, suggesting no accumulation of OPA-15406 after Week 1. Regarding pharmacokinetics investigated in the subgroups, the median $R_{4w,ac}(C_{max}/Dose)$ at Week 4 was 0.907 in the 0.3% OPA-15406 group and 1.58 in the 1% OPA-15406 group while the median $R_{4w,ac}(AUC_{8h}/Dose)$ at Week 4 was 1.13 in the 0.3% OPA-15406 group and 1.75 in the 1% OPA-15406 group, suggesting a slight accumulation of OPA-15406 after multiple doses compared to a single-dose.

1.2.9 Phase 2 Trial in Pediatric Atopic Dermatitis Patients in Japan (Trial 271-102-00002)

In the phase 2 trial in AD patients (aged 2 - 14 years old) in Japan, the safety, efficacy, and pharmacokinetics of the 4-week twice-daily multiple doses of the OPA-15406 ointment were investigated by selecting 0.3% and 1% formulations (20 subjects for each group) for which the efficacy was suggested in the phase 1 in the US using the vehicle of OPA-15406 ointment (placebo) as the control. No SAEs were observed in either group. The AE leading to discontinuation was dermatitis atopic and it occurred in 1 subject (4.2%), 1 subject (4.0%) and 4 subjects (16.7%) in the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group, respectively. Of these, 1 subject in the 1% OPA-15406 group was judged to be IMP-related. In the results of the clinical laboratory tests, vital signs, and 12-lead ECG, no marked difference was observed among the 3 groups. The efficacy endpoint was established as the success rate in IGA (percentage of subjects with IGA score of 0 or 1 with improvement by at least 2 grades) at Week 4, and the success rate in IGA was 37.50%, 40.00%, and 8.33% in the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group, respectively. The success rates were much higher in the 0.3% and 1% OPA-15406 groups than in the vehicle group ($p = 0.0114$ and $p = 0.0113$, CMH test). The mean plasma trough concentration of

OPA-15406 (median treatment area: 12.0% to 20.0%) was 0.842 ng/mL (Week 1) and 0.946 ng/mL (Week 4) in the 0.3% OPA-15406 group and 2.90 ng/mL (Week 1) and 2.21 ng/mL (Week 4) in the 1% OPA-15406 group. The plasma trough concentrations of OPA-15406 adjusted for amount of administration were similar at Week 1 and Week 4, suggesting no accumulation of OPA-15406.

1.3 Known and Potential Risks and Benefits

As of the data cutoff date (18 Feb 2018), in the phase 1 trial in healthy adults in the US (Trial 271-11-202), the trial for phototoxicity in the US (Trial 271-12-212), the trial for photoallergy in the US (Trial 271-12-213), the phase 1 trial in healthy adult male subjects in Japan (Trial 271-14-001), the phase 1 trial in AD patients in the US (Trial 271-12-204), the phase 2 trial outside Japan (Trial 271-12-205), the phase 2 pharmacokinetic trial outside Japan (Trial MEDI-MM36-206), the phase 2 trial in adult AD patients in Japan (Trial 271-15-001) and the phase 2 trial in pediatric AD patients in Japan (Trial 271-102-00002), OPA-15406 was administered to 174 healthy adult subjects and 358 AD patients. The longest duration of dosing was 8 weeks.

In AD patients treated with OPA-15406, 5 SAEs (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.

In trials in patients with AD, the most frequently reported AEs in the OPA-15406 treatment group were upper respiratory tract infection, viral upper respiratory tract infection, headache, upper respiratory tract inflammation, dermatitis atopic, and pruritus. Of those, the AEs in the OPA-15406 treatment groups that were reported at higher frequency than in the vehicle group and observed in at least 2% of the subjects are upper respiratory tract infection, headache, and upper respiratory tract inflammation, all of which were judged as not IMP-related (Table 1.3-1).

For other information, refer to the Investigator's Brochure.

Table 1.3-1 Adverse Events in OPA-15406 Treatment Groups Reported at a Higher Frequency Than in the Vehicle Group and Observed in at Least 2 Percent of the Subjects in Trials Enrolling Subjects With Atopic Dermatitis

Preferred Term	OPA-15406 (N=358) n (%)							Vehicle (N=142) n (%)
	Severity				Seriousness		Total	
	Mild	Moderate	Severe	Un-classified	Serious	Non-serious		
Upper respiratory tract infection	1 (0.3)	1 (0.3)	0 (0.0)	6 (1.7)	0 (0.0)	8 (2.2)	8 (2.2)	0 (0.0)
Headache	1 (0.3)	0 (0.0)	0 (0.0)	7 (2.0)	0 (0.0)	8 (2.2)	8 (2.2)	0 (0.0)
Upper respiratory tract inflammation	8 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.2)	8 (2.2)	2 (1.4)

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 indicated for AD have been approved in Japan.

2 Trial Rationale and Objectives

2.1 Trial Rationale

In the phase 2 trial in pediatric AD patients in Japan (Trial 271-102-00002), which were conducted prior to the present trial, the safety, efficacy, and tolerability of the 4-week twice-daily multiple doses of the 0.3% or 1% OPA-15406 ointment or the vehicle (placebo) were investigated. There were no particular safety concerns since no SAEs related to the IMP or adverse reactions were identified in the trial. The efficacy endpoint success rate in IGA (percentage of subjects with IGA score of 0 or 1 with improvement by at least 2 grades) at Week 4 was 37.50%, 40.00% and 8.33% in the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group, respectively. The success rates were much higher in the 0.3% and 1% OPA-15406 groups than in the vehicle group ($p = 0.0114$ and $p = 0.0113$, CMH test).

In the phase 2 pharmacokinetic trial in pediatric AD patients outside Japan who received the 1% OPA-15406 ointment (Trial MEDI-MM36-206), no SAEs related to the IMP or safety concerns were identified.

In the phase 2 trial in adult AD patients in Japan (Trial 271-15-001), the efficacy, safety, and pharmacokinetics of the multiple doses of the 0.3% or 1% OPA-15406 ointment or the vehicle (placebo) were investigated when administered twice-daily for 8 weeks. The efficacy endpoint success rate in IGA (percentage of subjects with IGA score of 0 or 1 with improvement by at least 2 grades) at Week 4 was 14.93%, 22.39% and 9.09% in the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group, respectively. In the 1% OPA15406 group, a significant difference was observed in the success rate in IGA compared to the vehicle group ($p = 0.0328$, CMH test). There were no SAEs related to the IMP or safety concerns.

As described above, efficacy of the 0.3% and 1% OPA-15406 ointment groups surpassed that of the vehicle group in pediatric AD patients in the Japanese phase 2 trial results, and significant difference was observed in the efficacy of the 1% OPA-15406 ointment group against the vehicle group in adult AD patients in the Japanese phase 2 trial results. The number of patients in the phase 2 pediatric AD trial in Japan is approximately one third of that in the phase 2 adult AD trial. Thus, it was considered that the recommended dose should be established after evaluating the efficacy of 0.3% and 1% OPA-15406 ointment in pediatric AD patients in a large-scale trial and considering the risk-benefit profile not only in the overall group but also by ages. Therefore, it was judged ethically and scientifically appropriate to conduct this trial to demonstrate the superiority of 0.3% and 1% OPA-15406 ointment to the vehicle in pediatric AD patients when administered the 0.3% or 1% OPA-15406 ointment twice-daily for 4 weeks.

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 2 trial in pediatric patients in Japan (Trial 271-102-00002), the efficacy endpoint was established as the success rate in IGA (percentage of subjects with IGA score of 0 or 1 with improvement by at least 2 grades) at Week 4. The success rate was comparable between 0.3% and 1% OPA-15406 groups and significantly higher in OPA-15406 groups than in the vehicle group. There was no significant difference in the

safety endpoints among the vehicle, 0.3% formulation and 0.1% formulation. Thus, it was considered that the recommended dose should be established in consideration of the risk-benefit profile after the efficacy of 0.3% and 1% OPA-15406 ointment was evaluated in a large-scale trial in pediatric AD patients.

Therefore, the 0.3% and 1% formulations are selected.

2.3 Rationale for Severity and Age Setting

Atopic dermatitis is mainly treated with topical drugs. However, for severe patients, oral agents and ultraviolet therapy are often combined due to inadequate response to topical drugs alone. Thus, the phase 2 trials in Japan (Trials 271-15-001 and 271-102-00002) were conducted in mild to moderate AD patients in whom topical drugs are the main treatment and the efficacy of OPA-15406 could be evaluated appropriately. As the results of these trials demonstrated the efficacy and safety, the present trial was designed to include patients with mild to moderate AD.

The phase 2 trial (Trial 271-102-00002) in Japan was conducted in pediatric patients (aged 2 - 14 years old), showing the efficacy of OPA-15406 ointment without any particular safety concerns. Therefore, subjects aged 2 to 14 years old were included in this trial.

