STATISTICAL ANALYSIS PLAN

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)

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for

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List of Abbreviations and Definition of Terms

List of Abbreviations

Abbreviation	Expansion
AD	Atopic Dermatitis
BSA	Body Surface Area
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
FAS	Full Analysis Set
IGA	Investigator's Global Assessment
IMP	Investigational Medicinal Product
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
OC	Observed Cases
POEM	Patient-Oriented Eczema Measure
QTcB	QT interval as correlated by Bazett's formula
QTcF	QT interval as correlated by Fridericia's formula
SS	Safety Set
TEAE	Treatment-emergent Adverse Event
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale

List of Pharmacokinetic Parameters

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

Definition of Terms

Term	Definition
Descriptive statistics	Number of subjects, mean, standard deviation, minimum, median, and maximum
Descriptive statistics of pharmacokinetic parameters	Number of subjects, arithmetic mean, geometric mean, coefficient of variation, standard deviation, minimum, median, and maximum (For t_{max}, number of subjects, minimum, median, and maximum only)
Descriptive statistics of plasma OPA-15406 concentrations	Number of subjects, arithmetic mean, coefficient of variation, standard deviation, minimum, median, and maximum
Frequency distribution	Number and percentage of subjects

1 Introduction

This statistical analysis plan (SAP) documents the detailed methodology of summarization/analyses and evaluation to provide the trial data required for the preparation of a clinical study report of Trial 271-15-001. This document has been created based on Protocol No. 271-15-001, Version 4.0, issued on 29 Dec 2016.
The pharmacokinetic analyses are detailed in Section 11.

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 atopic dermatitis (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 Design

This 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) 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 the screening examination and the day of the baseline examination (2-30 days). The subjects who meet the inclusion criteria and do not meet the 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 the baseline examination and the day of Week 8 examination (or

the day of discontinuation). The allocated investigational medicinal product (IMP) will be administered to the treatment area from the day of the 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 the 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 the 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.

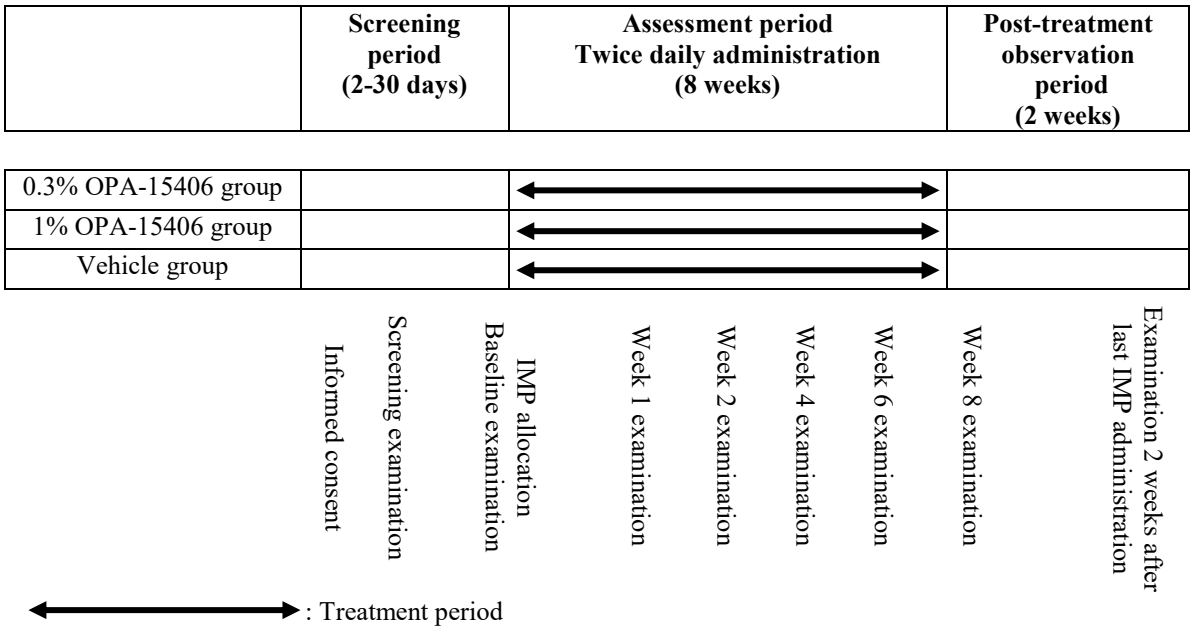

Figure 3-1 Trial Design

4 Implementation of Planned Analyses

The SAP will be finalized prior to database lock, and analyses will be performed using the final data.

