CLINICAL STUDY PROTOCOL

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

NCT Number: 02914548

PRT NO. 271-15-001

PRT Version Date: 29 December 2016 (Version 4)

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

(Phase 2 Trial)

Clinical Protocol

Protocol No.: 271-15-001

(Translated Version)

Confidential

Otsuka Pharmaceutical Co., Ltd.

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Statement of Confidentiality

The trial protocol is to be treated as confidential information and is to be made available only to persons involved in the trial. The content of the protocol is not to be disclosed to any third party without the prior written consent of Otsuka Pharmaceutical Co., Ltd., except in the case of its being explained to a candidate trial subject. Disclosure of the results of the trial to academic societies or journals, etc, in part or in whole, will require the prior written approval of Otsuka Pharmaceutical Co., Ltd.

Trial Protocol Synopsis

Name of Investigational Medicinal Product	OPA-15406 Ointment
Trial Title	A Multicenter, Randomized, Double-blind, Vehicle-controlled, Parallel-group Comparison Trial to Assess the Efficacy and Safety of 0.3% and 1% OPA-15406 Ointments in Patients With Atopic Dermatitis (Phase 2 Trial)
Trial Objectives	Primary Objective: To evaluate Week 4 efficacy of OPA-15406 (0.3% and 1%) compared to the vehicle when administered twice daily for 8 weeks using incidence of success in Investigator's Global Assessment (IGA) as the primary endpoint in patients with atopic dermatitis. Secondary Objective: To evaluate the safety of OPA-15406 (0.3% and 1%) when administered twice daily for 8 weeks in patients with atopic dermatitis.
Phase of Development	Phase: 2 Type of trial: Dose-finding trial
Trial Design	Multicenter, randomized, double-blind, vehicle-controlled, parallel-group comparison trial
Target Population	Atopic dermatitis (AD)
Target Number of Subjects	180 subjects in total 0.3% OPA-15406 group: 60 subjects 1% OPA-15406 group: 60 subjects Vehicle group: 60 subjects
Inclusion Criteria	Subjects who meet all of the following criteria will be eligible for inclusion in this trial. At the screening examination: 1) Sex: Either male or female 2) Hospitalization status: Outpatient 3) Age: 15 to 70 years, inclusive (at time of obtaining informed consent)

	4) Able to provide written informed consent. For subjects under 20 years of age, written informed consent must be obtained from both the subject and the subject's legal guardian. 5) Diagnosis of AD based on the criteria of Hanifin and Rajka[1] (Appendix 1) 6) History of AD for at least 3 years At screening and baseline examinations: 7) Atopic dermatitis affecting ≥5% to ≤40% of body surface area (BSA) 8) IGA score of 2 (mild) or 3 (moderate)
Exclusion Criteria	Subjects who fall under any of the following criteria at either the screening or baseline examination will be excluded from the trial: 1) Subjects who are pregnant, possibly pregnant, or breastfeeding, who desire to become pregnant or to have their partner become pregnant during the trial period and up until 30 days after the final administration of IMP, or who are unable to either remain abstinent or employ at least two of the specified birth control methods (vasectomy, tubal ligation, vaginal diaphragm, intrauterine device [IUD], birth control pill, condom with spermicide, etc) 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 sudden intensification of atopic dermatitis, 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 atopic dermatitis in the present trial 4) Subjects who have an active viral skin infection (eg, herpes simplex, herpes zoster, chicken pox) or clinically infected AD 5) Subjects with a current or history of malignancy within the previous 5 years. However, subjects in whom basal-cell skin carcinoma or squamous-cell skin carcinoma is judged to have been cured at the

	time of the screening examination can be included in the trial. 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 assessments: • 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, hepatitis B, hepatitis C) • Renal disease • Hematologic disease • Immunologic or immunocompromised disease (eg, lymphoma, 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 trial assessment 8) Subjects with any of the following hematology or serum chemistry results at screening examination: • White blood cell count: ≤3, 000/μL or >14, 000/μL • Platelets: ≤100, 000/μL • Hemoglobin: <11 g/dL • Serum creatinine: ≥2 mg/dL • Aspartate aminotransferase (AST) (GOT): >1.5 × ULN • Alanine aminotransferase (ALT) (GPT): >1.5 × ULN • Total bilirubin: ≥2.0 mg/dL

	• Any other abnormal laboratory test result that the investigator or subinvestigator judges to be a clinically significant abnormality 9) Subjects who are judged by the investigator or subinvestigator to have clinically significant electrocardiogram (ECG) findings (eg, AV block, prolongation of QRS complex to ≥120 msec, or QTcF interval of ≥450 msec) at screening examination 10) Clinically significant blood pressure or pulse rate findings at screening examination of: • Age 18 to 70, inclusive: seated resting (≥3 minutes) systolic blood pressure of <100 mmHg or ≥150 mmHg or diastolic blood pressure of <50 mmHg or ≥90 mmHg, or pulse rate of <50 bpm or >100 bpm • Age 15 to 17, inclusive: seated resting ≥3 minutes) systolic blood pressure of <95 mmHg or ≥140 mmHg or diastolic blood pressure of <50 mmHg or ≥90 mmHg, or pulse rate of <50 bpm or >100 bpm 11) Subjects who are unable to stop using topical corticosteroids, topical immunomodulators, topical retinoids and topical antihistamine from 7 days prior to the baseline examination until the Week 8 assessment. However, corticosteroids categorized as low or medium potency in the "Guidelines of care for the management of atopic dermatitis, Section 2"[2] 12) may be used up until the baseline examination if, in the opinion of the investigator or subinvestigator, their use is necessary, such as when the subjects have been using the corticosteroids prior to providing informed consent to participate in the trial and use of the corticosteroids will be tapered off and stopped during the screening period. 13) Subjects who are unable to stop using systemic corticosteroids, systemic immunomodulators, systemic antimetabolites, systemic retinoids and biologics from 28 days prior to the baseline examination until the Week 8 examination. Intra-ocular, intra-nasal, and intra-auricular corticosteroids or inhaled corticosteroids may be considered if, in the opinion of the investigator or subinvestigator, their use will not impact assessment of the affected area. 14) Subjects who are unable to stop treatment with

	ultraviolet light A, narrowband ultraviolet B, or ultraviolet light B from 28 days prior to the baseline examination until the Week 8 examination 15) Subjects who are unable to stop using systemic antihistamines, sodium cromoglicate, tranilast, or suplatast tosilate from 7 days prior to the baseline examination until the Week 8 examination 16) Subjects with known hypersensitivity (including history) to any drugs (prescription, OTC, etc) or any ingredient of OPA-15406 ointment 17) Subjects with known plans to receive any of the prohibited concomitant drugs or therapies during the trial period 18) 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 19) Subjects who have never been treated with a prescription medication for AD or who are satisfied with their current AD treatment regimen 20) Subjects who are judged by the investigator or subinvestigator to be inappropriate to participate in the trial for any other reason
Discontinuation Criteria	If any of the following events occur during the trial period, the investigator or subinvestigator will withdraw the subject from the trial: 1) Request from the subject or subject's legal guardian to discontinue participation in the trial 2) Discovery that the subject was included in the trial despite violation of the inclusion or exclusion criteria 3) Occurrence of any adverse event that makes it difficult for the subject to continue administration of IMP (including a suspected treatment-related adverse event of skin hypersensitivity on the treatment area) 4) Increase in the total treatment area to more than 40% of BSA 5) Discovery that the subject is pregnant or suspected to be pregnant 6) Judgment by the investigator or subinvestigator that it is necessary to withdraw the subject from the trial
Investigational	Test Product: 0.3% and 1% OPA-15406 ointments

Medicinal Products, Dose and Regimen, and Treatment Period	Comparator: Vehicle of OPA-15406 ointment Twice daily administration (approximately 12 hours apart between morning and night administration) for 8 weeks
Prohibited Concomitant Drugs, Prohibited Concomitant Therapies	1) From 28 days prior to the baseline examination until the Week 8 examination, use of the following drugs and therapies is prohibited. • Systemic corticosteroids, systemic immunomodulators, systemic antimetabolites, systemic retinoids, and biologics Intra-ocular and intra-nasal corticosteroids or inhaled corticosteroids may be considered if, in the opinion of the investigator or subinvestigator, their use will not impact assessment of the affected area. • Ultraviolet light A, narrowband ultraviolet B, and ultraviolet light B 2) From 7 days prior to the baseline examination until the Week 8 examination, use of the following drugs and therapies is prohibited. • Topical corticosteroids, topical immunomodulators, topical retinoids, and topical anti-histamine. • Corticosteroids categorized as low or medium potency in the "Guidelines of care for management of atopic dermatitis, Section 2" • may be used up until the baseline examination (up until the Week 8 examination on the face, neck, and head) if, in the opinion of the investigator or subinvestigator, their use is necessary, such as when the subjects have been using the corticosteroids prior to providing informed consent to participate in the trial and use of the corticosteroids will be tapered off and stopped during the screening period. • Systemic antihistamines, sodium cromoglicate, tranilast, suplatast tosilate 3) From the baseline examination until the Week 8 examination, use of the following drugs and products on the treatment area is prohibited. • All topical drugs (including ethical drugs, over-the-counter products, herbal medicine, quasi-drugs, and cosmetic products) However, if cosmetic products were being used on the face, neck, and head prior to obtaining consent, their use may be continued

	only if the same products are used at the same frequency.
Variables	Efficacy Endpoints: Primary Outcome Variable: Incidence of success in IGA at Week 4: Percentage of subjects in whom IGA score is 0 (clear) or 1 (almost clear) and improved at least 2 grades from baseline Secondary Outcome Variables: 1) Incidence of success in IGA at Week 1 and Week 8 2) Change from baseline in IGA at Week 1, Week 4, and Week 8 3) Change from baseline in the total score of Eczema Area and Severity Index (EASI) and each symptom score at Week 1, Week 4, and Week 8 4) Change from baseline in Visual Analogue Scale (VAS) for pruritus at Week 1, Week 4, and Week 8 5) Change from baseline in Verbal Rating Scale (VRS) for pruritus up to Day 7 6) Change from baseline in the total score of Dermatology Life Quality Index (DLQI) at Week 1, Week 4, and Week 8 7) Change from baseline in the total score of Patient-Oriented Eczema Measure (POEM) at Week 1, Week 4, and Week 8 8) Change from baseline in the total affected BSA (%) at Week 1, Week 4, and Week 8 9) Time to response in IGA and VRS Safety Endpoints: Adverse events, physical examination, vital signs (including body weight), clinical laboratory values, and 12-lead ECG Pharmacokinetics: 1) Plasma trough concentrations of OPA-15406 (prior to IMP administration at Week 1, Week 4, and Week 8 of IMP administration; all subjects) 2) Plasma concentrations of OPA-15406 (prior to IMP

	administration and 2 hours, 4 hours, and 8 hours postdose on Day 1 and at Week 4; specific trial sites; target of 6 subjects from each group) • Pharmacokinetic parameters of OPA-15406: C_{max}, t_{max}, and AUC_{0-8h} on Day 1 and at Week 4 of IMP administration • Accumulation of OPA-15406: Ratio of C_{max} and AUC_{0-8h} at Week 4 and on Day 1 of IMP administration
Scheduled Duration of the Trial	21 Jul 2016 to 31 Jul 2017

<Schedule of Observations/Examinations/Evaluations>

Evaluation	Screening period (2–30 days)	Assessment period (8 weeks)							Post-treatment observation period (2 weeks)
	Screening examination	Baseline examination	Week 1 examination[a]	Week 2 examination[b]	Week 4 examination[b]	Week 6 examination[b]	Week 8 examination[b] Withdrawal examination[d]	Unscheduled visit	Examination 2 weeks after last IMP administration[c]
Informed consent	○								
Inclusion and exclusion criteria	○	○							
Subject demographics	○								
Physical examination	○	○	○	○	○	○	○	○[e]	○
Vital signs (including body weight)	○	○	○	○	○	○	○	○[e]	
12-lead ECG	○	○[g]			○		○	○[e]	
Clinical laboratory tests	○	○[g]			○		○	○[e]	
Pregnancy test[h]	○	○[g]			○		○	○[e]	
IGA	○	○	○	○	○	○	○		
EASI		○	○	○	○	○	○		
VAS for pruritus		○	○	○	○	○	○		
VRS for pruritus		○[i] ⟷	○						
DLQI		○	○	○	○	○	○		
POEM		○	○	○	○	○	○		

<Schedule of Observations/Examinations/Evaluations, Continued>

Evaluation	Screening period (2–30 days)	Assessment period (8 weeks)							Post-treatment observation period (2 weeks)
	Screening examination	Baseline examination	Week 1 examination[a]	Week 2 examination[b]	Week 4 examination[b]	Week 6 examination[b]	Week 8 examination[b] Withdrawal examination	Unscheduled visit	Examination 2 weeks after last IMP administration[c]
Affected BSA	○	○	○	○	○	○	○	○	
Treatment area		○	○	○	○	○		○	
Blood sampling for plasma drug concentration measurement			○[j]		○[j]		○[k]		
Administration diary		○[l] ←	—	—	—	—	→ ○		
Severity of AD		○							
Status of IMP administration			○	○	○	○	○		
Prescription and collection of IMP		○[m]	○[n]	○	○	○	○[o]	○[n]	
Adverse events	←	—	—	—	—	—	—	—	→
Concomitant medications and therapies	←	—	—	—	—	—	—	→	
Patch test[p]		←	—	—	—	—	—	—	→

AD = atopic dermatitis; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; POEM = Patient-Oriented Eczema Measure; VAS = Visual Analogue Scale; VRS = Verbal Rating Scale.