2.4 Trial Objectives

Primary Objective: To demonstrate the superiority of the investigational medicinal product (IMP; 0.3% OPA-15406 ointment, 1% OPA-15406 ointment, or vehicle) to the vehicle when administered twice daily for 4 weeks using success rate in IGA at Week 4 as the primary endpoint in pediatric patients with AD.

Secondary Objective: To evaluate the efficacy (secondary endpoint) and safety of the IMP (0.3% OPA-15406 ointment, 1% OPA-15406 ointment, or vehicle) when administered twice daily for 4 weeks in pediatric patients with AD and to confirm the dose-response relationship.

3 Trial Design

3.1 Type/Design of Trial

This trial is a multicenter, randomized, double-blind, vehicle-controlled, parallel group, comparison trial to demonstrate the superiority of 0.3% and 1% OPA-15406 ointment to

the vehicle in pediatric AD patients. 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 informed consent from the subject's legal guardian (and, if possible, after obtaining assent from the subject), the investigator or subinvestigator will perform a screening examination. The screening period is defined as the period between the day of screening examination and the day of baseline examination (2 - 30 days).

2) Assessment period (treatment period)

The assessment period is defined as the period between the day of baseline examination and the end of Week 4 examination (or the end of withdrawal examination). The subjects who meet the inclusion and exclusion criteria at the baseline examination will be allocated to the IMP (0.3% and 1% formulation of OPA-15406) or the comparator (vehicle [placebo]). The allocated IMP will be administered to the treatment area from the day of baseline examination twice daily for 4 weeks. After the baseline examination, the examinations will be performed at Weeks 1, 2, and 4.

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

3) Trial period

The trial period for individual subjects is the period from the day of obtaining the written informed consent from the subject's legal guardian to the day of the Week 4 examination or withdrawal examination. For subjects who missed the Week 4 examination or withdrawal examination, the day of discontinuation will be the day when the investigator or subinvestigator determined that the subject was to be withdrawn from the trial. It does not include the follow-up period for AEs.

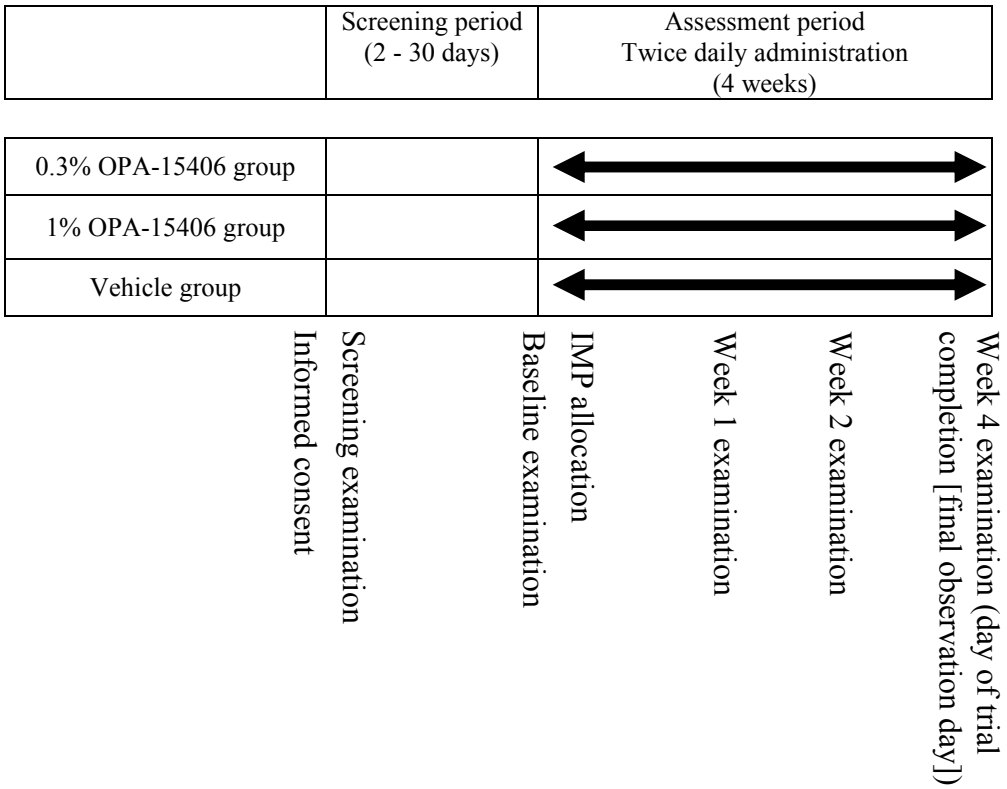

Figure 3.1-1 Trial Design

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 10 g/m^2 BSA and 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.

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

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

(Mosteller 1987)[5]

2) The treatment area will be specified

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."[6] In consideration of this standard AD treatment policy, in the phase 2 trial in pediatric patients in Japan (Trial 271-102-00002), patients received the IMP for 4 weeks and the primary efficacy endpoint was established as the success rate in IGA (percentage of subjects with IGA score of 0 or 1 with improvement by at least 2 grades) at Week 4. As a result, the success rate was significantly higher in the 0.3% OPA-15406 group and 1% OPA-15406 group than in the vehicle group. Also, no particular safety concerns were identified at Week 4.

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 Section 3.7.5.5, Affected Body Surface Area).
- 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's legal guardian (if possible, the subject) regarding the method of administration by specifying the treatment area (%) and the total amount of administration (g) for each treatment area using the human body drawing (see Appendix 3 or Appendix 4), and will give the human body drawing (copy) to the subject or subject's legal guardian. The investigator or subinvestigator will record the treatment area (%) of the 4 body regions [face, neck, and head (excluding scalp); 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 AD patient with an IGA score of 2 or 3. Subjects will be included in the trial to reach the target number of 240 subjects for IMP administration (the target inclusion ratio for “2 - 6 years old” and “7 - 14 years old” of age is 1:1). Any withdrawals will not be supplemented.

3.3.2 Issue of Subject Identification Number

A subject identification number ([3 digit number of site ID] + subject number [S + 5 digit number]) will be assigned to the subject providing written informed consent. The sponsor will provide the trial site number. The subject number will be a serial number assigned at the trial site starting from S00001 in the order of subjects providing written informed consent.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Freely given written informed consent will be obtained from the subject’s legal guardian (guardians or legal representatives, as applicable by law) instead of the subject. The relationship between the subject and the subject’s legal guardian will be confirmed and recorded. If possible, assent (consent not bound by the legal restrictions obtained from pediatric subjects) will be obtained from the subject. A signed informed consent form (ICF) and signed assent form will be retained as documents. The explanatory document, ICF, and assent form will be approved by the same institutional review board (IRB) responsible for approval of this protocol.

Each explanatory document and ICF should include the elements required by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice (GCP)[7] 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 the subject’s legal guardian before obtaining consent. However, written informed consent must be obtained 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 the 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 the 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 subject's age have been provided by the investigator or subinvestigator, the IRB-approved ICF 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 ICF 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 #7 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	Able to obtain written informed consent from the subject's legal guardian
5	Diagnosis of AD based on the Japanese Dermatological Association's criteria[1] (refer to Appendix 1)
6	Atopic dermatitis affecting ≥5% to ≤40% of BSA (excluding scalp)
7	IGA score of 2 or 3

[Rationale for Inclusion Criteria]

1) Atopic dermatitis occurs in both males and females.

2) Most patients to be included in this trial are outpatients.

3) The phase 2 trial (Trial 271-102-00002) in Japan was conducted in pediatric patients (aged 2 - 14 years old), showing efficacy OPA-15406 ointment without no particular safety concerns. Therefore, subjects aged 2 to 14 years old are included in the present trial.

4) To conduct the trial without any ethical problems.

5) Patients with AD who meet the Japanese Dermatological Association's criteria are included in order to evaluate the efficacy and safety of the IMP in AD patients in Japan.