5 Statistical Analysis Sets

5.1 Definitions of Analysis Sets

5.1.1 Full Analysis Set

The full analysis set (FAS) consists of all subjects who have received the IMP at least once.

5.1.2 Safety Set

The safety set (SS) consists of all subjects who have received the IMP at least once

6 Considerations for Data Analysis

6.1 Software

SAS ver.9.4 (SAS Institute Inc.)

6.2 Dictionaries

Coding of adverse events and medical history/complications: Medical Dictionary for Regulatory Activities (MedDRA)/J Version 20.0

Coding of prior and concomitant medications: WHO Drug Dictionary (dated 1 Mar 2016)

6.3 Data Conversion and Calculation

6.3.1 Response in Investigator's Global Assessment

Responders and non-responders in investigator's global assessment (IGA) are defined 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.

6.3.2 Treatment Compliance

Treatment compliance = (total amount of the IMP applied from the start of administration to the assessment point[1])/(sum of the specified amounts of the IMP per dose from the start of administration to the assessment point[2]) × 100

[1] [Total amount of the IMP prescribed from the start of administration to the assessment point] − [total amount of the IMP returned from the start of administration to the assessment point]

If the total amount of the IMP returned is missing, the total amount of the IMP applied from the start of administration to the assessment point will be handled as a missing value.

[2] Calculation of "amount of the IMP (g) per dose"

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

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

2) Based on the subject's BSA (m^2), the amount of administration (g) for 1% of BSA will be selected from the table below.

Table 6.3-1 Amount of Administration (g) for 1% of BSA Based on the Subject's 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

3) [Amount of the IMP (g) per dose] at the assessment point will be calculated as [amount of administration (g) for 1% of BSA] × [treatment area (%) at the assessment point (including baseline)].

Treatment compliance with the number of administrations will be calculated as follows:

Treatment compliance with the number of administrations = (number of administrations from the start of administration to the assessment point)/(number of days from the start of administration to the assessment point × 2) × 100

6.3.3 Overall Eczema Area and Severity Index Score

Overall Eczema Area and Severity Index (EASI) total score is the sum of the scores for 4 body regions (face, neck, and head; upper limbs; trunk; and lower limbs). The score for each region will be calculated as shown in Table 6.3-2.

Table 6.3-2 EASI Score for Each Region

Body region	Calculation of the score for each region
Face, neck, and head	(E+I+Ex+L) × score of affected BSA × 0.1
Upper limbs	(E+I+Ex+L) × score of affected BSA × 0.2
Trunk	(E+I+Ex+L) × score of affected BSA × 0.3
Lower limbs	(E+I+Ex+L) × score of affected BSA × 0.4

- 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

6.3.4 EASI Symptom Score

Each EASI symptom score (erythema, infiltration/papules, excoriation, and lichenification) will be determined as the sum of the severity scores (Body Regions Scores) for 4 regions (face, neck, and head; upper limbs; trunk; and lower limbs) (The scores of affected BSA or multipliers will not be used in the calculation).

6.4 Study Week Windows

The definitions of timepoints for analysis are described in Table 6.4-1 and Table 6.4-2. Timepoints, including unscheduled visits and visit at discontinuation, will be determined based on the number of days from the start of IMP administration. However, for Verbal Rating Scale (VRS), the timepoint will be determined based on the amount of time that has elapsed from the start of IMP administration. For efficacy variables, the data obtained between the day of the start of IMP administration and 7 days after the last IMP administration will be used in analyses. If multiple data exist within the allowable window of the timepoint, the data obtained last will be used for analyses. Data for the Last Visit will be defined as the last data obtained between the day of the start of IMP administration and 7 days after the last IMP administration (including data obtained at discontinuation) for efficacy valuables or as the last data obtained after the start of the IMP administration for safety variables.

In analyses, baseline data will be defined as data obtained on the day or at the date and time before and nearest to the start of IMP administration, including the screening data.