[a] Acceptable window of ±2 days

[b] Acceptable window of ±3 days

[c] Acceptable window of ±7 days

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

[e] May be conducted, as necessary.

[f] Should be conducted prior to blood sampling, as much as possible.

[g] Results of the screening examination should be used when the baseline examination is planned within 7 days of the screening examination.

[h] Should be conducted only for women with childbearing potential.

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

[j] On the day of blood sampling, the first IMP application should not be done until after blood sampling when visiting the trial site.

[k] On the day of examination, the subjects should not administer the IMP.

[l] The subjects should keep a diary every day from the baseline examination to the Week 8 examination (withdrawal examination).

[m] Only IMP prescription.

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

[o] Only IMP collection.

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

<Schedule of Blood Sampling for Plasma Drug Concentration> (For specific sites)

Evaluation	Screening period (2–30 days)	Assessment period (8 weeks)							Post-treatment observation period (2 weeks)
	Screening examination	Baseline examination	Week 1 examination[a]	Week 2 examination[b]	Week 4 examination[b]	Week 6 examination[b]	Week 8 examination[b] Withdrawal examination[d]	Unscheduled visit	Examination 2 weeks after last IMP administration[c]
Prior to administration		○			○[e]				
2 hours postdose[f]		○			○				
4 hours postdose[f]		○			○				
8 hours postdose[f]		○			○				

[a] Acceptable window of ±2 days

[b] Acceptable window of ±3 days

[c] Acceptable window of ±7 days

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

[e] Same as trough concentration of OPA-15406

[f] Acceptable window of ± 10 minutes

Table of Contents

List of Abbreviations and Definition of Terms

List of Abbreviations

Abbreviation	Expansion
AD	Atopic dermatitis
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
BSA	Body Surface Area
cAMP	Cyclic adenosine 3', 5'-monophosphate
COM	Clinical Operation Manual
DLQI	Dermatology Life Quality Index
EDC	Electronic Data Capture
EASI	Eczema Area and Severity Index
FAS	Full Analysis Set
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment
IUD	Intrauterine Device
IWRS	Interactive Web Response System
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measure
OC	Observed Case
PDE	Phosphodiesterase
POEM	Patient-Oriented Eczema Measure
QTcF	QT interval as correlated by Fridericia's formula
SS	Safety Set
TEAE	Treatment-emergent Adverse Event
NB-UVB	Narrow-band UVB
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale

Definitions of Terms

Term	Definition
Screen failure	A screen failure is a subject from whom written informed consent was obtained, but to whom an investigational medicinal product was not allocated.
Individual subject trial start date	The day of obtaining the subject's written informed consent
Individual subject trial discontinuation date	The day of discontinuation of a subject who was withdrawn from the trial before the Week 8 examination will be the day of examination 2 weeks after the last IMP administration. For those who missed the examination 2 weeks after the last IMP administration, the day of discontinuation will be the day when the investigator or subinvestigator determined that the subject was to be withdrawn from the trial.
Individual subject trial completion date	For subjects who underwent the Week 8 examination, the day of trial completion will be the day of examination 2 weeks after the last IMP administration.
Individual subject trial period	Period from the day of obtaining the subject's written informed consent to the day of trial discontinuation or completion. Does not include the follow-up period.

List of Pharmacokinetic Parameters

Abbreviation and Term (Unit)		Expansion or Definition
AUC	ng•h/mL	Area under the plasma concentration-time curve
AUC_{8h}	ng•h/mL	Area under the plasma concentration-time curve from time zero to 8 hours
AUC_{∞}	ng•h/mL	Area under the plasma concentration-time curve from time zero to infinit
C_{max}	ng/mL	Maximum plasma concentration of the drug

1 Introduction (Background Information of the Present Trial)

1.1 Background of Trial Plan

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."[2] In some patients, atopic dermatitis that occurred in infancy may spontaneously resolve with age. Some patients experience the onset or recurrence of the disease in adulthood, namely, refractory atopic dermatitis in adults.

Diagnostic criteria for the disease were established by Hanifin and Rajka in 1980[1], and in Japan, Guidelines for Management of Atopic Dermatitis was published by the Japanese Dermatological Association[2]. The 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 therapeutic strategies of AD are also common in the world. Topical agents such as steroids and calcineurin inhibitors (immunosuppressors) are used for the treatment of inflammation, topical moisturizers and protective agents for skin care to treat abnormal physiological functions, and oral antihistamines and antiallergic agents for pruritus as adjuvant treatment. Elimination of as many aggravating factors as possible has been established by current consensus as a basic therapy for AD. Inflammation can generally be suppressed by topical steroids. However, long-term use of steroids may induce adverse drug reactions (eg, skin atrophy, hairiness); therefore, drugs with long-term safety have been anticipated.

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

OPA-15406 is a PDE4 inhibitor synthesized by Otsuka Pharmaceutical Co., Ltd. In a mouse chronic contact hypersensitivity model, OPA-15406 ointment demonstrated

its efficacy on dermatitis by improving the symptoms. Therefore, development of OPA-15406 ointment was started with the expectation of efficacy for AD.

Clinical development OPA-15406 has preceded outside Japan, and the phase 2 trial in AD patients (271-12-205) has been completed. In Japan, the phase 1 trial in healthy adult male subjects has been completed. In healthy adult subjects and AD patients, OPA-15406 ointment showed no clinical relevant safety issues but good tolerability. Also, in the phase 2 trial outside Japan, 1% OPA-15406 ointment demonstrated the efficacy on AD. Based on these results, the present trial is designed to assess the efficacy and safety of OPA-15406 ointment in Japanese AD patients. While this trial will be conducted in adult patients (aged 15 years and older), the trial design will be the same as that of the phase 2 trial outside Japan to the extent possible to allow comparability with the foreign trial results.

1.2 Study Results and Trial Rationale

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

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

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

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

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

In a 4-week repeated-dose percutaneous toxicity study in rabbits, white petrolatum, OPA-15406 ointment 0% (vehicle), 0.1%, 0.3%, 1%, or 3% was administered to intact skin (open cutaneous) approximately equivalent to 10% of total BSA once daily. The OPA-15406 ointment was classified as weak skin irritation at all concentrations according to the Draize scale for skin irritation.

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

1.2.2 Clinical Study Results

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

1.2.2.1 Phase 1 Trial in Healthy Adult Subjects in the US (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 were reported and no subjects were withdrawn from the trial due to adverse events.

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

In the phase 1 trial in healthy adult male subjects (aged 20-40 years old) in Japan, a single-dose or 2-week twice-daily multiple doses of the 0.3%, 1%, or 3% OPA-15406 ointment (8 subjects for each group) was administered to a 1,000 cm^2 area (about 5% of 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 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 adverse events were reported, and no subjects were withdrawn from the trial. In physical findings and subjective symptoms, vital signs, skin findings, standard 12-lead ECG, and clinical laboratory tests, no clinically relevant variations or changes were observed. Also, no particular concerns were reported regarding the safety of OPA-15406 ointment up to concentrations of 3%.

1.2.2.3 Phase 1 Trial in AD Patients in the US (271-12-204)

In the phase 1 trial in AD patients (aged 18-64 years old) in the US, 1 g of the 0.3%, 1%, or 3% formulation of OPA-15406 (15 subjects for each group) was administered to 5% of BSA (about 1,000 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 of total BSA at 1 g 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 serious adverse event of cholelithiasis occurred in the 1% OPA-15406 group, but its causal relationship with the investigational medicinal product (IMP) was ruled out. Two subjects discontinued treatment with the IMP due to adverse events; one of the subjects was in the 3% OPA-15406 group (name ofadverse

event: hypersensitivity) and the other was in the 0.1% tacrolimus group (name of adverse event: allergic dermatitis), and both events were judged to be IMP-related.

For efficacy, 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.

1.2.2.4 Phase 2 Trial in AD Patients Outside Japan (271-12-205)

In the phase 2 trial in AD patients (aged 10-70 years old) outside Japan, the efficacy, safety, and pharmacokinetics of 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. The primary efficacy endpoint was established as the incidence of success in IGA (percentage of subjects with IGA score of 0 or 1 with improvement by at least 2 grades) at Week 4, and the incidence of success in IGA was 14.63%, 20.93%, and 2.70% in the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group, respectively. The 0.3% OPA-15406 group showed a higher incidence of success in IGA than in the vehicle group; however, no significant difference was observed between the groups ($p = 0.0690$, CMH test). In the 1% OPA-15406 group, a significant difference was observed in the incidence of success in IGA compared to the vehicle group ($p = 0.0165$, CMH test). Discontinuations due to adverse events occurred with 4 subjects (9.8%), 3 subjects (7.0%), and 7 subjects (18.9%) in the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group, respectively. 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.

1.2.2.5 Trial for Phototoxicity in Healthy Adult Subjects in the US (271-12-212)

In the trial for phototoxicity in 40 healthy adult subjects in the US, the phototoxicity was evaluated by a single administration of 0.3%, 1%, or 3% formulation of OPA-

15406 ointment or the corresponding vehicle (placebo) on the back of the subject. At the treatment area, no adverse events were observed. Also, no serious adverse events were reported, and no subjects were withdrawn from the trial due to adverse events.

1.2.2.6 Trial for Photoallergy in Healthy Adult Subjects in the US (271-12-213)

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

1.2.3 Trial Rationale

In this phase 2 trial, the 0.3% or 1% formulation of OPA-15406 will be administered to Japanese AD patients twice daily for 8 weeks to assess the efficacy and safety of OPA-15406 ointment.

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 1 trial (271-12-204) and the phase 2 trial (271-12-205) were conducted outside Japan in mild to moderate AD patients for whom the symptoms were controllable only by topical drugs. As the results of these trials demonstrated the efficacy and safety, the present trial was designed to include patients with mild to moderate AD.

Skin preparations are always exposed to opportunities of being removed after administration to the skin, such opportunities as washing the face, bathing, adhesion to clothing, or sweating resulting in dilution. To be sure that effective concentration on the skin is maintained, it is desirable that the IMP be administered multiple times a day. In consideration of the fact that people generally wash their face and hands after getting up and when bathing at night, twice-daily administration is considered highly convenient for patients, and it may contribute to achieving the best adherence. Therefore, twice-daily administration is employed.

In the phase 1 trial in AD patients in the US (271-12-204), the efficacy of OPA-15406 was suggested in the 0.3% and 1% formulations from among the 0.3%, 1%, and 3% formulations tested. In the phase 2 trial outside Japan (271-12-205), the efficacy of OPA-

15406 was investigated by selecting the 0.3% and 1% formulations. The results showed that the 1% formulation had a significantly higher efficacy in the primary efficacy endpoint compared to the vehicle, and the 0.3% formulation also had a higher efficacy compared to the vehicle. For this trial, the concentrations of 0.3% and 1% are selected in the same manner as those in the phase 2 trial outside Japan (271-12-205).

In the phase 1 trial in healthy Japanese adult subjects (271-14-001) and the phase 2 trial in patients aged 10 years and older outside Japan (271-12-205), no particular safety concerns were identified. In the present trial, adult patients (aged 15 years and older) will be included.

Usually, topical drugs for AD are evaluated for their efficacy once in 1 to 2 weeks, and if no improvements are observed within a month, the patient is generally considered for referral to a more specialized institution. Thus, Week 4 is established as an assessment point of the primary efficacy endpoint, and the treatment is also to be continued after Week 4 to assess the efficacy and safety thereafter. In the phase 2 trial in AD patients outside Japan (271-12-205), the incidence of success in IGA at Week 8 was 17.07%, 16.28%, and 10.81% in the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group, respectively. The incidence of success in IGA was higher in the 0.3% and 1% OPA-15406 groups than in the vehicle group, while no significant difference was observed. Also, no particular safety concerns were identified with the 0.3% and 1% formulations of OPA-15406. In this trial, the duration of treatment is established as 8 weeks to assess the efficacy and safety of the IMP in Japanese patients up to Week 8 and to compare the results with those of the phase 2 trial outside Japan (271-12-205).

Accordingly, it was judged scientifically and ethically appropriate to conduct this trial.

See the investigator's brochure for further details of data mentioned in this protocol and other trial results.

2 Trial Objectives

Primary objective: To evaluate Week 4 efficacy of OPA-15406 (0.3% and 1%) compared to the vehicle when administered twice daily for 8 weeks using incidence of success in Investigator's Global Assessment (IGA) as the primary endpoint in AD patients.

Secondary objective: To evaluate the safety of OPA-15406 (0.3% and 1%) when administered twice daily for 8 weeks in AD patients.

3 Trial Plan

3.1 Trial Design

This trial is a multicenter, randomized, double-blind, vehicle-controlled, parallel-group, comparison trial to evaluate the efficacy and safety of OPA-15406 ointment in patients with atopic dermatitis. This trial consists of the 0.3% OPA-15406 group (60 subjects), the 1% OPA-15406 group (60 subjects), and the vehicle group (60 subjects) and will be conducted according to Figure 3.1-1.