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

3.4.3 Exclusion Criteria

Subjects who fall under any of the criteria in Table 3.4.3-1 at either the screening or baseline examination will be excluded from the trial:

Table 3.4.3-1	Exclusion Criteria
1	Female children aged 7 to 14 years old who are pregnant or possibly pregnant, or whose legal guardians are unable to agree to avoid sexual activity during the trial period and up until 30 days after the final administration of IMP.
2	Subjects who have an AD or contact dermatitis flare-up defined as a rapid intensification of AD, within 28 days prior to the baseline examination
3	Subjects who have a concurrent or history of skin disease other than AD (eg, acne, psoriasis, etc) and who are judged inappropriate for assessment of AD in the present trial
4	Subjects who have an active viral skin infection (eg, herpes simplex, herpes zoster, chicken pox) or clinical signs of such infection
5	Subjects with a current or history of malignancy

Table 3.4.3-1 Exclusion Criteria	
6	Subjects with a current or history of recurrent bacterial infection resulting in hospitalization or requiring intravenous antibiotic treatment within the past 2 years
7	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 assessment of the IMP: • Cardiac disease (eg, rheumatic fever or heart valve replacement) • Endocrinologic disease (eg, severe or uncontrolled diabetes) • Pulmonary disease • Neurologic disease • Psychiatric disease • Hepatic disease (eg, carriers of hepatitis B, hepatitis C, etc) • Renal disease • Hematologic disease • Immunologic or immunocompromised disease (eg, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome, carriers of human immunodeficiency virus [HIV] antibodies) • 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 efficacy assessment of the IMP
8	Subjects who are judged by the investigator or subinvestigator to be unable to safely complete the trial based on laboratory results at screening examination.
9	Subjects who are judged by the investigator or subinvestigator to have a clinically abnormal blood pressure or pulse rate at the screening and baseline examinations
10	Subjects who are judged by the investigator or subinvestigator to be unable to undergo blood sampling.
11	Subjects who are unable to stop allergen immunotherapy (or desensitization therapy) from 3 months prior to providing informed consent until the Week 4 examination (or at the time of withdrawal examination). However, if the subjects have continued the allergen immunotherapy for more than 3 months prior to providing informed consent and symptoms of AD have not changed judged by the investigator or subinvestigator , subjects may continue such therapy until the Week 4 examination as long as no changes are made to the therapy (types or amount of allergen or frequency of therapy, etc).
12	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
13	Subjects who are unable to stop using systemic corticosteroids, systemic immunosuppressants, systemic antimetabolites, systemic retinoids, and biologics from 28 days prior to the baseline examination until the Week 4 examination
14	Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as very strong or higher potency in the "Guidelines for Management of Atopic Dermatitis[1]" from 21 days prior to the baseline examination until the Week 4 examination.
15	Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as strong potency in the "Guidelines for Management of Atopic Dermatitis[1]", topical corticosteroids other than those for skin, topical immunosuppressants, topical retinoids, topical antihistamine and topical non-steroidal anti-inflammatory drugs (excluding for scalp) from 7 days prior to the baseline examination until the Week 4 examination. Intra-ocular, intra-nasal, intra-auricular, and inhaled corticosteroids and antihistamines may be considered if the investigator or subinvestigator judges that their use will not impact assessment of the affected area.

Table 3.4.3-1	Exclusion Criteria
16	Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as low or medium potency in the "Guidelines for Management of Atopic Dermatitis[1]" from 4 days prior to the baseline examination until the Week 4 examination.
17	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
18	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)
19	Subjects with known plans to receive any of the prohibited concomitant drugs or therapies during the trial period
20	Subjects who have participated in previous trials for OPA-15406 and have been administered the IMP
21	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
22	Subjects who have never been treated with a prescription medication for AD or who are satisfied with their current AD treatment regimen
23	Subjects who do not respond at all to treatment with existing topical drugs for AD
24	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) In consideration of safety to eliminate any unknown impact of the IMP on pregnant women, fetuses, and infants.

2) Due to a possible impact on the efficacy assessment of the IMP.

3) Due to a possible impact on the safety and efficacy assessments of the IMP.

4)-6) In consideration of safety.

7) Due to a possible impact on the safety and efficacy assessments of the IMP.

8)-10) In consideration of safety.

11)-17) Due to a possible impact on the efficacy assessment of the IMP.

18) In consideration of safety.

19) Due to a possible impact on the efficacy and safety assessments of the IMP.

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

22)	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.
23)	To exclude severe patients who do not respond to topical drugs.
24)	To allow the investigator or subinvestigator to judge in consideration of other factors.

3.5 Endpoints

3.5.1 Primary Endpoint

Success rate in IGA at Week 4: percentage of subjects with IGA score of 0 or 1 with improvement by at least 2 grades. Subjects with missing IGA data will be handled as non-responders.

[Rationale for Primary Endpoint]

Investigator's Global Assessment evaluates the systemic clinical characteristics (erythema, infiltration, papulation, oozing, and crusting) by the severity score of IGA (0 = Clear, 1 = Almost clear, 2 = Mild disease, 3 = Moderate disease, 4 = Severe disease/Very severe disease) and clearly distinguishes each score. In patients with AD, as remission or close to remission is the goal of the treatment[1], clinical characteristics of remission or close to remission are defined as IGA score of 0 (Clear) or 1 (Almost clear), and clinically significant improvement as improvement in IGA by at least 2 grades.

Based on the above, the success rate in IGA (percentage of subjects with IGA score of 0 or 1 with improvement by at least 2 grades) at Week 4 is established as the primary efficacy endpoint.

3.5.2 Secondary Endpoints

- Success rate in IGA at Week 4: percentage of subjects with IGA score of 0 or 1
- Change from baseline in IGA at Week 4
- Success rate in EASI 75 (improvement ≥75% in EASI), EASI 90 (improvement ≥90% in EASI) and EASI 50 (improvement ≥50% in EASI) at Week 4
- Change from baseline in the total score of EASI and each clinical sign score at Week 4
- Change from baseline in Verbal Rating Scale (VRS) for pruritus at Week 4
- Change from baseline in VRS for pruritus up to Day 7

- Change from baseline in the total score of Patient-Oriented Eczema Measure (POEM) at Week 4
- Change from baseline in the total affected BSA (%) at Week 4

3.5.3 Safety Endpoints

- Adverse events

1) AEs occurring after the start of IMP administration (Treatment-emergent adverse event [TEAE])
2) TEAEs by severity
3) TEAEs resulting in death
4) Serious TEAEs
5) TEAEs leading to discontinuation of IMP administration
6) TEAEs (skin and subcutaneous tissue disorders) by grade
7) TEAEs at treatment areas

- Clinical laboratory tests
- Vital signs and body weight

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 SAE.

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.

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 "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 subjects will be allocated using dynamic allocation (minimization method). Details will be provided in a separate specification.

3.7 Trial Procedures

Table 3.7-1 shows the schedule of assessment.

Table 3.7-1 Schedule of Assessments

Evaluation	Screening period (2–30 days)	Assessment period (4 weeks)				
	Screening examination	Baseline examination	Week 1 examination[a] (± 2 days)[b]	Week 2 examination[a] (± 3 days)[c]	Week 4 examination[a] (± 3 days)[c] Withdrawal examination[d]	Unscheduled visit
Informed consent	○[e]					
Inclusion and exclusion criteria	○	○				
Subject demographics	○					
Physical examination	○	○	○	○	○	○[f]
Vital signs and body weight	○	○	○	○	○	○[f]
Clinical laboratory tests	○	○			○	○[f]
Pregnancy test[g]	○	○			○	○[f]
IGA	○	○	○	○	○	○[f]
EASI	○	○	○	○	○	○[f]
VRS for pruritus[h]		○[i] ◄►	○[i]	○	○	○[f]
POEM		○	○	○	○	○[f]
Affected BSA	○	○	○	○	○	○
Treatment area		○	○	○		○[f]
Administration diary		○[j] ◄			► ○	
Severity of AD	○	○				
Photograph of the target site		○	○	○	○	○[f]
Status of IMP administration			○	○	○	
Prescription and collection of IMP		○[k]	○[l]	○	○[m]	○[l]
IMP administration		○[n] ◄►				
AEs	◄►					
Concomitant medications and therapies	◄►					
Patch test[o]		◄►				

[a]The reference date of the Week 1 examination, Week 2 examination and Week 4 examination will be the same day of the week as the baseline examination.

[b]Acceptable window of ±2 days

[c]Acceptable window of ±3 days

[d]Withdrawal examination should be conducted as soon as possible.

[e]Informed consent is to be obtained prior to screening examination (possibly on the same day).

[f]Is to be conducted, as necessary.

[g]Should be conducted only for female children aged 7 to 14 years old.

[h]Should be conducted only for female children aged 7 to 14 years old (at time of obtaining informed consent). The most intense pruritus in the past 24 hours will be evaluated. The investigator or subinvestigator will interview the subjects during scheduled visits after the baseline examination.

[i]The subjects will keep a pruritus diary once daily, every day, at the same time in principle as the time of baseline examination from the day after the baseline examination until the day before the Week 1 examination. However, the subjects should keep the pruritus diary up to Day 8 if they are to visit on Day 9 or later.

[j]The subjects should keep an administration diary every day from the baseline examination to the Week 4 examination (withdrawal examination).

[k]Only IMP prescription.

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

[m]Only IMP collection.

[n]The IMP administration should be started at the trial site after all baseline examinations are finished.

[o]If any AE 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 (see Section 5.5, Implementation of Patch Test)

3.7.1 Schedule of Assessments

Regarding assessments to be performed by the investigator or subinvestigator, the tasks that a clinical trial associate is able to perform (eg, subject demographics survey and tasks related to clinical laboratory tests) may be performed by the clinical trial associate under the supervision of the investigator.