Table 6.4-1 Timepoints and Allowable Windows for Efficacy Variables (Except VRS) and Safety Variables

Timepoint	Study Day	Allowable Window (Days After the Start of IMP Administration)		
Week 1	8	1	-	10
Week 2	15	11	-	21
Week 4	29	22	-	35
Week 6	43	36	-	48
Week 8	57	49	-	73

Table 6.4-2 Timepoints and Allowable Windows for VRS

Timepoint	Allowable Window (Hours After the Start of IMP Administration)		
Hour 4	1	-	< 6
Hour 8	6	-	< 10
Hour 12	10	-	< 18
Hour 24	18	-	< 30
Hour 36	30	-	< 42
Hour 48	42	-	< 54
Hour 60	54	-	< 66
Hour 72	66	-	< 78
Hour 84	78	-	< 90
Hour 96	90	-	< 102
Hour 108	102	-	< 114
Hour 120	114	-	< 126
Hour 132	126	-	< 138
Hour 144	138	-	< 150
Hour 156	150	-	< 162
Hour 168	162	-	< 174

6.5 Handling of Missing Values

Missing data for incidence of success in IGA, the primary endpoint, will be handled as described in "Section 6.3.1 Response in Investigator's Global Assessment ." Other variables at each timepoint will be analyzed based on the OC and LOCF data sets.

6.6 Significance Level and Confidence Coefficient

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

6.6.1 Multiple Comparisons and Multiplicity

For the primary analysis of incidence of success in IGA, the primary endpoint, a comparison will be performed between the vehicle group and 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 issue of multiplicity. 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.

For variables other than the primary variable, p-values will also be computed for a reference indication of differences between the treatment groups. The multiplicity adjustment will not be conducted.

7 Disposition of Subjects

7.1 Disposition of Subjects

Data will be summarized for the overall population and by age group (<18 or ≥18). The numbers of screened and randomized subjects will be provided. The following frequency distributions will be provided for overall population and by treatment group, unless otherwise specified. The frequency distribution (number and percentage relative to all subjects randomized) of subjects treated, those who completed the trial, and those who discontinued the trial will be calculated. For subjects who discontinue the trial, the frequency distribution will be calculated by reason for discontinuation.

7.2 Statistical Analysis Sets

Data will be summarized for the overall population and by age group (<18 or ≥18). For the randomized subjects, the number and percentage of subjects included in the FAS, SS, and pharmacokinetic analysis set will be provided.

7.3 Protocol Deviations

The number and percentage of subjects with major protocol deviations will be provided for the overall population and by treatment group. The number and percentage of major protocol deviations occurring in each trial site will be provided for the overall population and by treatment group.

8 Description of Analysis Dataset

8.1 Demographics and Baseline Characteristics

Data will be summarized for the overall population and by age group (<18 or ≥18). For the randomized subjects, age, gender, duration of AD, body weight, height, BMI, race, baseline IGA score, and nation will be summarized for overall population and by treatment group using descriptive statistics or frequency distribution.

Affected BSA at baseline will be categorized as follows and summarized for overall population and by treatment group using frequency distribution.

Affected BSA categories: ≥5% to <10%, ≥10% to <30%, and ≥30%

8.2 Medical History/Complications

Medical history and complications will be coded by MedDRA/J system organ class (SOC) and preferred term (PT). The medical history and complications will be listed, but not summarized.

8.3 Prior and Concomitant Medications

For the randomized subjects, the numbers and percentages of subjects who take any concomitant medication before the start of IMP administration, during the treatment period, and after the last IMP administration will be provided by medication for the overall population and by treatment group. The medications will be coded using the WHO Drug Dictionary, and summarized by ATC Classification Level 2 and Preferred Name.

8.4 Concomitant Therapies

The concomitant therapies will be listed, but not summarized.

9 Efficacy Analyses

Efficacy analyses will be conducted in the FAS.

9.1 Primary Endpoint

The primary endpoint is incidence of success in IGA at Week 4.

Comparisons of incidences of success in IGA at Week 4 between the 1% OPA-15406 group and the vehicle group, and between the 0.3% OPA-15406 group and the vehicle group will be conducted using the Cochran-Mantel-Haenszel test stratified by baseline IGA score (mild or moderate). The closed testing procedure will be employed to avoid issue of multiplicity. 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. The difference in incidence of success in IGA between each OPA-15406 group and the vehicle group and its two-sided 95% confidence interval (a Mantel-Haenszel estimator of the common risk difference and its two-sided 95% confidence interval) will be computed. Additionally, two-sided 95% confidence interval for the incidence of success in IGA in each treatment group will also be calculated using Clopper-Pearson method.

The SAS code to compare the incidence of success in IGA by the Cochran-Mantel-Haenszel test and to calculate the difference in incidence of success in IGA and its two-sided 95% confidence interval is shown below.

```
proc freq ;
  tables BaselineIGA*Treatment*Response/riskdiff(common) cmh ;
run;
```

9.1.1 Sensitivity Analysis

The analyses described in Section 9.1 will be applied to the 3 assessments defined in "Section 6.3.1 Response in Investigator's Global Assessment , 2) Sensitivity Analysis."