1) Screening period
   After obtaining informed consent, 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). The subjects who meet the inclusion and exclusion criteria at the baseline examination will be dynamically allocated to the test product (0.3% or 1% formulation of OPA-15406) or the comparator (vehicle of OPA-15406), using the trial site and IGA at the baseline examination as the allocation factors.
2) Assessment period (treatment period)
   Regarding the subjects who meet the inclusion criteria and do not meet the exclusion criteria at the baseline examination, the assessment period is defined as the period between the day of baseline examination and the day of Week 8 examination (or the day of discontinuation). The allocated IMP will be administered to the treatment area from the day of baseline examination twice daily for 8 weeks. After the baseline examination, the examinations will be performed at Weeks 1, 2, 4, 6, and 8.
   If a subject discontinues the IMP administration between the day of baseline examination and the day of Week 8 examination, a withdrawal examination will be performed for that subject.
3) Post-treatment observation period
   Post-treatment observation period is defined as the period between the end of Week 8 examination and the day of examination 2 weeks after the last IMP administration. The examination will be performed at 2 weeks after the last IMP administration. If any adverse event remains not recovered at the examination 2 weeks after the last IMP administration (or the day of last examination if the examination 2 weeks after the last IMP administration was not performed), it should be followed up according to the specification.
4) Trial period
   The trial period for individual subjects is the period from the day of obtaining the subject's written informed consent to the day of trial discontinuation or completion and does not include the follow-up period.

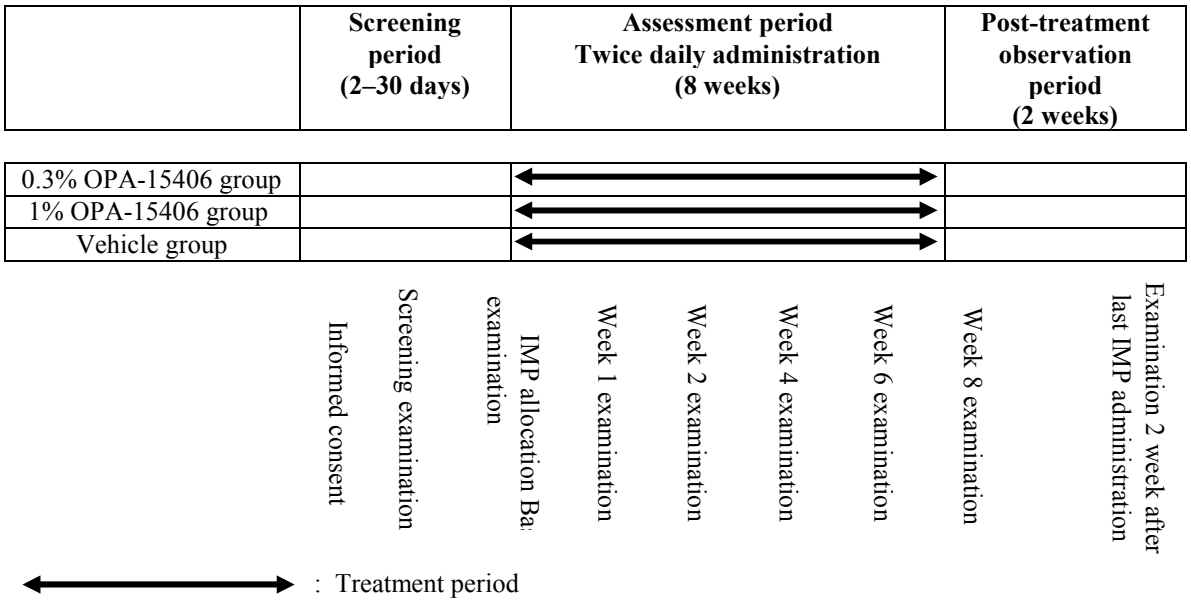

Figure 3.1-1 Trial Design

3.2 Rationale for Trial Design

This trial will be conducted to evaluate the efficacy and safety of OPA-15406 ointment in Japanese AD patients. For objective evaluation of the efficacy and safety, a vehicle control is established. Also, to minimize bias in the subject selection and evaluation, a randomization and double-blind design is employed.

3.3 Variables

3.3.1 Efficacy

3.3.1.1 Primary Variable(s)

Incidence of success in IGA at Week 4: Percentage of subjects in whom IGA score is 0 (clear) or 1 (almost clear) and improved at least 2 grades from baseline

3.3.1.2 Secondary Variable(s)

1) Incidence of success in IGA at Week 1 and Week 8
2) Change from baseline in IGA at Week 1, Week 4, and Week 8
3) Change from baseline in the total score of Eczema Area and Severity Index (EASI) and each symptom score at Week 1, Week 4, and Week 8

4) Change from baseline in Visual Analogue Scale (VAS) for pruritus at Week 1, Week 4, and Week 8
5) Change from baseline in Verbal Rating Scale (VRS) for pruritus up to Day 7
6) Change from baseline in the total score of Dermatology Life Quality Index (DLQI) at Week 1, Week 4, and Week 8
7) Change from baseline in the total score of Patient-Oriented Eczema Measure (POEM) at Week 1, Week 4, and Week 8
8) Change from baseline in the total affected BSA (%) at Week 1, Week 4, and Week 8
9) Time to response in IGA and VRS

3.3.2 Safety

Adverse events, physical examination, vital signs (including body weight), clinical laboratory values, and 12-lead ECG

3.3.3 Pharmacokinetics

Plasma trough concentration of OPA-15406 (trough concentration at Week 1, Week 4, and Week 8)

1) Plasma trough concentrations of OPA-15406 (prior to IMP administration at Week 1, Week 4, and Week 8 of IMP administration; all subjects)
2) Plasma concentration of OPA-15406 (prior to IMP administration and 2 hours, 4 hours, and 8 hours postdose on Day 1 and at Week 4; specific sites [target of 6 subjects from each group])
    - Pharmacokinetic parameters of OPA-15406: C_{max}, t_{max}, $AUC_{0\text{-}8h}$ on Day 1 and at Week 4 of IMP administration
    - Accumulation of OPA-15406: Ratio of C_{max} and $AUC_{0\text{-}8h}$ at Week 4 and on Day 1 of IMP administration

[Rationale for variable selection]

[Efficacy]

The primary variable of IGA is an indicator to assess the severity of AD and also a reliable indicator to determine the efficacy of the IMP; therefore, IGA has been established as the primary efficacy endpoint. IGA is evaluated based on the severity of overall symptoms (erythema, infiltration, papules, effusion, and scab formation) at treatment area and does not include other factors (eg, excoriation, symptoms of lichenification, severity of each part, subjective symptoms, affected BSA). Therefore, EASI, VAS and VRS for pruritus, DLQI, POEM, and affected BSA have been established as the secondary variables to evaluate the efficacy from multiple

points of view.

[Safety]

To appropriately assess the safety of this product.

[Pharmacokinetics]

To determine pharmacokinetics of OPA-15406 and the internal exposure to OPA-15406 in Japanese AD patients.

3.4 Target Number of Subjects

180 subjects in total [group composition]

Group	Target number of subjects
0.3% OPA-15406 group	60 subjects
1% OPA-15406 group	60 subjects
Vehicle group	60 subjects

4 Investigational Medicinal Products

4.1 Test Product and Comparator

4.1.1 Test Product

Code Name	OPA-15406
Generic Name	TBD
Content and Formulation	Ointment containing 0.3% or 1% of OPA-15406
Excipients Excipients	White petrolatum Mineral oil Paraffin White wax Propylene carbonate
Storage Conditions	Stored at room temperature

4.1.2 Comparator

Placebo formulation apparently indistinguishable from the test product (vehicle)

4.2 Packaging and Labeling

4.2.1 Packaging

Six aluminum tubes, each containing 27 g of the 0.3% or 1% formulation of OPA-15406 ointment or the vehicle, are packed in a packing box.

4.2.2 Contents of Label

The following information is written on the labels of the aluminum tube: statement that the drug is for use in a clinical trial, the code name of the IMP, Protocol No., lot number, drug number, and name of the sponsor.

The following information is written on the labels of the packing box: statement that the drug is for use in a clinical trial, the code name of the IMP, Protocol No., lot number, expiration date, storage conditions, drug number, name and address of the sponsor, and other precautions.

5 Trial Population

5.1 Target Disease

Atopic dermatitis

5.2 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible for inclusion in this trial.

At the screening examination:

1) Sex: Either male or female
2) Hospitalization status: Outpatient
3) Age: 15 to 70 years, inclusive (at time of obtaining informed consent)
4) Able to provide written informed consent. For subjects under 20 years of age, written informed consent must be obtained from both the subject and the subject's legal guardian.
5) Diagnosis of AD based on the criteria of Hanifin and Rajka[1] (Appendix 1)
6) History of AD for at least 3 years

At screening and baseline examinations:

7) AD affecting ≥5% to ≤40% of BSA
8) IGA score of 2 (mild) or 3 (moderate)

[Rationale for Inclusion Criteria]

1) AD occurs in both males and females.
2) Most patients to be included in this trial are outpatients.
3) In the phase 1 trial in healthy Japanese adult subjects (271-14-001) and the phase 2 trial in patients aged 10 years and older outside Japan (271-12-205), no particular safety concerns were identified. Therefore, in the present trial, adult patients (aged 15 years and older) will be included.
4) To conduct the trial without any ethical problems.
5) The criteria of Hanifin and Rajka have been most commonly used worldwide and have the same major diagnostic criteria as those of the Japanese Dermatological Association; therefore, the criteria can be used also in Japan without problems.
6) -8) To appropriately evaluate the efficacy of the IMP on the target disease.

5.3 Exclusion Criteria

Subjects who fall under any of the following criteria at either the screening or baseline examination will be excluded from the trial:

1) Subjects who are pregnant, possibly pregnant, or breastfeeding, who desire to become pregnant or to have their partner become pregnant during the trial period and up until 30 days after the final administration of IMP, or who are unable to either remain abstinent or employ at least two of the specified birth control methods (vasectomy, tubal ligation, vaginal diaphragm, intrauterine device [IUD], birth control pill, condom with spermicide, etc) 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 sudden 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 within the previous 5 years. However, subjects in whom basal-cell skin carcinoma or squamous-cell

skin carcinoma is judged to have been cured at the time of the screening examination can be included in the trial.

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 assessments:

- 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, hepatitis B, hepatitis C)
- Renal disease
- Hematologic disease
- Immunologic or immunocompromised disease (eg, lymphoma, 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 trial assessment

8) Subjects with any of the following hematology or serum chemistry results at screening examination:

- White blood cell count: ≤3, 000/μL or >14, 000/μL
- Platelets: ≤100, 000/μL
- Hemoglobin: <11 g/dL
- Serum creatinine: ≥2 mg/dL
- Aspartate aminotransferase (AST) (glutamic oxaloacetic transaminase [GOT]): >1.5 × ULN
- Alanine aminotransferase (ALT) (glutamic pyruvic transaminase [GPT]): >1.5 × ULN
- Total bilirubin: ≥2.0 mg/dL
- Any other abnormal laboratory test result that the investigator or subinvestigator judges to be a clinically significant abnormality

9) Subjects who are judged by the investigator or subinvestigator to have clinically significant electrocardiogram (ECG) findings (eg, AV block, prolongation of QRS complex to ≥120 msec, or QT interval as correlated by Fridericia's formula [QTcF] interval of ≥450 msec) at screening examination

10) Clinically significant blood pressure or pulse rate findings at screening examination of:

- Age 18 to 70, inclusive: seated resting (≥3 minutes) systolic blood pressure of <100 mmHg or ≥150 mmHg or diastolic blood pressure of <50 mmHg or ≥90 mmHg, or pulse rate of <50 bpm or >100 bpm
- Age 15 to 17, inclusive: seated resting (≥3 minutes) systolic blood pressure of <95 mmHg or ≥140 mmHg or diastolic blood pressure of <50 mmHg or ≥90 mmHg, or pulse rate of <50 bpm or >100 bpm

11) Subjects who are unable to stop using topical corticosteroids, topical immunomodulators, topical retinoids and topical antihistamine from 7 days prior to the baseline examination until the Week 8 assessment. However, corticosteroids categorized as low or medium potency in the "Guidelines of care for management of atopic dermatitis, Section 2"[2] may be used up until the baseline examination if, in the opinion of the investigator or subinvestigator, their use is necessary, such as when the subjects have been using the corticosteroids prior to providing informed consent to participate in the trial and use of the corticosteroids will be tapered off and stopped during the screening period.

12) Subjects who are unable to stop using systemic corticosteroids, systemic immunomodulators, systemic antimetabolites, systemic retinoids and biologics from 28 days prior to the baseline examination until the Week 8 examination. Intra-ocular, intra-nasal, and intra-auricular corticosteroids or inhaled corticosteroids may be considered if, in the opinion of the investigator or subinvestigator, their use will not impact assessment of the affected area.

13) Subjects who are unable to stop treatment with ultraviolet light A, narrowband ultraviolet B, or ultraviolet light B from 28 days prior to the baseline examination until the Week 8 examination

14) Subjects who are unable to stop using systemic antihistamines, sodium cromoglicate, tranilast, or suplatast tosilate from 7 days prior to the baseline examination until the Week 8 examination

15) Subjects with known hypersensitivity (including history) to any drugs (prescription, OTC, etc) or any ingredient of OPA-15406 ointment

16) Subjects with known plans to receive any of the prohibited concomitant drugs or therapies during the trial period

17) Subjects who have used any other investigational drug within 4 months prior to the baseline examination or who are scheduled to participate in any other clinical trial during the trial period

18) Subjects who have never been treated with a prescription medication for AD or who are satisfied with their current AD treatment regimen

19) 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) In consideration of safety.
5) In consideration of safety. However, patients cured of basal-cell skin carcinoma or squamous-cell skin carcinoma are allowed to be registered because of the low possibility of recurrence.
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) -14) Due to a possible impact on the efficacy assessment of the IMP.
15) In consideration of safety.
16) Due to a possible impact on the safety and efficacy assessments of the IMP.
17) In reference to the "Criteria for Period to Avoid Participation in Clinical Studies" of the Japan Association of Contract Institutes for Clinical Pharmacology.
18) To exclude patients who are not in need of treatment and to prevent registering patients who are satisfied with their current treatment, because trials have aspects of research.
19) To allow the investigator or subinvestigator to judge in consideration of other factors.