3.7.1.1 Acquisition of Informed Consent

The investigator or subinvestigator will obtain written consent from the subject's legal guardian. The investigator or subinvestigator will assign a subject identification number ([3 digit number of site ID] + subject number [S + 5 digit serial number starting from 00001]) to the subject providing consent.

3.7.1.2 Screening Examination

After acquisition of informed consent, the investigator or subinvestigator will perform the following examinations, observations, and evaluations, and select subjects who meet the inclusion criteria and do not fall under any of the exclusion criteria.

- Subject demographics
- Physical examination
- Vital signs and body weight
- Clinical laboratory tests
- Pregnancy test (only for female children aged 7 - 14 years old)
- IGA
- EASI
- Affected BSA
- Severity of AD
- AEs
- Concomitant medications and therapies

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

3.7.1.3 Subject Demographics

The investigator or subinvestigator is to record the following information in the source document and CRF.

- Date of informed consent
- Sex
- Date of birth

- Height (unit in cm: measurement indicated as an integer value; if measurement to one decimal place is possible, then the number is to be rounded to nearest 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 identification number
- Country where the trial is conducted (Japan)
- Race
- Ethnicity
- Possibility of pregnancy

3.7.1.4 Subject Registration

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

3.7.1.5 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.

- Confirmation of inclusion/exclusion criteria
- Physical examination
- Vital signs and body weight
- Pregnancy test (only for female children aged 7 - 14 years old)
- IGA
- EASI
- VRS for pruritus (only for subjects aged 7 - 14 years old)
- POEM
- Affected BSA
- Treatment area
- Severity of AD
- Photograph of the target site
- AEs
- Concomitant medications and therapies

3.7.1.6 Randomization (Allocation of Investigational Medicinal Products to Subjects)

The investigator or subinvestigator will enter the necessary information for the 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, 1% OPA-15406 group, or vehicle group. The investigator or subinvestigator will confirm the allocation result and the amount 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 (unit in g; rounded to the one decimal place; same method for all subsequent IMP weight measurements hereinafter). The IMP administration will be started at the trial site after all baseline examinations are finished. The investigator or subinvestigator will instruct the subjects to record the status of IMP administration in the administration diary daily and bring the diary with them to their next visits.

Information on randomization (date of randomization or registration, subject number or treatment group) will be recorded in the source document and CRF.

3.7.1.7 Between the Day After the Baseline Examination and the Day Prior to the Week 1 Examination

The investigator or subinvestigator will instruct the subject to evaluate and record the following item in the pruritus diary in relation to the most intense pruritus in the past 24 hours once daily, every day, at the same time as the baseline examination in principle from the day after the baseline examination to the day before the Week 1 examination. However, the subject will keep the pruritus diary up to Day 8 if scheduled to visit on Day 9 or later.

- VRS for pruritus (only for subjects aged 7 - 14 years old)

3.7.1.8 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 and body weight
- IGA
- EASI
- VRS for pruritus (only for subjects aged 7 - 14 years old)
- POEM
- Affected BSA

- Treatment area
- Photograph of the target site
- AEs
- 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 dispensed IMP will be measured. The investigator or subinvestigator will instruct the subjects to record the status of IMP administration in the administration diary daily and bring the diary with them to their next visits.

3.7.1.9 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 and body weight
- IGA
- EASI
- VRS for pruritus (only for subjects aged 7 - 14 years old)
- POEM
- Affected BSA
- Treatment area
- Photograph of the target site
- AEs
- 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 investigator or subinvestigator will instruct the subjects to record the status of IMP administration in the administration diary daily and bring the diary with them to their next visits.

3.7.1.10 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. Withdrawal examinations should be conducted if at all possible.

- Physical examination
- Vital signs and body weight
- Clinical laboratory tests
- Pregnancy test (only for female children aged 7 - 14 years old)
- IGA
- EASI
- VRS for pruritus (only for subjects aged 7 - 14 years old)
- POEM
- Affected BSA
- Photograph of the target site
- AEs
- Concomitant medications and therapies
- Status of IMP administration

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

3.7.1.11 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
- AEs
- Concomitant medications and therapies

The following examinations will be conducted as necessary:

- Physical examinations
- Vital signs and body weight
- Clinical laboratory values
- Pregnancy test (only for female children aged 7 - 14 years old)
- IGA
- EASI
- VRS for pruritus (only for subjects aged 7 - 14 years old)

- POEM
- Treatment area
- Photograph of the target site

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 Investigational Medicinal Product Administration

Details of the administration diary will be recorded in the CRF. Administration status will be recorded as poor if the frequency of IMP administration is less than 80%. The investigator or subinvestigator will confirm the status of IMP administration based on details in the administration diary and instruct the subjects as needed.

3.7.3 Photograph of the Target Site

The investigator or subinvestigator will take photographs of the target site in accordance with the photography manual. The investigator or subinvestigator will select one affected BSA (excluding the face to prevent individuals from being identified) showing the severity of IGA in the subject as the target site and record the site on the human body drawing at the baseline examination. The investigator or subinvestigator will continue taking photographs of the target site even after the symptoms at the target site are resolved. The investigator or subinvestigator will retain the photographs (electronic data) as the source document and the sponsor will collect the photographs (electronic data).

3.7.4 Severity of Atopic Dermatitis

The investigator or subinvestigator will determine the severity[8] of AD (mild, moderate, severe, or very severe) and record the result in the source document and CRF.

Table 3.7.4-1 Definition of Severity of Atopic Dermatitis

Definition	Severity
Only mild rashes[a] regardless of the area	Mild
Skin eruption with severe inflammation[b] on less than 10% of the BSA	Moderate
Skin eruption with severe inflammation[b] on ≥10% to <30% of the BSA	Severe
Skin eruption with severe inflammation[b] on ≥30% of the BSA	Very severe

[a]Mild rash: Lesions are seen chiefly with mild erythema, dry skin, or desquamation.

[b]Rashes with severe inflammation: Lesion with erythema, papule, erosion, infiltration, or lichenification, etc.

3.7.5 Efficacy Assessments

3.7.5.1 Investigator's Global Assessment

The investigator or subinvestigator will evaluate skin symptoms according to IGA.[9] The investigator or subinvestigator will score the severity (0 = Clear; 1 = Almost clear; 2 = Mild disease; 3 = Moderate disease; 4 = Severe disease/Very severe disease) of clinical characteristics (erythema, infiltration, papulation, oozing, and crusting). The result will be recorded in the source document and CRF. The same subject should be evaluated by the same physician.

Table 3.7.5.1-1 Investigator's Global Assessment

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 disease
Moderate erythema and moderate papulation/infiltration	3 = Moderate disease
Severe erythema, and severe papulation/infiltration Severe erythema, and severe crusting papulation/infiltration with oozing	4 = Severe disease/Very severe disease

3.7.5.2 Eczema Area and Severity Index

The investigator or subinvestigator will evaluate skin symptoms according to EASI.[10] The investigator or subinvestigator will score the severity (0 - 3 points) and affected BSA (%) based on the 4 clinical signs (erythema, infiltration/papulation, excoriation, and lichenification) on the 4 body regions (face, neck, and head [excluding scalp]; 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 should be evaluated by the same physician.

Table 3.7.5.2-1 Eczema Area and Severity Index

Body region	Calculation of the score for each region
Face, neck, and head	(E + I + Ex + L) × score of BSA ×0.1 (×0.2 for subjects aged 2 - 7 years old [at time of obtaining informed consent])
Upper limbs	(E + I + Ex + L) × score of BSA ×0.2
Trunk	(E + I + Ex + L) × score of BSA ×0.3
Lower limbs	(E + I + Ex + L) × score of BSA ×0.4 (×0.3 for subjects aged 2 - 7 years old [at time of obtaining informed consent])

E = severity score of erythema; I = severity score of infiltration/papulation; Ex = severity score of excoriation; L = severity score of lichenification

Severity score: no disease = 0; very mild = 0.5; mild = 1; mild-moderate = 1.5; moderate = 2; severe = 2.5; very severe = 3

Score of affected BSA (for each region): no eruption = 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

3.7.5.3 Verbal Rating Scale for Pruritus

The most intense pruritus in the past 24 hours will be evaluated according to the following VRS criteria:[11]

0: None

1: Mild

2: Moderate

3: Severe

The investigator or subinvestigator will interview the subject during the scheduled visits after the baseline examination. The subject will evaluate the pruritus and record the outcome in the pruritus diary once daily, every day at the same time in principle as the baseline examination from the day after the baseline examination until the Week 1 examination. However, the subject will keep the pruritus diary up to Day 8 if scheduled to visit on Day 9 or later.

The investigator or subinvestigator will record the results on visits in the source document and CRF, and details of the pruritus diary written by the subject in the CRF. The pruritus diary will be kept as the source document.