9.2 Secondary Endpoints

9.2.1 Incidence of Success in IGA at Week 1 and Week 8

Incidence of success in IGA at Week 1 and Week 8 (as well as Week 2 and Week 6) will be analyzed in the same manner as described in Section 9.1.

The change in incidence of success in IGA (the incidence of success in IGA in the primary analysis and the incidence of success in IGA defining responders as subjects with an improvement in IGA to 0 [clear] or 1 [almost clear]) will be plotted by timepoint for each treatment group.

9.2.2 Change From Baseline in IGA at Week 1, Week 4, and Week 8

Based on the OC data set, the change from baseline in IGA (at Week 1, Week 2, Week 4, Week 6, and Week 8; if the timing of discontinuation falls within the allowable window of a timepoint, the data at discontinuation will be included as the data for the timepoint) will be analyzed using the mixed-model repeated measures (MMRM) analysis with treatment (0.3% or 1% OPA-15406 groups, and vehicle group), timepoint, and interaction between treatment and timepoint as factors and baseline IGA as a covariate.
An unstructured covariance matrix will be used to model the within-subject errors and Kenward-Roger method will be used to calculate the standard error of fixed-effects and the degree of freedom. If the MMRM procedure fails to converge under unstructured covariance structure, the following structure will be used in the order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, 3) heterogeneous compound symmetry, and the first (co)variance structure converging to the best fit will be used.

The least square mean of each treatment group will be calculated by timepoint. The difference in the least square mean between the vehicle group and each OPA-15406 group, and the two-sided 95% confidence interval and p-value will also be calculated at Week 1, Week 4, and Week 8 (as well as at Week 2 and Week 6). The least square mean and the standard error will be plotted by timepoint for each treatment group.

The SAS code to conduct the MMRM analysis is shown below.

```
proc mixed method = reml ;
    class Treatment Visit Subject ;
    model Change = Treatment Visit Treatment*Visit Baseline/s ddfm = kr ;
    repeated Visit/type = un sub = Subject ;
    lsmeans Treatment*Visit/pdiff cl alpha = 0.05 ;
run;
```

“Baseline” represents the IGA at baseline.

The SAS code to use when the MMRM procedure fails to converge under the unstructured covariance structure is shown below. (Designate *type = TOEPH for* heterogeneous toeplitz, type = ARH(1) for heterogeneous autoregressive of order 1, and type = CSH for heterogeneous compound symmetry).

```
proc mixed method = reml empirical ;
    class Treatment Visit Subject ;
    model Change = Treatment Visit Treatment*Visit Baseline/s ;
    repeated Visit/type = TOEPH sub = Subject ;
    lsmeans Treatment*Visit/pdiff cl alpha = 0.05 ;
run;
```

Based on the OC and LOCF data sets, analysis of covariance (ANCOVA) model with treatment (0.3% or 1% OPA-15406 group, and vehicle group) as a factor and baseline IGA as a covariate will be applied to the change from baseline up to each timepoint. The least square mean of each treatment group will be calculated by timepoint. The difference in the least square mean between the vehicle group and each OPA-15406 group, and the two-sided 95% confidence interval and p-value will also be calculated at Week 1, Week 4, and Week 8 (as well as at Week 2 and Week 6). Based on the OC and LOCF data sets, measured values and changes from baseline in IGA at Week 1, Week 4, and Week 8 (as well as at Week 2 and Week 6) will be summarized by treatment group using descriptive statistics.

The mean with standard error of measured values (in the OC and LOCF data sets) will be plotted by timepoint for each group.

Shift tables will be created for the change from baseline in IGA (−3, −2, −1, ±0, +1, +2) at Week 1, Week 4, and Week 8.

9.2.3 Changes From Baseline in Overall EASI Score and EASI Symptom Scores at Week 1, Week 4, and Week 8

Based on the OC data set, the change from baseline in EASI score (at Week 1, Week 2, Week 4, Week 6, and Week 8; If the timing of discontinuation falls within the allowable window of a timepoint, the data at discontinuation will be included as the data for the timepoint) will be analyzed using the MMRM analysis with treatment (0.3% or 1% OPA-15406 group, and vehicle group), timepoint, and interaction between treatment and

timepoint as factors and baseline EASI score as a covariate. An unstructured covariance matrix will be used to model the within-subject errors and Kenward-Roger method will be used to calculate the standard error of fixed-effects and the degree of freedom. If the MMRM procedure fails to converge under unstructured covariance structure, the following structure will be used in the order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, 3) heterogeneous compound symmetry, and the first (co)variance structure converging to the best fit will be used.