6 Trial Design

6.1 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 8 weeks.

The amount of IMP (g) per dose is calculated as follows.

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

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

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

(Mosteller 1987)[4]

2) Based on the subject's BSA (m^2), the amount of administration (g) for 1% of BSA will be selected from Table 6.1-1.
3) The treatment area will be specified (see 6.2 "Treatment Area").
4) The amount of IMP (g) per dose will be calculated as "the amount of administration for 1% of BSA (g)" × "treatment area (%)."

Table 6.1-1 Amount of Administration (g) for 1% of BSA Based on the Subjects' BSA (m^2)

BSA (m^2)	<1.0	≥1.0 and <1.3	≥1.3 and <1.6	≥1.6 and <1.9	≥1.9
Amount of administration (g) for 1% of BSA	0.1	0.15	0.2	0.25	0.3

[Rationale for dose, regimen, and treatment period]

[Regimen]

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.

[Dose]

In the phase 1 trial in AD patients in the US (271-12-204), the efficacy of OPA-15406 was suggested in the 0.3% and 1% formulations out of the 0.3%, 1%, and 3% formulations tested. In the phase 2 trial outside Japan (271-12-205), the efficacy of OPA-15406 was investigated by selecting the 0.3% and 1% formulations. The results showed that the 1% formulation had a significantly higher efficacy in the primary efficacy endpoint compared to the vehicle, and the 0.3% formulation also had a higher efficacy compared to the vehicle. For this trial, the concentrations of 0.3%

and 1% are selected in the same manner as those in the phase 2 trial outside Japan (271-12-205).

[Treatment period]

Usually, topical drugs for AD are evaluated for their efficacy once in 1 to 2 weeks, and if no improvements are observed within a month, the patient is generally considered for referral to a more specialized institution.[2] Thus, Week 4 is established as an assessment point of the primary efficacy endpoint, and the treatment is also to be continued after Week 4 to assess the efficacy and safety thereafter. In the phase 2 trial in AD patients outside Japan (271-12-205), the incidence of success in IGA at Week 8 was 17.07%, 16.28%, and 10.81% in the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group, respectively. The incidence of success in IGA was higher in the 0.3% and 1% OPA-15406 groups than in the vehicle group, while no significant difference was observed. Also, no particular safety concerns were identified in the 0.3% and 1% formulations of OPA-15406. In this trial, the
duration of treatment is established as 8 weeks to assess the efficacy and safety of the IMP in Japanese patients up to Week 8 and to compare the results with those of the phase 2 trial outside Japan (271-12-205).

6.2 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 7.2.1.7 "Affected BSA").
- After the baseline examination, when the affected area has expanded or a new affected area is detected, the expanded or newly affected area will also be included in the treatment area.
- Even when the affected area is relieved, the IMP administration should be continued there as the treatment area.

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

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

6.3 Prior and Concomitant Treatment

6.3.1 Prohibited Concomitant Drugs and Therapies

1) From 28 days prior to the baseline examination until the Week 8 examination, use of the following drugs and therapies is prohibited

- Systemic corticosteroids, systemic immunomodulators, systemic antimetabolites, systemic retinoids, biologics
  Intra-ocular, intra-nasal, and intra-auricular corticosteroids or inhaled corticosteroids may be considered if, in the opinion of the investigator or subinvestigator, their use will not impact assessment of the affected area.
- Ultraviolet light A, narrowband ultraviolet B, ultraviolet light B

2) From 7 days prior to the baseline examination until the Week 8 examination, use of the following drugs and therapies is prohibited.

- Topical corticosteroids, topical immunomodulators, topical retinoids, and topical antihistamine.
  However, corticosteroids categorized as low or medium potency in the "Guidelines of care for management of atopic dermatitis, Section 2"[2] may be used up until the baseline examination if, in the opinion of the investigator or subinvestigator, their use is necessary, such as when the subjects have been using the corticosteroids prior to providing informed consent to participate in the trial and use of the corticosteroids will be tapered off and stopped during the screening period.
- Systemic antihistamines, sodium cromoglicate, tranilast, suplatast tosilate

3) From the baseline examination until the Week 8 examination, use of the following drugs and products on the treatment area is prohibited.

- All topical drugs (including ethical drugs, over-the-counter products, herbal medicine, quasi-drugs, and cosmetic products)
  However, if cosmetic products were being used on the face, neck, and head prior to obtaining consent, their use may be continued only if the same products are used at the same frequency.

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 8 examination. If any drug other than the IMP is used between 30 days before the screening examination and the Week 8 examination, the name of the drug, purpose of use, amount per dose, dose frequency, route of administration, and dates of start and end of administration will be recorded in the source

document and CRF, regardless of it being prohibited or allowed for concomitant use. If any concomitant therapy is given between 30 days before the screening examination and the Week 8 examination, regardless of it being prohibited or allowed for concomitant use, the name of the therapy, purpose of use, and the dates of the start and end of the therapy will be recorded in the source document and CRF.

[Rationale for prohibited concomitant drugs and therapies] Due to a possible impact on the efficacy and safety assessments of the IMP.

6.4 Method of Minimizing or Avoiding Bias

This trial is a randomized, double-blind trial.

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

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

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

The emergency code list will be kept under strict control by the registration system until the end of the trial. If a medical emergency occurs in a subject and knowledge of his or her IMP randomization code is considered important for treatment, the emergency code will be broken according to the "8.2.4 Emergency Code Breaking (Procedure for Unblinding During the Trial Period)."

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

The subjects will be allocated to the 0.3% OPA-15406 group, the 1% OPA-15406 group, and the vehicle group in a ratio of 1:1:1 using dynamic allocation to ensure

balance within the trial sites and that of the baseline IGA (mild or moderate at the baseline examination).

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

7 Observations/Examinations/Variables, Methods and Implementation Timings

7.1 Schedule and Procedures

The schedule of observations/examinations/evaluations is presented on pages 11 (Schedule of Observations/Examinations/Evaluations) to 14 (Schedule of Blood Sampling for Plasma Drug Concentration). Items that trial associates are capable of performing may be performed by trial associates under the supervision of the investigator.

7.1.1 Acquisition of Informed Consent

The investigator or subinvestigator will obtain written consent directly from subjects prior to the screening examination. If the subject is under 20 years old, written informed consent should be obtained from the subject and the subject's legal guardian. The investigator or subinvestigator will assign a subject identification code and subject number (3 digit number of site ID + S +5 digit serial number starting from 00001) to the subject providing consent.

7.1.2 Screening Examination (From the Day of Informed Consent to 2 Days Prior to the Baseline 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 (including body weight)
- Clinical laboratory tests
- Pregnancy test (only for women of childbearing potential)
- 12-lead ECG
- IGA
- Affected BSA

- Adverse events
- 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.

7.1.2.1 Subject Demographics

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

- Date of informed consent
- Sex
- Date of birth
- Height (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 number
- Country where the trial is conducted (Japan)
- Race (Asian)
- Ethnicity
- Possibility of pregnancy

7.1.3 Subject Registration

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

7.1.4 Baseline Examination (2-30 Days After the Screening Examination)

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

- Physical examination
- Vital signs (including body weight)
- Clinical laboratory tests (The screening examination results can be used within 7 days of the screening examination.)

- Pregnancy test (only for women of childbearing potential. The screening examination results can be used within 7 days of the screening examination.)
- 12-lead ECG (The screening examination results can be used within 7 days of the screening examination.)
- IGA
- EASI
- VAS for pruritus
- VRS for pruritus
- DLQI
- POEM
- Affected BSA
- Blood sampling for plasma drug concentration (to be conducted at specific trial sites)
- Severity of AD
- Adverse events
- Concomitant medications and therapies

The investigator or subinvestigator will select subjects who meet the inclusion criteria and do not meet any of the exclusion criteria based on results of the screening and baseline examinations. Also, the investigator or subinvestigator will record the results of the subject's eligibility on the list of screened subjects and the list of enrolled subjects.

7.1.5 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, the 1% OPA-15406 group, or the 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, and the time and date of administration will be recorded. The subjects will be instructed to visit the trial site without morning IMP administration on the day of their next visit.

7.1.6 Baseline Examination (2 Hours, 4 Hours, and 8 Hours Postdose): To be Conducted at Specific Trial Sites

Application will be started within the trial site after all the baseline examinations are finished, and the source document and CRF will be recorded accordingly.

- Blood sampling for plasma drug concentration

7.1.7 Between the Day of Baseline Examination and the Day of Week 1 Examination

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

- VRS for pruritus

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 (including body weight)
- IGA
- EASI
- VAS for pruritus
- DLQI
- POEM
- Affected BSA
- Blood sampling for plasma drug concentration measurement
- Adverse events
- Concomitant medications and therapies
- Status of IMP administration

The investigator or subinvestigator will determine the treatment area (%) and enter it in the IWRS. Also, the investigator or subinvestigator will confirm the subject's

allocation status on the IWRS screen and, if necessary, prescribe additional IMP. When the IMP is additionally prescribed, the weight of dispensed IMP will be measured.

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 (including body weight)
- IGA
- EASI
- VAS for pruritus
- DLQI
- POEM
- Affected BSA
- Adverse events
- Concomitant medications and therapies
- Status of IMP administration

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

7.1.10 Week 4 Examination (±3 Days)

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

- Physical examination
- Vital signs (including body weight)
- Clinical laboratory tests
- Pregnancy test (only for women of childbearing potential)
- 12-lead ECG
- IGA
- EASI
- VAS for pruritus
- DLQI

- POEM
- Affected BSA
- Blood sampling for plasma drug concentration measurement
- Adverse events
- Concomitant medications and therapies
- Status of IMP administration

The investigator or subinvestigator will collect the IMP and measure the weight of the collected IMP. The investigator or subinvestigator will determine the treatment area (%) and enter it in the IWRS. The investigator or subinvestigator will confirm the amount of IMP to be prescribed for the next 2 weeks and prescribe it. The weight of the dispensed IMP will be measured.

7.1.11 Week 4 Examination (2 Hours, 4 Hours, and 8 Hours Postdose): To Be Conducted at Specific Trial Sites)

Application will be started within the trial site after all Week 4 examinations are finished, and the source document and CRF will be recorded accordingly.

- Blood sampling for plasma drug concentration

7.1.12 Week 6 Examination (±3 Days)

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

- Physical examination
- Vital signs (including body weight)
- IGA
- EASI
- VAS for pruritus
- DLQI
- POEM
- Affected BSA
- Adverse events
- Concomitant medications and therapies
- Status of IMP administration

The investigator or subinvestigator will collect the IMP and measure the weight of the collected IMP. The investigator or subinvestigator will determine the treatment area (%) and enter it in the IWRS. The investigator or subinvestigator will confirm the

amount of IMP to be prescribed for the next 2 weeks and prescribe it. The weight of the dispensed IMP will be measured. The subjects will be instructed to visit the trial site without morning IMP administration on the day of the next visit.

7.1.13 Week 8 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 (including body weight)
- Clinical laboratory tests
- Pregnancy test (only for women of childbearing potential)
- 12-lead ECG
- IGA
- EASI
- VAS for pruritus
- DLQI
- POEM
- Affected BSA
- Blood sampling for plasma drug concentration measurement
- Adverse events
- Concomitant medications and therapies
- Status of IMP administration

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

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

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

- Physical examination
- Adverse events

7.1.15 Unscheduled Visits

The investigator or subinvestigator will instruct the subjects to visit the trial site if the area of affected BSA markedly enlarges. The investigator or subinvestigator will

perform the following examinations, observations and evaluations, and record the results in the source document and CRF.

- Affected BSA
- Adverse events
- Concomitant medications and therapies

The following examinations may be conducted as necessary:

- Physical examinations
- Vital signs (including body weight)
- 12-lead ECG
- Clinical laboratory values
- Pregnancy test

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

7.2 Method of Evaluation

7.2.1 Efficacy Evaluation

7.2.1.1 Investigator's Global Assessment (IGA)

The investigator or subinvestigator will score the severity (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe/very severe) of systemic symptoms (erythema, infiltration, papules, effusion [liquid], and scab formation).[5] The result will be recorded in the source document and CRF. The same subject will be evaluated by the same dermatologist, as much as possible.

Symptom	Severity score
No inflammatory signs of AD	0 = Clear
Just perceptible erythema and just perceptible papulation/infiltration	1 = Almost clear
Mild erythema and mild papulation/infiltration	2 = Mild
Moderate erythema and moderate papulation/infiltration	3 = Moderate
Severe erythema and severe papulation/infiltration with oozing/crusting	4 = Severe/very severe

7.2.1.2 Eczema Area and Severity Index (EASI)

The investigator or subinvestigator will score the severity (0-3 points) and BSA (0-6 points) based on the 4 symptoms (erythema, infiltration/papules, excoriation, and lichenification) on the 4 body regions (face, neck, and head; upper limbs; trunk; and lower limbs) and record the results in the source document and CRF.[6] As shown in the table below, the score of each region will be calculated and totalized. The maximum EASI score is 72 points. The same subject will be evaluated by the same dermatologist, as much as possible.

Body region	Calculation of the score for each region
Face, neck, and head	(E ＋ I ＋ Ex ＋ L) × score of BSA ×0.1
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

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

7.2.1.3 Visual Analogue Scale (VAS) for Pruritus

The investigator or subinvestigator will evaluate the level of pruritus based on VAS[7]. The subjects will mark the point of pruritus intensity during the last 24 hours on the line of a 100-mm VAS sheet (Appendix 2) between the left end (no pruritus) and the right end (very severe pruritus). The investigator or subinvestigator will record the length from the left end to the mark (integer value with mm as unit) in the medical record and CRF. The VAS sheet will be kept as the source document.