3.7.5.4 Patient-Oriented Eczema Measure

Eczema will be evaluated according to POEM (see Appendix 2).[12] The subjects will answer 7 questions and describe their eczema. If it is difficult to obtain answers from the subject, the subject's legal guardian will evaluate the subject's eczema and answer questions. The investigator or subinvestigator will confirm their responses and record the results in the source document and CRF. The total score of POEM is 28 points at the most. The POEM will be kept as source documents.

3.7.5.5 Affected Body Surface Area

The investigator or subinvestigator will draw the affected BSA (range of skin eruption with inflammation at the time of examination) on the human body drawing (see Appendix 3 or Appendix 4) to determine the affected areas (%) on the respective 4 body regions (head, face, and neck [excluding scalp]; upper limbs; trunk; and lower limbs). The respective affected areas (%) will be recorded in the source document and CRF. The affected BSA does not include dry skin sites. One palm of the subject corresponds to 1% BSA.

3.7.6 Safety Assessments

3.7.6.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.6.2 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.

Table 3.7.6.2-1 Clinical Laboratory Assessments	
Hematology Hemoglobin Hematocrit Red blood cell count White blood cell count and differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) Platelets Qualitative urinalysis Glucose Protein	Serum chemistry Alkaline phosphatase ALT (GPT) AST (GOT) Total bilirubin Blood urea nitrogen Total cholesterol Creatinine γ-glutamyl transpeptidase Lactate dehydrogenase Total protein Albumin Serum electrolytes (Ca, Na, K, Cl) Additional tests Urine and/or serum pregnancy for female children aged 7 to 14 years old[a]

[a]A serum pregnancy test will be conducted if the urine test results in positive or false positive outcome, or if the urine pregnancy test cannot be conducted.

The tests will be performed at the central laboratory. The investigator or subinvestigator will confirm the tests 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 tests 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 the Week 4 examination).

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

3.7.6.3 Physical Examination

The investigator or subinvestigator will assess the subject's physical condition by interview, visual examination, auscultation, or palpation. The same investigator should conduct the individual subject's physical examination by the same investigator throughout the trial period.

3.7.6.4 Vital Signs and 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.

3.7.7 Previous Medications and Concomitant Medications

The investigator or subinvestigator will record in the source document and CRF the name, purpose of use, dosage per administration, frequency, route of administration, and start/end date of administration of any medications other than the IMP (excluding cosmetics) used from 30 days prior to the screening examination until the Week 4 examination (or examination at discontinuation) regardless of whether or not their concomitant use is allowed. The investigator or subinvestigator will also record in the source document and CRF the name, purpose for conduct, and start/end date of any concomitant therapies conducted 30 days prior to screening examination until Week 4 examination (or examination at discontinuation) regardless of whether or not such is prohibited.

3.7.8 End of Trial

The “end of trial date” is defined as “the last date of visit or contact” or “the date judged as terminated” for the last subject completing or withdrawing from the trial. It does not include the period for follow-up of the last subject’s AEs.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Termination or Interruption of the Entire Trial

When the sponsor decides to terminate or interrupt the trial for some reason, the sponsor will promptly notify the head of the trial site and the regulatory authority in accordance with regulatory requirements.

3.8.2 Termination or Interruption of the Trial at Individual Trial Sites

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and GCP. The head of the trial site will notify the sponsor promptly if the trial is terminated by the investigator or the IRB at the 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 randomization, the investigator or subinvestigator may discontinue IMP administration for various reasons. These reasons for discontinuation include a request from the subject or subject's legal guardian who is not satisfied with IMP administration or occurrence of an AE, 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 or subject's legal guardian with all possible choices to continue with the IMP administration according to Section 3.8.3.5, Procedures to Encourage Continued Trial Participation.

3.8.3.2 Discontinuation Criteria

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 AE 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 AE that makes it difficult for the subject to continue administration of IMP (including a suspected treatment-related AE of skin hypersensitivity on the treatment area)
4) Discovery that the subject is pregnant or suspected to be pregnant
5) Judgment by the investigator or subinvestigator that it is necessary to withdraw the subject from the trial

3.8.3.3 Documenting Reasons for Treatment Discontinuation

All subjects and subject's legal guardians have the right to discontinue the trial and the investigator or subinvestigator can also discontinue a subject's participation in the trial at any time if medically necessary. If subjects discontinue their participation in the trial, only one reason (main reason) for withdrawal should be recorded in the CRF.

- Reasons related to AEs:
  - Request from the subject due to distress or discomfort associated with a non-serious AE 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 concern)
    - SAE
    - Other safety concerns or AEs possibly related to IMP
- Death
- Withdrawal of consent (complete documented withdrawal of consent)
- Judgment by physician
- Lost to follow-up
- Pregnancy (see Section 5.6, Pregnancy)
- Entire or partial discontinuation of the trial by the sponsor
- Lack of efficacy
- Deviation from the protocol
- Other

If the subject discontinued the IMP administration due to an AE, the investigator, subinvestigator, or other clinical trial associates will follow the AE until it resolves or stabilizes, or the subject is lost to follow-up or dies, as much as possible, according to the procedures specified in Section 3.8.3.1, Treatment Discontinuation.

3.8.3.4 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 and the subject's legal guardian withdraw 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 and the 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 and the subject's legal guardian refuses all of the following follow-up procedures (These methods of follow-up will also be noted in the trial ICF).

- 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 (if some parts of the follow-up procedures are refused by the subject and/or the subject's legal guardian, those agreed between the subject, 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, spouse, partner, 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 (see Section 3.8.3.1, Treatment Discontinuation and Section 3.8.3.2, Discontinuation Criteria), 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 accordance with Section 3.8.3.3, 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.

3.8.3.5 Procedures to Encourage Continued Trial Participation

If discontinuation of IMP administration or withdrawal of consent is expected, the investigator or subinvestigator will meet with the subject and the subject's legal guardian and talk about the possible options for them to continue participating (preferably, to continue treatment) in the trial. The investigator or subinvestigator will confirm the reason(s) for the subject's and the subject's legal guardian's desire to withdraw 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 who has a signed ICF, but who has not been randomized or to whom an IMP was not allocated.

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

Subject identification number, date of informed consent, date of screening examination, date of birth, sex, date of judgment as screen failure, 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 safety 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 Week 4 examination are defined as completed subjects.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on and before the Week 4 examination during the treatment period, subjects who do not have a known reason for discontinuation (eg, withdrew consent or AE) and subjects whose survival is unknown on the trial completion day will be classified as lost to follow-up. 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 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 considered as "lost to follow-up." If the subject is lost to follow-up, the contact date and contact method will be recorded in the source document and the last date on which an attempt was made to reach the subject and the contact method will be recorded in the CRF.

3.12 Subject (including 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.
- The subject will evaluate the most intense pruritus in the past 24 hours once daily, every day, at the same time as the baseline examination in principle from the day after the baseline examination until the day before the Week 1 examination and describe it in a pruritus diary for subjects aged 7 to 14 years old. However, the subject will keep the pruritus diary up to Day 8 if scheduled to visit on Day 9 or later.
- 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 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.

3.13 Deviations from the Trial Protocol

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator, subinvestigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator or subinvestigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the

investigator or subinvestigator and the sponsor, and reviewed by the site monitor. If any major deviations occur, the date of occurrence and details of the major deviation will be recorded in the CRF.

The investigator or subinvestigator will record all deviations from the protocol. Major protocol deviations will be recorded in the CRF such as "subjects who entered the trial even though they did not meet the inclusion or exclusion criteria," "subjects who developed withdrawal criteria during the trial but were not withdrawn," "protocol deviations that affect the primary endpoint assessment," "subjects who received the wrong treatment or incorrect dose," or "subjects who received a prohibited concomitant therapy."

4 Restrictions

4.1 Prohibited Concomitant Drugs and Therapies

Prohibited concomitant drugs and therapies are shown in Table 4.1-1. The use of drugs on the scalp is not restricted since the IMP will not be applied to the scalp.