The least square mean of each treatment group will be calculated by timepoint. For overall EASI score, the least square mean and the standard error will be plotted by timepoint for each treatment group. The difference in the least square mean between the vehicle group and each OPA-15406 group, and the two-sided 95% confidence interval and p-value will be calculated at Week 1, Week 4, and Week 8 (as well as at Week 2 and Week 6). Based on the OC and LOCF data sets, ANCOVA model with treatment (0.3% or 1% OPA-15406 group, and vehicle group) as a factor and baseline EASI score as a covariate will be applied to the change from baseline up to each timepoint. The least square mean in each treatment group will be calculated by timepoint. The difference in the least square mean between the vehicle group and each OPA-15406 group, and the two-sided 95% confidence interval and p-value will be calculated at Week 1, Week 4, and Week 8 (as well as at Week 2 and Week 6). Based on the OC and LOCF data sets, measured values and changes from baseline in IGA at Week 1, Week 4, and Week 8 (as well as at Week 2 and Week 6) will be summarized by treatment group using descriptive statistics. For the overall EASI score, the mean with standard error of measured values (in the OC and LOCF data sets) will be plotted by timepoint for each treatment group.

EASI scores for body regions (face, neck, and head, upper limbs, trunk, and lower limbs) will be analyzed in the same manner as the overall EASI score.

9.2.4 Change From Baseline in Visual Analogue Scale for Pruritus at Week 1, Week 4, and Week 8

The change from baseline in visual analogue scale (VAS) for pruritus will be analyzed in the same manner as that in the overall EASI score or each EASI symptom score.

9.2.5 Change From Baseline in VRS for Pruritus up to Day 7

The change from baseline in VRS for pruritus up to Day 7 will be analyzed in the same manner as that in overall EASI score or each EASI symptom score. Data will be collected

at baseline, 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). The same analysis will be performed by the time zone of assessment (morning or evening). Morning or evening will be determined based on the time label entered in the case report form (CRF), not using the timepoints defined in Table 6.4-2, except the baseline, which is irrespective of the time zone of assessment. Data will be collected at baseline, and the timepoints specified above on Day 1 to Day 7.

9.2.6 Change From Baseline in Dermatology Life Quality Index Score at Week 1, Week 4, and Week 8

The change from baseline in Dermatology Life Quality Index (DLQI) score will be analyzed in the same manner as that in the overall EASI score or each EASI symptom score. The DLQI scores will be classified into the following categories and a shift table at baseline, Week 1, Week 4, and Week 8 will be created.

DLQI score categories: 0 to 1, 2 to 5, 6 to 10, 11 to 20, and 21 to 30

9.2.7 Change From Baseline in Patient-Oriented Eczema Measure Score at Week 1, Week 4, and Week 8

The change from baseline in Patient-Oriented Eczema Measure (POEM) score will be analyzed in the same manner as that in the overall EASI score or each EASI symptom score.

9.2.8 Change From Baseline in Overall Percentage Affected BSA at Week 1, Week 4, and Week 8

The change from baseline in overall percentage affected BSA will be analyzed in the same manner as that in the overall EASI score or each EASI symptom score.

9.2.9 Percent Changes From Baseline in Overall EASI Score, EASI Symptom Scores, VAS for Pruritus, DLQI, and POEM Scores at Week 1, Week 4, and Week 8

The percent changes from baseline in overall EASI score, EASI symptom scores, EASI scores for body regions, VAS for pruritus, DLQI score, and POEM score will be

analyzed at Week 1, Week 4, and Week 8 (as well as Week 2 and Week 6), in the same manner as the changes from baseline in the respective scores.

9.2.10 Time to Response in IGA

For the time to response in IGA (days to the first response in IGA in each subject), a cumulative response rate will be computed by each treatment group using the Kaplan-Meier method and plotted. At each timepoint, the number of subjects (at risk), the p-value of the log-rank test comparing the vehicle group and each OPA-15406 group, and the time until one half of the subjects have achieved a response (medial survival time [MST]) will be provided. Subjects with an IGA of 0 (clear) or 1 (almost clear) with an improvement by at least 2 grades from the baseline are defined as responders. The starting point is the baseline. Subjects who have failed to achieve a response will be treated as censored on the day of the final IGA assessment.