7.2.1.4 Verbal Rating Scale (VRS) for Pruritus

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

0: None

1: Mild

2: Moderate

3: Severe

The investigator or subinvestigator will record details of the pruritus diary in the CRF. The pruritus diary will be kept as the source document.

7.2.1.5 Dermatology Life Quality Index (DLQI)

The investigator or subinvestigator will evaluate the effect of OPA-15406 on daily life according to the DLQI[8] (Appendix 3). The subjects will answer 10 questions about the effects of the symptoms on their daily life. The investigator or subinvestigator will record the results in the source document and CRF. The total DLQI score is 30 points at the most.

7.2.1.6 Patient-Oriented Eczema Measure (POEM)

The investigator or subinvestigator will evaluate eczema according to the POEM[9] (Appendix 4). The subjects will answer 7 questions about their eczema. The investigator or subinvestigator will record the results in the source document and CRF. The total score of POEM is 28 points at the most.

7.2.1.7 Affected BSA

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

7.2.2 Safety Evaluation

7.2.2.1 Physical Examination

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

7.2.2.2 Vital Signs (Including Body Weight)

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

7.2.2.3 Clinical Laboratory Tests

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

- Hematology: differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), white blood cell count, red blood cell count, hemoglobin, hematocrit, platelets
- Serum chemistry: total cholesterol, total protein, albumin, BUN, creatinine, total bilirubin, AST (GOT), ALT (GPT), γ-GTP, LDH, ALP, serum electrolytes (Ca, Na, K, Cl)
- Qualitative urinalysis: glucose, protein

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

7.2.2.4 12-Lead ECG

After the subject has rested for at least 10 minutes in a supine position, an ECG will be obtained. The ECG recording should be completed before blood sampling, as much as possible. For the ECG measurement, heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval will be measured, using a 12-lead electrocardiograph obtained from the central ECG reading facility. The measurement results will be analyzed at the central ECG reading facility. The investigator or subinvestigator will confirm the "12-lead ECG analysis report" from the central ECG reading facility, assess whether the ECG result is normal or abnormal, and record the time and date of the measurement, assessment result, and findings in the source document and CRF. Then, the investigator or subinvestigator will put the confirmation date and his or her printed name and personal seal or signature on the "12-lead ECG analysis report" from the central ECG reading facility and retain it for each subject as the source document.

If it is necessary to allocate IMP before receiving the results from the central ECG reading facility, the automated analysis result from the 12-lead electrocardiograph at the screening examination (the same ECG data as that to be sent to the central ECG reading facility) can be used to determine the subject's eligibility. In such cases, the investigator or subinvestigator will put the date of confirmation and his or her printed name and personal seal or signature on the automated analysis result and retain it as the source document.

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

7.2.3 Pharmacokinetics

Plasma OPA-15406 concentrations will be measured except for subjects in the vehicle group. On the day of blood sampling, the subjects will visit the trial site without morning IMP administration.

1) Blood sampling timepoints
   Plasma trough concentration of OPA-15406 (prior to IMP administration at Week 1, Week 4, and Week 8 of IMP administration; all subjects)

   Plasma concentration of OPA-15406 (prior to IMP administration and 2 hours, 4 hours, and 8 hours postdose on Day 1 and at Week 4. [however, prior to IMP administration at Week 4 is the same as trough concentration at Week 4]): specific trial sites (target of 6 subjects from each group)
2) Rationale for blood sampling timepoints
   Timepoints are selected to confirm the drug concentration of OPA-15406 and the internal exposure to OPA-15406 in Japanese AD patients and to obtain comparable internal exposure data to those of the phase 2 trial outside Japan (271-12-205).
3) Method of blood sampling and processing
   Sufficient caution should be taken for the parts of sterilization and site of blood sampling to avoid the blood samples from contamination with any IMP remnant on the skin surface. Approximately 5 mL of blood will be collected per dose from arm vein using vacuum blood collection tube (with heparin Na contained) and sufficiently mixed. The sample will be mixed by inversion and cooled in ice water, and it will be centrifuged at approximately 3000 rpm for 10 minutes within 30 minutes after blood sampling, and from which approximately the same amount of plasma will be promptly taken into two polypropylene tubes and stored frozen at −15°C or less. When a refrigerated centrifuge is available, the blood will be centrifuged at 4°C. For each subject, the time and date of latest IMP administration and blood sampling will be record on the source document and CRF.
4) Sending plasma samples
   The contract research organization for clinical laboratory tests will send the samples divided into two tubes frozen on dry ice to the bioanalytical laboratory. The plasma concentration of OPA-15406 will be determined at the bioanalytical laboratory by using the liquid chromatography with tandem mass spectrometry (LC-MS/MS). The bioanalytical laboratory will measure samples of the OPA-15406 group according to the randomization table. Residual plasma samples after measurement will be stored at −15°C or less by the bioanalytical laboratory until the sponsor allows their disposal. The sponsor will report the completion of measurement to the bioanalytical laboratory. The bioanalytical laboratory will submit the report on results of drug concentration measurement (copy) and the measurement results (electronic data) to the sponsor.

7.2.4 Status of IMP 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%.

7.2.5 Severity of AD

The investigator or subinvestigator will determine the severity[10] (mild, moderate, severe, or very severe) and record the result in the source document and CRF.

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

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

7.3 Measures to Be Taken for Subjects Visiting or Planning to Visit Other Hospitals or Departments

At the time of obtaining informed consent, the investigator or subinvestigator will confirm whether or not the subject is receiving treatment at another hospital or department. If the subject is receiving treatment at another hospital or department, the investigator or subinvestigator will inform the attending physician of that hospital or department about the subject's participation in the clinical trial and the IMP being used, with the subject's consent. The investigator or subinvestigator will also obtain and record in the CRF information on the treatment that the subject is receiving at the other hospital or department (name of disease being treated and information on the type of treatment or measures being implemented) and judge whether or not the subject should participate in the trial.

If a subject visits another hospital or department during the trial period, the investigator or subinvestigator will inform the attending physician of that hospital or department about the subject's participation in the clinical trial and the IMP being used. The investigator or subinvestigator will also obtain and record in the CRF information on the treatment that the subject receives at the other hospital or department (name of disease treated and information on the type of treatment or measures implemented) and judge whether or not the subject should continue to participate in the trial.

7.4 Subject Management

Subjects will be under control of the investigator or subinvestigator during the trial period. The investigator or subinvestigator will instruct the subjects to adhere to the following matters.

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

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Event

[ICH E2A guideline: Definition]

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. [a]

[a] "Clinical Safety Data Management", Notification No. 227 of the Examination Division, Pharmaceutical Affairs Bureau dated 20 Mar 1995 (ICH E2A).

For this trial, the term "medical product" is regarded as "IMP," and to secure the safety of subjects, adverse events occurring from consent to the start of IMP administration are included in the definition of adverse events in addition to the definition given by ICH.

If an event, symptom, or sign existing at the time of acquisition of informed consent worsens after acquisition of informed consent, or if an adverse event occurring between the acquisition of informed consent and start of IMP administration worsens after administration of the IMP, the exacerbation will be treated as a new adverse event.

"Annex 4: Common Terminology Criteria for Adverse Events v4.0 Japanese JCOG edition" will be cited as reference to judge the assessment of adverse events. Adverse events for which a causal relationship with the IMP cannot be ruled out are termed as "potentially IMP-related adverse events."

8.1.2 Serious Adverse Event

A serious adverse event is defined as an adverse event corresponding to one of the events listed in 1) to 6) below.[a]

The seriousness of adverse events occurring during the period from consent to the start of IMP administration will also be judged.

1) An event resulting in death
2) A life-threatening event
   The term "life-threatening" refers to an event in which the patient was at a risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, had it been more severe.
3) An event requiring in-patient hospitalization or prolongation of existing hospitalization for treatment
4) An event resulting in persistent or significant disability/incapacity
5) An event causing a congenital anomaly/birth defect
6) A major event resulting in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in 1) to 5) above. Examples of such events are intensive treatment in an emergency room for bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Explanation of hospitalization for treatment of a serious adverse event:

Hospitalization for treatment means that the subject must be hospitalized at a medical institution for treatment of an adverse event, typically for at least one night.

This includes hospitalization for treatment of the adverse event in which no particular medical procedures are carried out (rest therapy). However, it does not include hospitalization for undergoing tests or treatment for an underlying disease or complication that has not worsened since the subject's entry into the trial, hospitalization for social reasons or convenience not intended for treatment of the adverse event, or hospitalization for treatment or tests scheduled prior to participation in the trial.

8.2 Response to Occurrence of Adverse Events

8.2.1 Actions to Be Taken for Subjects

The investigator or subinvestigator will provide adequate medical care for all clinically significant, trial-related adverse events throughout the period of subject participation in the trial as well as thereafter. If treatment for an adverse event is necessary, the subject will be informed of this.

8.2.2 Expedited Reporting of Serious Adverse Events

(1) Serious Adverse Events and Sponsor-specified Events Requiring Expedited Reporting

1) Any serious adverse events occurring during the trial period regardless of causal relationship with the IMP
2) Serious adverse events occurring during the follow-up period (see 8.4, Follow-up Investigation of Adverse Events), if a follow-up investigation is performed, for which a causal relationship with the IMP cannot be ruled out, or adverse events that become serious during the follow-up period for which a causal relationship with the IMP cannot be ruled out
3) Among serious adverse events occurring after completion of the trial and reported by subjects to the investigator or subinvestigator, those for which the investigator or subinvestigator cannot rule out a causal relationship with the IMP

(2) Procedures for Expedited Reporting

1) When an adverse event falling under any of the above items 1) to 3) occurs, the investigator or subinvestigator will notify the sponsor promptly after becoming aware of the event (within 24 hours, in principle) orally or by telephone, facsimile, or e-mail (refer to Annex 1, Emergency Contact).
2) The investigator will then promptly submit a detailed report on any serious adverse events occurring after the start of IMP administration to the head of the trial site and the sponsor within 10 days after becoming aware of them using the report form of the trial site or sponsor. Any additional information will also be promptly relayed to the sponsor (within 24 hours, in principle) orally or by telephone, facsimile, or e-mail, and additional reporting will be performed if necessary.

3) When the investigator or subinvestigator is requested by the sponsor, the head of the trial site, or the institutional review board (IRB) to prepare additional information (autopsy report, terminal care report, or other required information) on a reported serious adverse event, the investigator or subinvestigator will respond to the request.

8.2.3 Subjects with Possibility of Drug-induced Liver Injury

After start of the IMP administration, if an AST (GOT) or ALT (GPT) level increases at least 3 times the upper limit of the normal range, and also if a total bilirubin level increases to at least 2 times the upper limit of the normal range, the investigator will promptly submit a detailed report (refer to Annex 1, Emergency Contact).

8.2.4 Emergency Code Breaking (Procedure for Unblinding During the Trial Period)

If a serious adverse event occurs and the investigator or subinvestigator judges emergency code breaking necessary for the safety of a subject, the investigator or subinvestigator may perform emergency code breaking for the subject according to the stipulated procedure ("Procedure for Emergency Code Breaking"). The investigator or subinvestigator will notice any case of emergency code breaking promptly to the sponsor, create records for the reasons and course of emergency code breaking and submit them to the sponsor.

8.2.5 Implementation of Patch Test

If any adverse event suspected of hypersensitivity occurs in the treatment area, the subject will be withdrawn from the trial and given the appropriate treatment. Verbal consent will be obtained from the subject (and also from the subject's legal guardian if the subject is under 20 years old) to conduct a patch test, and the record will be kept in the source document and CRF. The patch test should be conducted following a washout period after confirming recovery of symptoms in order to prevent the influence of medications used for treatment on the reading result of the patch test. In principal, the patch test will be performed after a 2-week washout period for those receiving systemic steroids or after a 1-week washout period for those receiving topical steroids or topical/systemic antihistamines. Test substances for the patch test are to consist of the IMP that has been allocated to the subject, vehicle, and white petrolatum. As a guide, 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 (acceptable window of 5 to 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 (refer to the Guidelines for Management of Contact Dermatitis[11] issued by the Japanese Dermatological Association for procedures of the patch test).

Table 8.2.5-1 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

8.3 Assessment of Adverse Events

The investigator or subinvestigator will assess adverse events for the following items and record them in the source document and CRF. Information on adverse events occurring on application sites will be recorded.

8.3.1 Terms for Adverse Events

If the disease responsible for an adverse event can be specified, the name of the diagnosed disease will be recorded in the source document and CRF and not the individual symptoms.

8.3.2 Date of Onset and Recovery

- Date of onset:

The date of onset of an adverse event or date confirmation of an adverse event will be recorded in the source document and CRF. If an event, symptom, or sign existing at the time of acquisition of informed consent worsens, the date of exacerbation will be recorded in the CRF as the date of onset of adverse event. Also, if an adverse event occurring between the acquisition of informed consent and start of IMP administration worsens after administration of the IMP, the exacerbation will be recorded in the CRF as a new adverse event with the date of exacerbation recorded as “date of onset of exacerbated adverse event.”

- Date of recovery:

The date of recovery of an adverse event or date of confirmation of recovery of an adverse event will be recorded in the CRF. Dates of blood sampling and urine

collection will be recorded for abnormal laboratory parameters reported as adverse events. If a subject dies, the date of death will be recorded.