Table 4.1-1 Prohibited Concomitant Drugs and Therapies

Duration	Provision
From 3 months prior to obtaining informed consent to the Week 4 examination (or withdrawal examination)	Allergen immunotherapy (desensitization therapy) However, if subjects have continued allergen immunotherapy for more than 3 months prior to informed consent or earlier, and the investigator or subinvestigator judges that no changes in AD symptoms are observed, subjects may continue such therapy until Week 4 examination as long as no changes are made to the therapy (types or amount of allergen, frequency, etc).
From 28 days prior to the baseline examination until the Week 4 examination (or withdrawal examination)	Ultraviolet light A, narrowband ultraviolet B (NB-UVB), ultraviolet light B
	Systemic corticosteroids, systemic immunosuppressants, systemic antimetabolites, systemic retinoids, and biologics
From 21 days prior to the baseline examination until the Week 4 examination (or withdrawal examination)	Topical corticosteroids for skin categorized as very strong or higher potency in the "Guidelines for Management of Atopic Dermatitis[1]"
From 7 days prior to the baseline examination until the Week 4 examination (or withdrawal examination)	Topical corticosteroids for skin categorized as strong potency in the "Guidelines for Management of Atopic Dermatitis[1]", topical corticosteroids other than those for skin, topical immunosuppressants, topical retinoids, topical antihistamine, and topical non-steroidal anti-inflammatory drugs. However, intra-ocular, intra-nasal, intra-auricular, and inhaled corticosteroids and antihistamines may be considered if the investigator or subinvestigator

Table 4.1-1 Prohibited Concomitant Drugs and Therapies	
	judges that their use will not impact assessment of the affected area.
	Systemic antihistamines, sodium cromoglicate, tranilast, suplatast tosilate However, if these medications were being used prior to obtaining consent, their use may be continued without changing the dosage and administration.
From 4 days prior to the baseline examination until the Week 4 examination (or withdrawal examination)	Topical corticosteroids for skin categorized as low or medium potency in the "Guidelines for Management of Atopic Dermatitis[1]"
From the baseline examination until the Week 4 examination (or withdrawal examination)	All topical drugs (including ethical drugs, over-the-counter products, herbal medicine, quasi-drugs, and cosmetic products) on the treatment area. However, if cosmetic products were being used on the face and neck prior to obtaining consent, their use may be continued only if the same products are used at the same frequency.

AD: Atopic dermatitis; NB-UVB: Narrow-band ultraviolet B

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.

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. Adverse Events 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.

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 or subinvestigator, 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.

Non-serious AEs 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 serious hepatotoxicity (see Section 5.4, Potential Serious Hepatotoxicity).
- 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. Pregnancies of the subjects or their partners will be included in the above.

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.

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.

Skin and subcutaneous tissue disorders will be graded according to the Common Terminology Criteria for Adverse Events v4.0 Japan Clinical Oncology Group edition.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is judged according to the following criteria:

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?” The names, dates of occurrence, dates of outcomes, seriousness, severity, causal relationship with the IMP, measures related to IMP administration, outcomes, and occurrences at administration sites of all AEs reported by the subject must be recorded on the source documents and CRFs provided by the sponsor. Eliciting AEs and SAEs will be started after the subject has signed an ICF.

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. 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 e-mail of any IREs in principle according to the procedure outlined below, in Section 5.3, Immediately Reportable Events. Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events

After either the investigator, subinvestigator, or designated person becomes aware of any SAE, any AE related to occupational exposure, potential serious hepatotoxicity, or confirmed pregnancy, the investigator or subinvestigator must immediately report the event to the sponsor by e-mail in principle (see cover page of this protocol for contact information). An IRE form, etc. must be completed and sent by e-mail in principle to the sponsor. Please note that the IRE form is NOT the AE section of CRF.

Subjects experiencing SAEs and IREs 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 Serious Hepatotoxicity

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, all values should be recorded on an IRE form, etc. and report as an AE on the CRF.

5.5 Implementation of Patch Test

If any AE 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 again, 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[13] 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 in this clinical trial, 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, the legal guardians of female pediatric subjects (potential) aged 7 to 14 years old 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 ICF stating that the above-mentioned risk factors and consequences were discussed with her.

At the screening, baseline, Week 4, and withdrawal examinations, female children aged 7 to 14 years old should undergo a urine pregnancy test. If a positive or false positive urine test result is obtained or the urine test is not possible, a serum pregnancy test (human chorionic gonadotropin test) will be conducted.

During the trial, female children and subject's 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, etc. and forward it to the sponsor. 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

The investigator or subinvestigator is encouraged to contact the sponsor to discuss their rationale for unblinding. However, to prevent delays to the investigator, subinvestigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor (ie, the investigator or subinvestigator will be able to obtain the code break information independent of the sponsor). The investigator or subinvestigator must contact the sponsor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Clinical Safety and Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP. Please refer to the "Procedure for Emergency Code Breaking" for more detailed information.

5.8 Follow-up of Adverse Events

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 (ongoing or recovered/resolved). All non-serious AEs (excluding IREs) that are ongoing at the day of trial completion (final observation day) 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 by the sponsor 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 day of trial completion (final observation day) will be recorded in medical records.

5.8.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

In this trial, subjects will be actively observed for occurrence of any SAEs and IREs until the Week 4 examination or withdrawal examination (the day of trial completion [final observation day]).

Serious Adverse Events and IREs that are identified up to the day of trial completion or are ongoing on the day of trial completion must be recorded on the AE section of CRF. If new information on applicable SAEs or IREs (eg, “recovered”) is obtained from the day of a subject’s trial completion to the day of trial completion of the last subject during the trial period, it should be reported to the sponsor using the IRE form, etc. and must be recorded on the AE section of CRF. Any SAEs or IREs should be followed and any significant follow-up information should be reported to the sponsor using the IRE form, etc. until the events are resolved or clinically stabilized, or the subject is lost to follow-up or dies.

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

Any new SAEs and IREs reported 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. These events may include SAEs and IREs that are captured on follow-up telephone contact or at any other timepoint after the defined trial period. The investigator or subinvestigator should follow

any SAEs and IREs identified after the defined trial period and report any significant follow-up information to the sponsor using the IRE form, etc. until the event has been resolved or clinically stabilized, or the subject is lost to follow-up or dies.

6 Pharmacokinetic Analysis

No pharmacokinetic analysis is planned.

7 Statistical Analysis

7.1 Sample Size

The target sample size is set to achieve a power of 90% for the comparison of the 1% OPA-15406 group and vehicle group, which is firstly conducted in a closed testing procedure. In the phase 2 trial in pediatric patients in Japan (Trial 271-102-00002), the success rate in IGA was 37.5% (9/24), 40.0% (10/25) and 8.3% (2/24) in the 0.3% OPA-15406 group, 1% OPA-15406 group and vehicle group, respectively. However, for reasons such as the sample size of the phase 2 trial in pediatric patients in Japan being small and in order to conservatively consider the robustness of the trial results based on the characteristics of the primary endpoint, it is assumed that if the number of responders increased by one and decreased by one in the 1% OPA-15406 group and vehicle group, respectively, then the success rate in IGA is 36% and 12%. In the case of this condition, it is necessary to have 72 subjects per group to achieve a power of 90% using a two-sided significance level of 5%. In consideration of an exploratory assessment of age categories, however, the target sample size has been set as 80 subjects in each group, for a total of 240 subjects.

7.2 Datasets for Analysis

- Safety Set (SS):
  The SS consists of all subjects who have received the IMP at least once.
- Full Analysis Set (FAS):
  The FAS consists of all subjects who have received the IMP at least once.

7.3 Handling of Missing Data

For the success rate in IGA, the primary endpoint, subjects with missing IGA data will be handled as non-responders.

7.4 Primary and Secondary Endpoint Analyses

Efficacy will be analyzed in the FAS.

7.4.1 Primary Endpoint Analysis

The primary endpoint is the success rate in IGA (percentage of subjects with an IGA score of 0 or 1 with an improvement of at least 2 grades) at Week 4.

The efficacy of the 0.3% and 1% OPA-15406 groups will be demonstrated compared to the vehicle group based on the primary endpoint, the success rate in IGA at Week 4. Overall type I errors will be controlled using a closed testing procedure. First, the 1% OPA-15406 treatment group and the vehicle group will be compared. If significant at the two-sided significance level of 5%, the 0.3% OPA-15406 treatment group and the vehicle group will then be compared at the two-sided significance level of 5%. The Cochran-Mantel-Haenszel test will be conducted for comparison using the baseline IGA (2 or 3) and age ("2 - 6 years" or "7 - 14 years") as a stratification factor. The difference in the success rate in IGA and its two-sided 95% confidence interval (common risk difference adjusted by Mantel Haenszel method and its two-sided 95% confidence interval) between the vehicle group and 0.3% or the 1% OPA-15406 group will be determined. Also, the two-sided 95% confidence interval of the success rate in IGA in each treatment group (based on Clopper-Pearson method) will be calculated. In addition, the success rate in IGA in each treatment group and its two-sided 95% confidence interval will be plotted and the dose-response relationship will be graphically assessed.

Also, a supplementary analysis will be performed using data which includes missing data imputed by Last Observation Carried Forward (LOCF) and Observed Cases (OC) data which does not include the imputed missing data in the same manner.

7.4.2 Secondary Endpoint Analysis

- The success rate in IGA achieving a score of 0 or 1 at Week 4 and the success rate in EASI 75, EASI 90, and EASI 50 at Week 4

The secondary endpoint will be analyzed in the same manner as the primary endpoint. For IGA, subjects who achieve a score of 0 or 1 in IGA will be handled as responders and subjects who do not achieve a score 0 or 1 in IGA will be handled as non-responders. Subjects with missing IGA data will be handled as non-responders.

EASI 75 will be set as the important secondary endpoint, and subjects whose percentage change in their total EASI score from baseline decreases by ≥75% will be handled as responders and subjects whose percentage change from baseline does not decrease by ≥75% will be handled as non-responders. Subjects with missing EASI 75 data will be handled as non-responders. EASI 90 and EASI 50 will be analyzed in the same manner. Similarities with the primary endpoint results will be assessed using the response rates in EASI (EASI 75, EASI 90, and EASI 50).

- Change from baseline at Week 4 in the IGA score; the total EASI score; each EASI clinical sign score; VRS for pruritus (including Day 7); the total POEM score; and the total affected BSA (%).

Based on the OC data set, change from baseline (Week 1, Week 2, and Week 4) will be analyzed using a mixed model repeated measure (MMRM) with treatment (0.3% OPA-15406 or 1% OPA-15406, and vehicle), timepoint, interaction between the treatment and timepoint as factors and baseline values as covariates. An unstructured error covariance matrix will be used and Kenward-Roger method will be used to calculate the degree of freedom. If the MMRM procedure fails to converge under unstructured covariance structure, the following structure will be used in the order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry, and the first error covariance structure converging will be used. The MMRM analysis with the structured error covariance matrix will use a sandwich estimator. The least square mean will be calculated by treatment group and timepoint.

7.4.3 Subgroup Analysis

Success rate in IGA by subgroup will be analyzed in the same manner as the analysis of the primary endpoint as follows:

- Age: 2 to 6 years old, 7 to 14 years old
- Sex: male, female
- IGA score at baseline: 2 or 3

7.4.4 Exploratory Analysis of Age Factor

Logistic regression analysis will be performed using treatment group as the main effect, baseline IGA (2 or 3) and age as covariates, and success rate in IGA at Week 4 as a response variable. An adjusted odds ratio and its 95% confidence interval will be determined.

For the age factor, in addition to age categories of “2 to 6 years old” and “7 to 14 years old,” no categorized age and other categorized age factor will be used.

7.5 Analysis of Demographic and Other Baseline Characteristics

For demographic and other baseline characteristics, the descriptive statistics or frequency distribution will be created by treatment group and for all subjects treated with OPA-15406 depending on the characteristics of the respective parameters in the FAS and SS.

7.6 Safety Analysis

Safety analysis will be performed in the SS.

7.6.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J) system organ class and preferred term. The percentage of subjects experiencing the following AEs will be calculated for all subjects treated with OPA-15406 by treatment group.

- TEAEs
- TEAEs by severity
- TEAEs resulting in death
- Serious TEAEs
- TEAEs leading to discontinuation of IMP administration
- TEAEs (skin and subcutaneous tissue disorders) by grade
- TEAEs at treatment areas

Treatment-emergent adverse events related to IMP will also be calculated in the same manner.

7.6.2 Clinical Laboratory Tests

For each parameter (except qualitative urinalysis), the descriptive statistics will be calculated for measured values and changes from the baseline at each timepoint for all subjects treated with OPA-15406 and by treatment group. For qualitative urinalysis values of clinical laboratory tests, a shift table at each timepoint against the baseline will be created for all subjects treated with OPA-15406 and each treatment group. For clinical laboratory tests except qualitative urinalysis, the number and percentage of subjects who are in the potentially clinically significant range will be calculated. The number and percentage of potential Hy's Law Cases will be calculated for all subjects treated with OPA-15406 and by treatment group.

7.6.3 Vital Signs and Body Weight

For each parameter and body weight, the descriptive statistics will be calculated for measured values and changes from baseline at each timepoint for all subjects treated with OPA-15406 and by treatment group. The number and percentage of subjects with clinically abnormal changes will be calculated for all subjects treated with OPA-15406 and by treatment group.

8 Management of Investigational Medicinal Product

For further information about the management of the IMP, refer to the Investigator's Brochure.

8.1 Packaging and Labeling

The IMP will be provided to 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 identification 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. The IMP manager may not 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, used 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 and be identified by protocol number with trial site number on the outermost shipping container. 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 product, empty blister)
- 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_271-102-00008@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 Product Quality Complaints

- Description of compliant
- Reporter identification (eg, subject, investigator or subinvestigator, trial site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (compound name, kit number)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return of the sample of complaints

8.5.3 Return Process in the Case of Product Quality Complaints

Indicate during the PQC report if the complaint sample is available for return. The sponsor may provide instructions for the return process of the sample, as necessary.

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 medical records, electronic data, screening logs, and recorded data from automated instruments.

All source documents pertaining to this trial will be maintained by the institutions 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 medical records 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 medical records.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical records as described above. Any changes to information in the medical records 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 investigator or subinvestigator. If electronic data systems are being utilized, a full audit trail of changes must be maintained.

Information from the medical records and other source documents will be entered by investigative site personnel directly onto electronic CRFs in the sponsor's electronic data capture. 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 E6 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 GCP Guidelines (E6), 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 number 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 country 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 identification 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 and 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 (Japanese Dermatological Association's Criteria)

1. Pruritus
2. Typical morphology and distribution:
   (1) Eczematous dermatitis
   - Acute lesions: erythema, exudation, papules, vesiculopapules, scales, crusts
   - Chronic lesions: infiltrated erythema, lichenification, prurigo, scales, crusts

   (2) Distribution
   - Symmetrical
     Predilection sites: forehead, periorbital area, perioral area, lips, periauricular area, neck, joint areas of limbs, trunk
   - Age-related characteristics
     Infantile phase: starts on the scalp and face, often spreads to the trunk and extremities
     Childhood phase: neck, the flexural surfaces of the arms and legs
     Adolescence and adult phase: tendency to be severe on the upper half of body (face, neck, anterior chest and back)
3. Chronic or chronically relapsing course (usually coexistence of old and new lesions):
   More than 2 months in infancy, and more than 6 months in childhood, adolescence, and adulthood

Definitive diagnosis of atopic dermatitis requires the presence of all three features without any consideration of severity. Other cases should be evaluated on the basis of the age and clinical course with the tentative diagnosis of acute or chronic, non-specific eczema.

Differential diagnosis (association may occur)	
• Contact dermatitis • Seborrhoeic dermatitis • Prurigo simplex • Scabies • Miliaria • Ichthyosis • Xerotic eczema	• Hand eczema (non-atopic) • Cutaneous lymphoma • Psoriasis • Immune deficiency diseases • Collagen diseases (systemic lupus erythematosus, dermatomyositis) • Netherton's syndrome
Diagnostic aids	
• Family history (bronchial asthma, allergic rhinitis and/or conjunctivitis, atopic dermatitis) • Complications (bronchial asthma, allergic rhinitis and/or conjunctivitis) • Follicular papules (goose-skin) • Elevated serum IgE level	
Clinical type (not applicable to the infantile phase)	
• Flexural surface type • Extensor surface type • Dry form in childhood • Head, neck, upper chest, back type	• Prurigo type • Erythroderma type • Combinations of various types are common
Significant complications	
• Ocular complication (cataract and/or retinal detachment): especially in patients with severe facial lesions • Kaposi's varicelliform eruption	• Molluscum contagiosum, • Impetigo contagiosa

Appendix 2 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 legal representatives 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

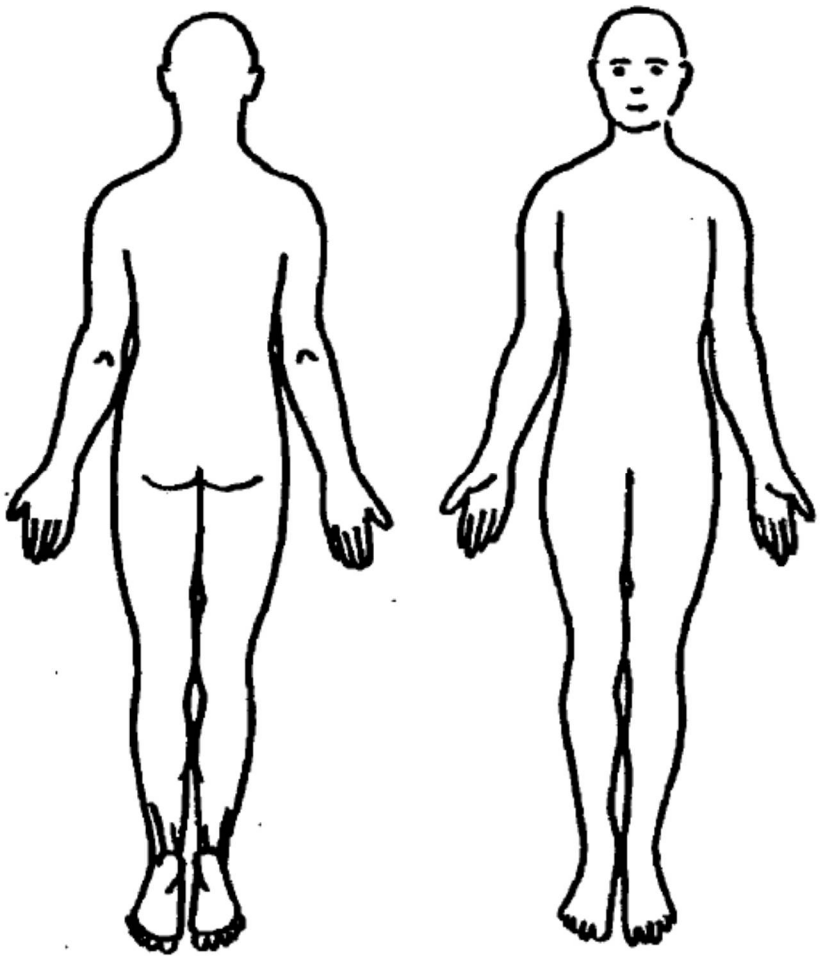
7. Over the last week, on how many days has your skin felt dry or rough because of your eczema?