8.3.3 Severity

Severity of adverse events will be classified using the following three categories. Skin and subcutaneous tissue disorders will be graded according to the Common Terminology Criteria for Adverse Events v4.0 Japanese JCOG edition (Annex 4).

1) Mild
   Discomfort noticed, but no disruption to daily activity
2) Moderate
   Discomfort sufficient to limit or affect normal daily activity
3) Severe
   Inability to work or perform normal daily activity

8.3.4 Causal Relationship With Investigational Medicinal Product

The causal relationship between the IMP and adverse events occurring after the start of IMP administration will be judged according to the following two categories.

1) Relationship is ruled out
   For reasons such as the following, the possibility of a relationship between occurrence of an adverse event and the IMP is not reasonably conceivable.
   a) The event can be assumed to be caused by an underlying disease, complication, or medical history.
   b) The event can be assumed to be associated with age, sex, or some other demographic factor.
   c) A temporal relationship between IMP administration and occurrence of the adverse event is unlikely.
      Example: An adverse event that occurs after a considerable lapse of time from the discontinuation of IMP administration.
   d) Considering the time course of the adverse event and IMP administration, a relationship with the IMP is unlikely.
      Example: Despite continuous administration of the IMP, the adverse event disappears spontaneously without any treatment (except cases in which it is judged that the subject became habituated to the IMP during continued administration).
   e) The event can be assumed to be caused by concomitant drug(s).
   f) The event can be assumed to be incidental (such as an accident or incidental disease).
      Example: “Femoral bone fracture” occurring in a traffic accident.

g) A relationship with the IMP can be ruled out for other reasons based on medical consideration.

2) Relationship cannot be ruled out

For reasons such as the following, the possibility of a relationship between occurrence of an adverse event and the IMP is reasonably conceivable.

a) A relationship is predictable from the pharmacological and toxicological effects of the IMP.
Examples: Occurrence of "pancytopenia" when effects on the hematopoietic system have been observed in non-clinical studies, or the occurrence of "dehydration" when the drug has a diuretic effect.

b) The event has been observed in previous non-clinical studies and/or clinical studies.

c) A temporal relationship is suspected between IMP administration and onset of the adverse event.
Example: "Allergic dermatitis" occurring several days after the start of IMP administration.

d) A relationship is suspected based on the outcome of an adverse event after discontinuation or dose reduction of the IMP.
Example: Prompt disappearance of "nausea" after discontinuation of the IMP

e) A relationship with the IMP cannot be ruled out for other reasons based on medical consideration.

8.3.5 Actions to Be Taken Regarding IMP Administration

Actions to be taken regarding IMP administration following an adverse event will be selected from among the following.

- No change
- Discontinuation of IMP administration
  Example: IMP administration was discontinued due to an adverse event
- Not applicable
  Examples: The adverse event resolved prior to initiation of IMP administration or the adverse event occurred after the end of IMP administration

8.3.6 Actions to Be Taken for Adverse Events

The performance of medical treatments (medications and/or other treatments) for adverse events and details of the treatments will be described in the CRF.

8.3.7 Outcome

The outcome of an adverse event will be selected from the following six categories (one only).

If the subject died, the date of death will be recorded in the CRF; if the subject's condition was recovering/resolving, not recovered/not resolved, or unknown, the date of outcome confirmation will be recorded in the CRF.

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown (for some reason, a follow-up investigation could not be performed even once)

8.4 Follow-up Investigation of Adverse Events

The term "recovered" used below means that a subject who had an adverse event prior to the start of IMP administration returned to his or her original condition, or a subject who had an adverse event after the start of IMP administration returned to his or her condition before the start of IMP administration.

1) If an adverse event has not resolved by the day of examination 2 weeks after the last IMP administration (or the day of last examination if the examination 2 weeks after the last IMP administration was not performed), the investigator or subinvestigator will explain to the subject the need for post-trial follow-up investigation and request the subject's cooperation. The investigator or subinvestigator will conduct a follow-up investigation within 4 weeks after the end of the trial, as much as possible, and record information regarding the adverse event in the subject's medical records. If an adverse event has not resolved by the day of examination 2 weeks after the last IMP administration (or the day of last examination if the examination 2 weeks after the last IMP administration was not performed), the investigator or subinvestigator will record the outcome in the CRF as "recovering/resolving", "not recovered/not resolved", or as otherwise appropriate.
2) If an adverse event has not resolved by the day of the follow-up investigation, follow-up investigation will be continued until the event resolves or becomes stable, regardless of a causal relationship with the IMP, and information regarding the adverse event will be recorded in the subject's medical records.
3) If, between the day of examination 2 weeks after the last IMP administration (or the day of last examination if the examination 2 weeks after the last

IMP administration was not performed) and the day of the follow-up investigation, a new serious adverse event for which a causal relationship with the IMP cannot be ruled out occurs, or if an adverse event that has not resolved by the day of examination 2 weeks after the last IMP administration (or the day of last examination if the examination 2 weeks after the last IMP administration was not performed) and for which a causal relationship with the IMP cannot be ruled out becomes serious, follow-up investigation will be conducted until the adverse event resolves or becomes stable and information regarding the adverse event will be recorded in the subject's medical records.

4) If a serious adverse event for which a relationship with the IMP cannot be ruled out is discovered after the day of examination 2 weeks after the last IMP administration (or the day of last examination if the examination 2 weeks after the last IMP administration was not performed), or after the day of the initial follow-up investigation (if performed), follow-up investigation will be conducted until the adverse event resolves or becomes stable or until follow-up of the subject becomes impossible and information regarding the adverse event will be recorded in the subject's medical records.

8.5 Pregnancy

If women of childbearing potential or male subjects whose partners are capable of becoming pregnant participate in the trial, the investigator or subinvestigator will attend to the following.

- Information on reproductive and developmental toxicity of the IMP
- Drug interactions between the IMP and hormonal contraceptives
- Information regarding pregnancy in the informed consent form (ICF)
- Explanation of contraceptive methods
- Reporting and follow-up of cases of pregnancy

8.5.1 Guidance to Subjects Including Contraceptive Methods

1) Before the start of the trial, the investigator or subinvestigator will explain to the subjects the importance of using contraception and the risks associated with pregnancy of a female subject or partner of a male subject and, after subjects have read the written information for subjects and understood it, the investigator or subinvestigator will have the subject's printed name and personal seal or signature on the ICF.
2) If women of childbearing potential or male subjects whose partners are capable of becoming pregnant wish to participate in the trial, the investigator or subinvestigator will instruct them to practice contraception during the period specified in the trial protocol.

3) Contraceptive methods include vasectomy, tubal ligation, vaginal diaphragm, IUD, birth control pill, and condom with spermicide, and at least 2 of these methods have to be employed (double-barrier method). However, if a female subject or male subject's partner is without question unable to become pregnant (ie, has undergone bilateral ovariectomy or hysterectomy or has not experienced menses for at least 12 consecutive months for whatever other medical reasons, or the male subject/partner has undergone bilateral orchidectomy), or if the subject and his/her partner remain abstinent, use of contraception is unnecessary.
4) The investigator or subinvestigator will instruct the subjects that if the contraceptive measures fail and evidence of pregnancy of the female subject or male subject's partner such as delay in menstruation is observed, this should be promptly reported to the investigator or subinvestigator.

8.5.2 Actions to Be Taken by the Investigator or Subinvestigator When Pregnancy Is Suspected

If the investigator, subinvestigator, or subject suspects that the subject has become pregnant before initiation of IMP administration, initiation of IMP administration will be withheld and a pregnancy test will be performed. If the test result is positive, the trial subject will be withdrawn without receiving IMP administration. If a pregnancy is suspected after initiation of IMP administration, IMP administration will be discontinued (refer to Section 9.2, Criteria and Procedures for Withdrawal of Individual Subjects).

8.5.3 Actions to Be Taken by the Investigator or Subinvestigator When a Subject Is Discovered to Be Pregnant

When a female subject is found to be pregnant, the investigator or subinvestigator will withdraw the subject from the trial and perform follow-up investigation until delivery or end of pregnancy, and report this in writing to the sponsor.

After discontinuation of IMP administration, the investigator or subinvestigator will perform the withdrawal examinations and follow-up observation stipulated in the protocol, in so far as they do not affect the pregnancy.

8.5.4 Expedited Reporting of Pregnancy

When a female subject or a partner of a male subject is found to be pregnant during the trial, the investigator or subinvestigator will promptly (within 24 hours, in principle) report this to the sponsor by telephone, facsimile, or e-mail (refer to Annex 1, Emergency Contact). The investigator or subinvestigator will then provide any additional information requested by the sponsor.

8.5.5 Follow-up Investigation of Pregnancy

If a female subject becomes pregnant, the investigator or subinvestigator will perform follow-up investigation of the pregnancy up to delivery or the end of pregnancy and report the results of follow-up in writing to the sponsor. When a subject or subject's partner has delivered, it is best that the neonate be observed for at least 6 months after delivery.

9 Withdrawal of Individual Subjects From the Trial

Any subject may discontinue participation in the trial at any time without 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.

9.1 Screen Failure

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

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

9.2 Criteria and Procedures for Withdrawal of Individual Subjects

In any of the events listed below, the investigator or subinvestigator will discontinue IMP administration, perform the tests to be performed at withdrawal stipulated in Section 7.1, Schedule and Procedures" and promptly inform the sponsor of the withdrawal. The investigator or subinvestigator will record the date and reason for withdrawal in the CRF.

If withdrawal is necessitated by problems with safety, such as the occurrence of an adverse event or aggravation of an underlying disease, the investigator or subinvestigator will promptly take appropriate measures and perform follow-up if necessary (refer to Section 8.4, Follow-up Investigation of Adverse Events).

1) Request from the subject or subject's legal guardian to discontinue participation in the trial
2) Discovery that the subject was included in the trial despite violation of the inclusion or exclusion criteria

3) Occurrence of any adverse event that makes it difficult for the subject to continue administration of IMP (including a suspected treatment-related adverse event of skin hypersensitivity on the treatment area)
4) Increase in the total treatment area to more than 40% of BSA
5) Discovery that the subject is pregnant or suspected to be pregnant
6) Judgment by the investigator or subinvestigator that it is necessary to withdraw the subject from the trial

9.3 Follow-up Investigation of Subjects Who Do not Visit the Trial Site

If a subject has missed visiting the trial site for an unknown reason, the investigator or subinvestigator will promptly contact the subject, family members, or other related persons to confirm whether any adverse event has occurred in the subject and to encourage the subject to visit the trial site. If the subject keeps missing visits, the following issues will be investigated, and the results will be recorded.

1) The date of investigation
2) The method of investigation
3) Whether or not the subject was contacted
4) Reason why the subject did not (or cannot) visit the trial site
5) Details of status of IMP administration
6) Occurrence or absence of adverse events. If an adverse event has occurred: Name of the event, date of onset and date of recovery, severity, relationship to the IMP, measures taken regarding IMP administration, treatment of adverse event, and outcome
7) If a follow-up investigation is impossible: The reason why

10 Collection of Case Report Form Data and Specification of Source Data

10.1 Collection of Case Report Form Data

1) Electronic Data Capture (EDC) will be used in the trial.
2) Subject data will be entered directly into the database from the trial site via a Web browser. These data collected by EDC will constitute the CRF.
3) Regarding quality assurance of CRFs, the guidelines specified in "Use of Electromagnetic Records and Electronic Signatures in Applications for Approval or Licensing of Drugs" (PFSB Notification No. 0401022, dated 01 Apr 2005) and "Guidance on Electronic Capture of Clinical Study Data" (Drug Evaluation Committee, Japan Pharmaceutical Manufacturers Association, dated 01 Nov 2007) will be observed.

4) For every subject who provides consent to participate in the trial, a CRF will be created on an EDC data entry screen that conforms to the items of CRF data collection described in the trial protocol.
5) The investigator, subinvestigator, or trial associate will create CRFs according to the manual provided by the sponsor. If source documents are available and the objectivity of the data can be ensured, then the data may be recorded in a CRF by a trial associate.
6) When entering data into CRFs from the trial site, a predetermined check will be automatically performed. The investigator, subinvestigator, or a trial associate will make corrections as necessary.
7) The sponsor will verify CRFs in comparison to source documents and conduct data reviews. If additional query is necessary, the sponsor will issue an intra-system query, and the investigator, subinvestigator, or a trial associate will perform data correction or provide a response to the sponsor's query as necessary.
8) A history of all revisions made after the initial data entry is saved on the server will be automatically recorded within the system (date of revision, name of person making revision, pre- and post-revision data, reason for revision, date of query, name of person issuing query, details of query, etc.).
9) After completion of all CRF data entry and confirmation that the content is correct and complete, including confirmation of the audit trail, the investigator will attach an electronic signature.
10) Details concerning data collection will be specified in a separate manual prepared in advance.

10.2 Source Documents

1) Source documents are defined as those documents that are the source of data transcribed into CRFs as trial results.
Medical records and other records (medical records, nursing records, prescription records), subject screening list, registration verification forms, ICFs, clinical laboratory test and other measurement reports, 12-lead ECG analysis reports, IMP management records, administration diaries, VAS sheets, pruritus diaries
2) The investigator or the trial site will retain all trial-related documents and records except CRFs in such a manner that enables the sponsor or the regulatory authority to have direct access to the documents and records.
3) The original ICFs will be retained according to the method specified by each trial site.
4) After completion of the trial, the sponsor will retain the original CRFs on CD-ROM or some other appropriate electronic medium and the investigator or the trial site will retain copies.
5) The original data regarding drug concentration measurement (eg, original bioanalytical reports, chromatograms) will be kept by the bioanalytical laboratory.

10.3 Case Report Form Items Treated as Source Data

Not applicable.

10.4 Data to Be Collected by the Sponsor

1) CRFs (data following acquisition of informed consent)
2) Results of clinical laboratory tests conducted by the central laboratory will be directly sent to the sponsor by the central laboratory in the form of electronic data.
3) Results of 12-lead ECG measurement performed by the central ECG reading facility will be directly sent to the sponsor by the central ECG reading facility in the form of electronic data.
4) Results of drug concentration measurement conducted by the bioanalytical laboratory will be directly sent to the sponsor by the bioanalytical laboratory in the form of electronic data.

11 Statistical Analysis

The definition of the analysis sets and analysis methods are described below. The details of the analysis plan are described separately in a statistical analysis plan. The statistical analysis plan will be finalized prior to database lock.

11.1 Statistical Analysis Sets

In this trial, a “Full Analysis Set” and “Safety Set” will be established.

11.1.1 Full Analysis Set (FAS)

Subjects to whom the IMP has been administered at least once.

11.1.2 Safety Set (SS)

Subjects to whom the IMP has been administered at least once.

11.2 Handling of Data

Regarding the incidence of success in IGA, the data will be handled as follows.

1) Primary analysis

- Subjects with an IGA score of 0 (clear) or 1 (almost clear) with an improvement by at least 2 grades from the baseline are defined as responders.

Subjects with missing IGA data at the time of evaluation will be handled as non-responders.

2) Sensitivity analysis

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

11.3 Analysis Items and Method

11.3.1 Efficacy Analysis

11.3.1.1 Primary Variable

1) Definition
Incidence of success in IGA at Week 4: percentage of subjects with an IGA score of 0 (no response) or 1 (almost no response) with an improvement by at least 2 grades (responders)

2) Analysis set
FAS

3) Method of analysis
The Cochran-Mantel-Haenszel test will be conducted using the baseline IGA (mild or moderate) as a stratification factor. In consideration of the issue of multiplicity, a comparison between the vehicle group and the 1% OPA-15406 group will be performed first based on the closed testing procedure. When superiority of the 1% OPA-15406 group compared to the vehicle group is demonstrated with a two-sided significance level of 0.05, a comparison between the vehicle group and the 0.3% OPA-15406 group will be performed. Also, the difference in the incidence of success in IGA and its two-sided 95% confidence interval will be determined between the vehicle group and the 0.3% OPA-15406 group or the 1% OPA-15406 group. Also, the sensitivity analysis will be performed using the 3 data handling methods in "2) Sensitivity analysis in Section 11.2 Handling of Data," under the same analysis procedure described above. In an exploratory manner, a logistic-regression analysis will be conducted, using the baseline IGA (mild or moderate) and the treatment group as explanatory variables and the incidence of success in IGA at Week 4 as the outcome variable.

11.3.1.2 Secondary Variables

1) Definition

- Incidence of success in IGA at Week 1 and Week 8
- Change from baseline in IGA at Week 1, Week 4, and Week 8
- Change from baseline in the total score of EASI and each symptom score at Week 1, Week 4, and Week 8
- Change from baseline in VAS for pruritus at Week 1, Week 4, and Week 8
- Change from baseline in VRS for pruritus up to Day 7
- Change from baseline in the total score of DLQI at Week 1, Week 4, and Week 8
- Change from baseline in the total score of POEM at Week 1, Week 4, and Week 8
- Change from baseline in the total affected BSA (%) at Week 1, Week 4, and Week 8
- Time to response in IGA and VRS

2) Analysis set
FAS

3) Method of analysis

- Incidence of success in IGA at Week 1 and Week 8
The analysis method will be the same as that for the primary variable.
- Change from baseline in IGA at Week 1, Week 4, and Week 8
A mixed-model repeated measure (MMRM) analysis with an unstructured error covariance matrix will be performed, using the OC data set containing the data at baseline, after administration (Week 1, Week 2, Week 4, Week 6, and Week 8), and at discontinuation, setting the change from the baseline at Week 1 through Week 8 as a response variable and the treatment (0.3% OPA-15406, 1% OPA-15406, or vehicle), timepoint, baseline IGA (mild or moderate), interaction between the treatment (0.3% OPA-15406, 1% OPA-15406, or vehicle) and timepoint as factors. Standard error and degree of freedom for the fixed effect will be calculated by the Kenward-Roger method. The least square mean will be calculated by treatment group and timepoint. Also, the difference in the least square means between the vehicle group and the respective OPA-15406 groups, the two-sided 95% confidence interval, and the p value will be calculated at Week 1, Week 4 and Week 8. Using the OC and LOCF data sets, the analysis of covariance (ANCOVA) with treatment (0.3% OPA-15406, 1% OPA-15406, or vehicle) and baseline IGA (mild or moderate) as factors will be applied to the change from the baseline at the respective timepoints as a response variable. The least square mean will be calculated by treatment group and timepoint. Also, the difference in the least square means between the vehicle group and the respective OPA-15406 groups, the two-sided 95% confidence interval, and the p value will be calculated at Week 1, Week 4 and Week 8. Using the OC and LOCF data sets, the descriptive statistics will be calculated for measured values and changes from

the baseline at the respective timepoints by treatment group and timepoint. For the change in IGA at Week 1, Week 4, and Week 8, the frequency distribution will also be generated.

- For the following items, the analysis will be performed in the same manner as that of the change from baseline at the respective timepoints in IGA. For the MMRM analysis, however, the treatment (0.3% OPA-15406, 1% OPA-15406, or vehicle), timepoint, and interaction between the treatment and timepoint will be used as factors, and baseline values of the respective variables will be used as covariates. For the ANCOVA model, baseline values of the respective variables will also be included as covariates, as well as the treatment. For EASI, VAS, and DLQI, the percent change from baseline at the respective timepoints will also be calculated in the same manner as the amount of change.
  a) Change from baseline in the total score of EASI and each symptom score at Week 1, Week 4, and Week 8
  b) Change from baseline in VAS for pruritus at Week 1, Week 4, and Week 8
  c) Change from baseline in the total score of DLQI at Week 1, Week 4, and Week 8
  d) Change from baseline in the total score of POEM at Week 1, Week 4, and Week 8
  e) Change from baseline in the total affected BSA (%) at Week 1, Week 4, and Week 8
- Change from baseline in VRS for pruritus up to Day 7
  Using the OC and LOCF data sets up to Day 7, the analysis of covariance (ANCOVA) with treatment (0.3% OPA-15406, 1% OPA-15406, or vehicle) and baseline values as factors will be applied to the change from the baseline at the respective timepoints as a response variable. The least square mean will be calculated by treatment group and timepoint. Also, the difference in the least square means between the vehicle group and the respective OPA-15406 groups, the two-sided 95% confidence interval, and the p value will be calculated. Using the OC and LOCF data sets, the descriptive statistics will be calculated for measured values and changes from the baseline at the respective timepoints by treatment group and timepoint. Assessments will be made at 4, 8, and 12 hours after the start of administration, 1 day after the start of administration (morning and night), and thereafter in the same manner up to Day 7 (morning).
- Time to response in IGA and VRS
  For time to response in IGA and VRS, Kaplan-Meier plots will be generated for each treatment group and vehicle group. For IGA, subjects with an IGA score of 0 (clear) or 1 (almost clear) with an improvement by at least 2 grades from the baseline are defined as responders. For VRS, subjects with VRS score of 0 (none) or 1 (mild) with an improvement by at least 1 grade from the baseline are defined as responders.

11.3.2 Safety Analysis

1) Definition
   Adverse events (Physical findings will be evaluated for reported adverse events), vital signs (including body weight), clinical laboratory values, 12-lead ECG
2) Analysis set
   SS
3) Method of analysis

- Adverse events
  Based on System Organ Classes and Preferred Terms of the ICH Medical Dictionary for Regulatory Activities (MedDRA), the number of subjects and incidences will be calculated for the following events occurring after IMP administration (treatment-emergent adverse events: TEAEs). For TEAEs for which the relationship to the IMP cannot be ruled out, the number of subjects and incidences will also be calculated, in the same manner.
  1. TEAEs
  2. TEAEs resulting in death
  3. Serious TEAEs
  4. TEAEs leading to discontinuation of IMP administration
  5. TEAEs by severity
  6. TEAEs at treatment areas
- Vital signs (including body weight)
  For each parameter, the descriptive statistics will be calculated for measured values and changes from the baseline by treatment group and timepoint.
- Clinical laboratory tests
  For each parameter (except qualitative urinalysis), the descriptive statistics will be calculated for measured values and changes from the baseline by treatment group and timepoint. Except for qualitative urinalysis parameters, shift tables will be created for predose and postdose values classified into normal, high, and low based on the standard value by treatment group. For qualitative urinalysis, shift tables will be created for predose and postdose values by each parameter.
- 12-lead ECG
  The descriptive statistics will be calculated for measured values and changes from the baseline by treatment group and timepoint.

11.3.3 Pharmacokinetic Analysis

1) Variables

   - Plasma trough concentration of OPA-15406 (prior to IMP administration at Week 1, Week 4, and Week 8 of IMP administration; all subjects)

- Plasma concentration of OPA-15406 (prior to IMP administration and 2 hours, 4 hours, and 8 hours postdose on Day 1 and at Week 4; specific sites (target of 6 subjects from each group)
- Pharmacokinetic parameters of OPA-15406: $C_{max,}$ $t_{max,}$ and $AUC_{0\text{-}8h}$ on Day 1 and at Week 4 of IMP administration
- Accumulation of OPA-15406: Ratio of C_{max} and $AUC_{0\text{-}8h}$ at Week 4 and on Day 1 of IMP administration

2) Analysis set
Pharmacokinetics analysis set

3) Method of analysis

- Method of calculation
Plasma concentrations below the lower limit of quantification will be treated as zero (0) for calculation of the descriptive statistics.
- Method of display
Arithmetic means and standard deviations will be used for figures and tables of plasma concentration.
  a) Regarding plasma trough concentration of OPA-15406, the descriptive statistics of plasma OPA-15406 concentrations (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) will be calculated by treatment group, by timepoint, and by baseline affected BSA (≥5% to <10%, ≥10% to <30%, or ≥30%). Also, the descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) will be calculated by age for each range of affected BSA, by affected BSA (%) at the baseline, and by amount of administration (g).
  b) Regarding plasma trough concentration of OPA-15406, the descriptive statistics of plasma OPA-15406 concentrations by treatment group and timepoint, and the descriptive statistics of plasma OPA-15406 concentrations (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) adjusted for affected BSA at the baseline will be calculated. The subject group for pharmacokinetic parameters should be calculated in the same way separately.
  c) Regarding pharmacokinetic parameters of OPA-15406, the descriptive statistics (number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum value, median value, and maximum value) by treatment group and timepoint will be calculated.

11.3.4 Demographic and Other Baseline Characteristics

1) Definition
Baseline data of sex, age, complications, medical history, previous medications

(for AD or for other diseases), concomitant medications, severity, IGA, EASI, VAS for pruritus, VRS for pruritus, DLQI, POEM, and affected BSA

2) Analysis set
SS, FAS
3) Method of analysis
The descriptive statistics or frequency distribution will be created by treatment groups depending on the characteristics of the respective parameters.

11.3.5 Subgroup Analysis

For the incidence of success in IGA at Week 1, Week 4, and Week 8, the analysis will be performed in the same manner as that for the primary variable by subgroups of baseline IGA (mild or moderate). Also, the frequency distribution will be generated by the trial sites.

11.3.6 Level of Significance and Confidence Coefficient

The two-sided significance level is 5% with a two-sided 95% confidence interval.

11.3.7 Multiple Comparison/Multiplicity

For the analysis of the primary variable, a comparison will be performed between the vehicle group and the 1% OPA-15406 group and between the vehicle group and the 0.3% OPA-15406 group. The closed testing procedure will be employed to avoid the issue of multiplicity. For variables other than the primary variable, the analysis will be performed for reference, and the multiplicity adjustment will not be conducted.

11.3.8 Adjustment by Covariates

The Cochran-Mantel-Haenszel test will be performed, using baseline IGA (mild or moderate) as a stratification factor.

11.4 Procedures for Reporting Deviations From the Original Statistical Analysis Plan

The statistical analysis plan of this trial will be finalized by the time of data fixation. If any content of the analysis methods specified in this protocol are to be changed, the detail and reason for the change will be described in the statistical analysis plan and clinical study report.

If any change or addition is made from the statistical analysis plan after unblinding, results of the changed or additional analysis will be clearly distinguished

from those of the planned analysis, and caution should be taken regarding the possible effects on the conclusion. Also, the reason for the change or addition will be stated in the clinical study report.

11.5 Rationale for Target Number of Patients

In the phase 2 trial outside Japan (271-12-205), the primary variable of incidence of success in IGA was 20.93% and 2.70% in the 1% OPA-15406 group and the vehicle group, respectively. In the present trial, with the assumption that the difference in the incidence of success in IGA between the vehicle group and the 1% OPA-15406 group is similar to that obtained in the foreign trial, a sample size of 54 subjects per group at a two-tailed 5% level of significance was calculated with at least an 80% power. In consideration of possible discontinuations and dropouts, the number of subjects is established as 60 subjects per group.

12 Quality Control and Quality Assurance for the Trial

To ensure quality of the trial, trial sites, contract research organizations, laboratories performing clinical laboratory tests, and the sponsor will perform quality control for the trial according to their respective Standard Operating Procedures.

The audit division of the sponsor company will carry out audits within the company and, as necessary, at the trial site and contract research organizations or organizations entrusted to perform related activities, and check whether quality control of the trial is appropriately performed according to the Standard Operating Procedures.