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

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

Appendix 3 Human Body Drawing for Children Aged 8 to 14 Years Old

_____Day/ ____Month/20___(_____examination) Subject identification number: _ _ _S000_ _



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

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

Total amount of administration _____g

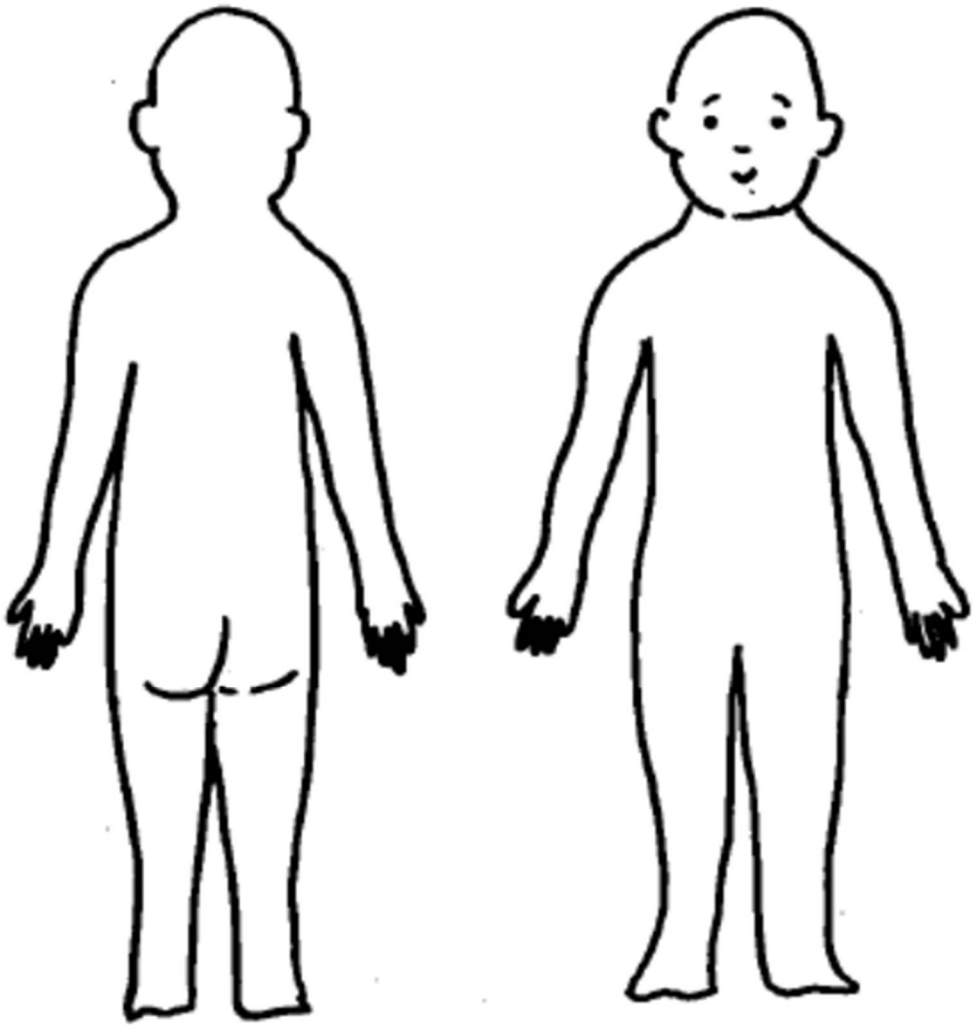
(Appropriate amount of administration per 1% g)

Signature of the investigator/subinvestigator

_____Day/_____Month/20_____

Appendix 4 Human Body Drawing for Children Aged 2 to 7 Years Old

_____Day/ ____Month/20___(_____examination) Subject identification number: _ _ _S000_ _



Affected site	Affected area (%)
Face, neck, and head (excluding scalp)	%
Upper limbs	%
Trunk	%
Lower limbs	%
Total	%

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

Total amount of administration
_____g

Appropriate amount of administration per 1%
g

Signature of the investigator/subinvestigator
_____Day/_____Month/20_____

Appendix 5 Protocol Amendments and Administrative Changes

Amendment No.: 2 (First amendment after submission of protocol)

Date created: 1 Feb 2019

Purpose: To clarify the prohibited concomitant drugs and therapies and exclusion criteria related to prohibited concomitant drugs and therapies and to provide more appropriate wording.

Background: Amendments were made upon judgment that clarifications on prohibited concomitant medication and more appropriate terminology were necessary.

Amendments to protocol:

- The sentence below was added to Section 4.1 Prohibited Concomitant Drugs and Therapies. Also, more details were added to clarify the language regarding steroids in Table 4.1-1 Prohibited Concomitant Drugs and Therapies.
  The use of drugs on the scalp is not restricted since the IMP will not be applied to the scalp.
- In accordance with the above changes, a sentence related to corticosteroids was added to Exclusion Criteria 14 to 16 to allow for the use of corticosteroids on the scalp, and changes to the wording related to corticosteroids were made.
- Exclusion Criteria 14
  Prior to change:
  Subjects who are unable to stop using topical corticosteroids categorized as very strong or higher potency in the "Guidelines for Management of Atopic Dermatitis[1]" from 21 days prior to the baseline examination until the Week 4 examination.
  After change:
  Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as very strong or higher potency in the "Guidelines for Management of Atopic Dermatitis[1]" from 21 days prior to the baseline examination until the Week 4 examination.
- Exclusion Criteria 15
  Prior to change:
  Subjects who are unable to stop using topical corticosteroids categorized as strong potency in the "Guidelines for Management of Atopic Dermatitis[1]", topical immunomodulators, topical retinoids, topical antihistamine and topical non-steroidal anti-inflammatory drugs from 7 days prior to the baseline examination until the Week 4 examination. Intra-ocular, intra-nasal, and intra-auricular corticosteroids, inhaled corticosteroids, intra-ocular and intra-nasal antihistamines or inhaled antihistamines may be considered if, in the opinion of the investigator or subinvestigator, their use will not impact assessment of the affected area.
  After change:
  Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as strong potency in the "Guidelines for Management of Atopic

Dermatitis[1]", topical corticosteroids other than those for skin, topical immunosuppressants, topical retinoids, topical antihistamine and topical non-steroidal anti-inflammatory drugs (excluding for scalp) from 7 days prior to the baseline examination until the Week 4 examination. Intra-ocular, intra-nasal, intra-auricular, and inhaled corticosteroids and antihistamines may be considered if the investigator or subinvestigator judges that their use will not impact assessment of the affected area.

- Exclusion Criteria 16
  Prior to change:
  Subjects who are unable to stop using topical corticosteroids categorized as low or medium potency in the "Guidelines for Management of Atopic Dermatitis[1]" from 4 days prior to the baseline examination until the Week 4 examination.
  After change:
  Subjects who are unable to stop using topical corticosteroids for skin (excluding scalp) categorized as low or medium potency in the "Guidelines for Management of Atopic Dermatitis[1]" from 4 days prior to the baseline examination until the Week 4 examination.
- The following sentence was added to Section 3.7.1 Schedule of Assessments:
  Regarding assessments to be performed by the investigator or subinvestigator, the assessments that a clinical trial associate is able to perform (eg, subject demographics and clinical laboratory tests) may be performed by the clinical trial associate under the supervision of the investigator.
- Other changes were made to correct minor typos and to reflect changes to the template.

  In this English translation version, the term "immunomodulators" was changed to "immunosuppressants" to standardize terminology across protocols.

Additional risks to subjects: No additional risks will be imposed on the subjects.

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, OPA-15406 ointment, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the clinical trial facility where OPA-15406 ointment will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority by the sponsor. I agree that clinical data entered on case report forms by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and sub-investigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____
Principal Investigator Name	Trial Site

_____	DD Mon 20XX
Signature	Date

The signature of the sponsor is electronically captured. The electronic signature page is attached to this agreement.