13 General Items of Caution Pertaining to the Trial

13.1 Ethics and GCP Compliance

This clinical trial is to be conducted in compliance with the ethical principles of the Declaration of Helsinki, the Pharmaceutical Affairs Law, the Ordinance on Good Clinical Practice (Ministry of Health and Welfare Ordinance No. 28 dated 27 Mar 1997), relevant notifications, and this trial protocol.

13.2 Institutional Review Board

Prior to performance of this trial, the appropriateness of performance of this trial will be reviewed from ethical, scientific, and medical perspectives by the IRB designated by the trial site, and this trial will be commenced only after obtaining the approval of the IRB.

13.3 Subject Consent

13.3.1 Procedures for Obtaining Consent

The term "consent" in this protocol is defined as legally established consent that is given by the subject or the subject's legal guardian.

1) Prior to the start of the screening examination, the investigator or subinvestigator will fully explain the matters listed in Section13.3.2 to each subject (and the subject's legal guardian if the subject is under 20 years old) who will be included in the trial, using the ICF, and give the ICF to the subject (or to the subject's legal guardian if the subject is under 20 years old). The subject will be provided sufficient time to make a decision regarding participation. After confirming that the subject has properly understood the explanation, the investigator or subinvestigator will obtain written voluntary consent for participation in the trial from the subject. If the subject is under 20 years old, the relationship between the subject and the subject's legal guardian will be confirmed and recorded.
2) The investigator or subinvestigator who has provided the explanation to the subject (and the subject's legal guardian if the subject is under 20 years old) will put his or her printed name and personal seal or signature on the ICF, and write the date on which he or she puts the printed name and personal seal or signature on the form. If a trial associate has provided a supplemental explanation of the trial, he/she will also put his or her printed name and personal seal or signature on the form and write the date on which he or she puts the printed name and personal seal or signature on the form. The subject (and the subject's legal guardian if the subject is under 20 years old) will also put his or her printed name and personal seal or signature, and the date on the ICF.
3) The original of the ICF that was marked with the printed name and personal seal or signature and dated will be retained by the investigator or subinvestigator according to the regulations of the trial site. A copy of the original ICF will be given to the subject (or to the subject's legal guardian if the subject is under 20 years old).
4) After obtaining informed consent from the subject (and the subject's legal guardian if the subject is under 20 years old), the investigator or subinvestigator will write the date of informed consent acquisition and subject identification code in the documents for enrolled subjects.

5) If new information becomes available that may influence the willingness of the subject to continue participation in the trial, the investigator or subinvestigator will promptly inform the subject (and the subject's legal guardian if the subject is under 20 years old) of such information and confirm the willingness of the subject to continue participation in the trial, and then record the result in the subject's medical records. If there is guidance regarding the recording of re-consent stipulated by the trial site, it will be followed.

13.3.2 Contents of Informed Consent Form

1) An explanation that the trial involves research
2) The type of IRB that reviews the appropriateness of trial conduct, matters to be reviewed by the IRB, and other relevant descriptions of the activity of the IRB
3) The objectives of the trial
4) The trial procedures (including research-related aspects of the trial, inclusion criteria for subjects, and, if random allocation is performed, the probability of randomization to each treatment arm)
5) The expected duration of the subject's participation in the trial
6) The planned number of subjects involved in the trial
7) The foreseeable IMP-related physical and mental benefits (if no benefits are expected, this should be indicated) as well as risks or inconveniences to the subject
8) The existence of alternative treatments for the subject, and their important potential benefits and risks
9) The treatment and compensation available to the subject in the event of trial-related injury to health
10) An explanation that the subject's participation in the trial is voluntary, and that the subject can refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which he or she would otherwise be entitled
11) An explanation that the subject will be informed in a timely manner if information becomes available that may be relevant to his or her willingness to continue participation in the trial
12) The circumstances or reasons under which the subject's participation in the trial should be terminated
13) An explanation that the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records without violating the confidentiality of the subject, and that by signing the ICF, the subject is authorizing such access
14) 1An explanation that if the results of the trial are published, the subject's identity will remain confidential
15) 1The anticipated expenses to the subject for participating in the trial

16) The anticipated payment, if any, to the subject for participating in the trial (agreements on payment, etc.)
17) The name, position, and contact address of the investigator or subinvestigator
18) The persons at the trial site to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury to health
19) Matters to be observed by subjects

13.3.3 Amendments to the Informed Consent Form

If revision of the ICF becomes necessary due to newly obtained information, the investigator will promptly revise the ICF to include that information after conferring with the sponsor.

The investigator, when revising the ICF, will report this to the head of the trial site and submit the revised document to the IRB designated by the trial site to obtain its approval.

If new information becomes available that may influence the willingness of subjects to continue participation in the trial and the ICF has been revised according to the new information, the investigator or subinvestigator will again obtain subjects' written informed consent to continue participation in the trial.

13.4 Management of Investigational Medicinal Products

1) The sponsor will issue a "Clinical Operation Manual (COM)" to the persons designated by the trial site.
2) The sponsor will issue the "Document on Investigational Medicinal Products Storage Conditions" to the investigator or subinvestigator, trial associates, and IMP manager.
3) The sponsor will deliver the IMPs to the trial site following the start of the trial period contracted with the trial site.
4) The IMP manager will manage the IMPs appropriately according to the "COM" prepared by the sponsor.
5) The IMP manager will prepare and retain the "Record of Management and Storage of Investigational Medicinal Products."

13.5 Direct Access to Source Documents and Monitoring

13.5.1 Direct Access to Source Documents

The head of the trial site and the investigator must accept monitoring and audits to be performed by the sponsor and inspection by the IRB and Japanese and foreign regulatory authorities, and must make source documents and all other trial-related records available to these agencies for direct access (including copying). Subjects authorize such direct access by signing the written ICF.

13.5.2 Monitoring

The sponsor bears responsibility for ethical, legal, and scientific conduct of the trial. The sponsor will perform monitoring according to the "Procedures for monitoring" specified for this trial. Monitoring includes periodic visits, phone calls, or other contact with the trial site for the provision, obtaining, and recording of updated trial-related information by monitors designated by the sponsor.

The sponsor may entrust a portion of monitoring activity to a contract research organization.

13.5.3 Documents to Be Retained by the Investigator

The trial-related documents to be retained by the investigator will be kept in the investigator's file, which will be managed by the investigator.

13.6 Deviations From and Changes or Amendments to the Trial Protocol

13.6.1 Deviations From the Trial Protocol

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

13.6.2 Amendments to the Trial Protocol

1) The investigator will promptly submit to the sponsor, the head of the trial site, and the IRB by way of the head of the trial site, a written report on any changes in the trial that may significantly affect conduct of the trial or increase risks to the trial subjects.
2) The sponsor, after conferring with the investigator, will agree with the investigator on the contents of the revised protocol and compliance with the revised protocol.
3) The sponsor will promptly submit the revised protocol to the head of the trial site.

13.7 Archiving of Records

1) The trial site will retain all the trial-related documents and records for the period of time indicated in a) or b) below, whichever is longer. However, if the sponsor requires a longer period of archiving, the head of the trial site will consult with the sponsor on the period and procedures of record retention.
   a) The date 2 years after an Application for Approval of a Pharmaceutical Product for the IMP is granted; or, if the head of the trial site receives notification from the sponsor that development has been terminated or that results of the trial will not be submitted with the approval application, the date 3 years after receipt of such notification.
   b) The date 3 years after termination or completion of the trial.
2) The investigator will retain the trial-related documents and records as directed by the head of the trial site.
3) If it becomes no longer necessary to retain the trial-related documents and records at the trial site, the sponsor will notify the head of the trial site.

13.8 Termination or Interruption of Part or All of the Trial

13.8.1 Termination or Interruption of the Trial at Individual Trial Sites

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

13.8.2 Termination or Interruption of the Entire Trial

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

13.9 Protection of Subjects' Personal Information

In completion and handling of CRFs, the investigator and subinvestigator will take adequate care to ensure protection of the personal information of subjects. Individual subjects will be identified by subject numbers. The sponsor will not provide the information obtained to any third party.

13.10 Compensation for Injury to Health

Trial subjects will be compensated for health damages according to the criteria established by the trial sponsor with reference to the "Guidelines for Health Damage Compensation to Trial Subjects" (revised 25 Nov 2009) of the Japan Pharmaceutical Industry Legal Affairs Association.

13.11 Agreement on Publication

The sponsor may use the findings obtained from this trial for purposes such as an "Application for Approval of a Pharmaceutical Product" for the IMP.

When the results of this trial and relevant data are to be published in scientific journals or at academic meetings, the investigator will obtain prior written approval from the sponsor.

14 Trial Administrative Structure

The administrative structure of this trial is shown in Annex 3.

15 Scheduled Duration of the Trial

21 Jul 2016 to 31 Jul 2017

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Date (examination) Subject Number -S-

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

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

Date (examination) Subject Number -S-

Appendix 2 Visual Analogue Scale (VAS) Sheet for Pruritus

No Itching Maximum Itching

0 ——————————————————— 100

Date (examination) Subject Number -S-

Appendix 3 Dermatology Life Quality Index (DLQI)

The DLQI questionnaire is shown on the next page.

© Dermatology Life Quality Index. AY Finlay, GK Khan, April 1992. www.dermatology.org.uk

Date (examination) Subject Number -S-

Dermatology Life Quality Index (DLQI)

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1) Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?

□ Very much
□ A lot
□ A little
□ Not at all

2) Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?

□ Very much
□ A lot
□ A little
□ Not at all

3) Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or going **garden**?

□ Very much
□ A lot
□ A little
□ Not at all
□ Not relevant

4) Over the last week, how much has your skin influenced the **clothes** you wear?

□ Very much
□ A lot
□ A little
□ Not at all
□ Not relevant

5) Over the last week, how much has your skin affected any **social** or **leisure** activities?

□ Very much
□ A lot
□ A little
□ Not at all
□ Not relevant

6) Over the last week, how much has your skin made it difficult for you to do any **sport**?

□ Very much
□ A lot
□ A little
□ Not at all
□ Not relevant

7) Over the last week, has your skin prevented you from **working** or **studying**?

□ Yes
□ No
□ Not relevant

Date (examination) Subject Number -S-

If "No", over the last week how much has your skin been a problem at **work** or **studying**?
□ A lot
□ A little
□ Not at all

8) Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?

□ Very much
□ A lot
□ A little
□ Not at all
□ Not relevant

9) Over the last week, how much has your skin caused any **sexual difficulties**?

□ Very much
□ A lot
□ A little
□ Not at all
□ Not relevant

10) Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?

□ Very much
□ A lot
□ A little
□ Not at all
□ Not relevant

Please check you have answered EVERY question. Thank you.

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Date (examination) Subject Number -S-

Appendix 4 Patient-Oriented Eczema Measure (POEM)

The POEM questionnaire is shown on the next page.

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Date (examination) Subject Number -S-

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): .....

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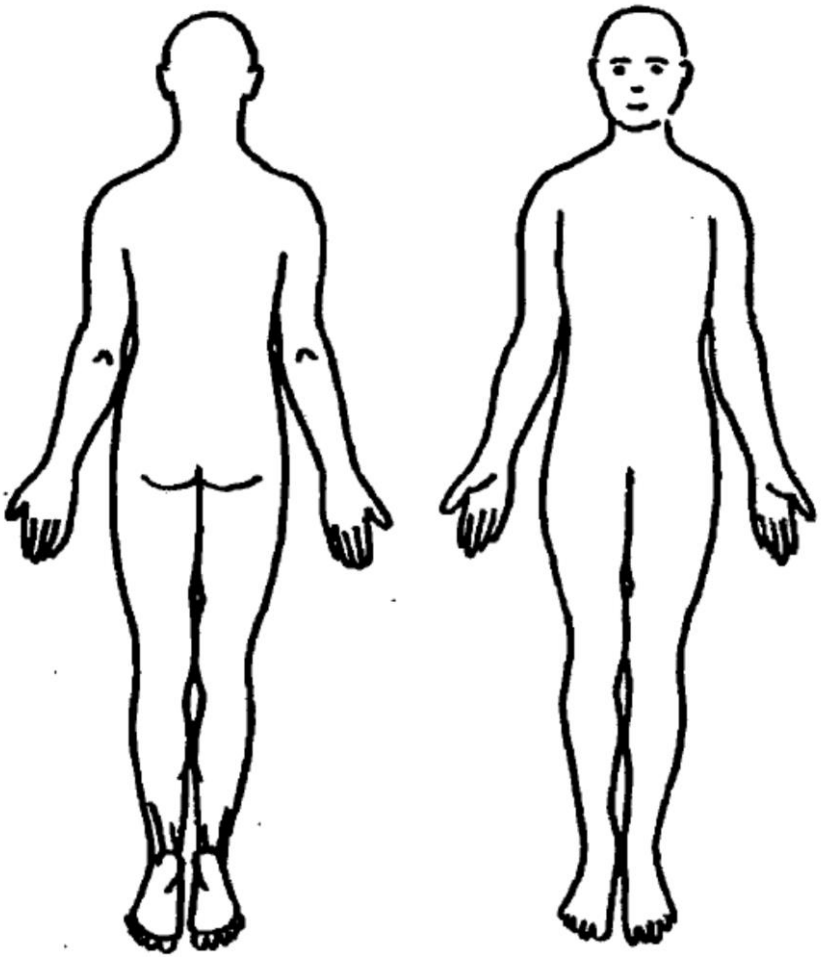
Date (examination) Subject Number -S-

Appendix 5 Human Body Drawing



Total amount of administration g

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

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

Signature of the investigator/subinvestigator

Day/ Month/20