9.2.11 Time to Response in VRS

The time to response in VRS (time to the first response in VRS in each subject) will be analyzed in the same manner as the time to response in IGA. Subjects with a VRS score of 0 (none) or 1 (mild) with an improvement by at least 1 grade from the baseline are defined as responders. The starting point is baseline. Subjects who have failed to achieve a response will be treated as censored on the day of the final VRS assessment.

9.3 Other Efficacy Endpoints

Not applicable.

9.4 Adjustments for Covariates

In the analysis of the incidence of success in IGA, the primary analysis, the Cochran-Mantel-Haenszel test stratified by baseline IGA (mild or moderate) will be conducted.

9.5 Subgroup Analysis

Incidence of success in IGA will also be analyzed in the following subgroups in the same manner as described in Section 9.1.

Age: <18 or ≥18 years old

Gender: Male or female

Baseline IGA score: 2 (mild) or 3 (moderate)

10 Safety Analysis

The following safety endpoints will be analyzed in the safety set (SS).

10.1 Exposure to the IMP (Number of Subjects, Duration, and Doses)

Treatment compliance with the amount of administration and the number of administrations, calculated as described in Section 6.3.2, will be classified into the following categories, and the number and percentage of subjects will be provided for the overall population and by treatment group. The treatment compliance from baseline to Week 4 or Week 8 will be provided. The number and percentage of subjects who received IMP administration during each week (Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, and every week thereafter, if necessary; Any Exposure) will be provided.

Categories of treatment compliance with the amount of administration and the number of administrations: <50%, ≥50% to <60%, ≥60% to <70%, ≥70% to <80%, ≥80% to <90%, ≥90% to <100%, ≥100% to <110%, ≥110% to <120%, ≥120%

10.2 Adverse Events

Data will be summarized for the overall population and by age group (<18 or ≥18). All AEs will be coded using the MedDRA/J SOC and PT.

The number and percentage of subjects experiencing the following treatment-emergent AEs (TEAEs) will be provided for the overall population and by treatment group. Skin and subcutaneous tissue disorders will also be summarized by the grade in the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 Japanese JCOG edition.

1. TEAEs
2. TEAEs resulting in death

3. Serious TEAEs
4. TEAEs leading to discontinuation of IMP administration
5. TEAEs by severity
6. TEAEs by CTCAE grade (only skin and subcutaneous tissue disorders)
7. TEAEs at treatment areas

For TEAEs and non-serious TEAEs reported in at least 5% of subjects in any treatment group, the number and percentage of subjects will be provided for the overall population and by treatment group.

10.3 Potentially Drug-related TEAEs

Potentially drug-related TEAEs (AEs for which a causal relationship with the IMP cannot be ruled out) will be summarized in the same manner as AEs. Serious potentially drug-related TEAEs will also be summarized.

10.4 Clinical Laboratory Tests

For laboratory parameters (except qualitative urinalysis), measured values and changes from baseline at each timepoint will be summarized for the overall population and by treatment group using descriptive statistics. Shift tables (except qualitative urinalysis) will be created for predose and postdose values classified into normal, high, or low based on the reference range by treatment group. For qualitative urinalysis, shift tables will be created for predose and postdose values by each parameter. The number and percentage of potential Hy's Law Cases will be provided for the overall population and by treatment group. A listing of the potential Hy's Law Cases will be provided. Potential Hy's Law Cases will be defined as follows:

> Potential Hy's Law Cases are defined as subjects with AST or ALT ≥ 3 times the upper normal limit or whose levels increase ≥ 3 times the initial screening value, and with an increase in total bilirubin level ≥ 2 times the upper normal limit or initial screening value.

10.5 Vital Signs (Including Body Weight)

Measured values and changes from baseline in body weight, body temperature, blood pressure (systolic/diastolic), and pulse rate at each timepoint will be summarized for the

overall population and by treatment group using descriptive statistics. For body temperature, blood pressure (systolic/diastolic), and pulse rate, the number and percentage of subjects with potentially clinically significant vital sign abnormalities (Table 16.1-1) will be computed for the overall population and by treatment group. A listing of subjects with potentially clinically significant abnormalities will be provided.

10.6 Electrocardiogram (12-Lead ECG)

Measured values and changes from baseline in heart rate, PR, QRS, QT, QTc (QT interval as correlated by Bazett's formula [QTcB] and QT interval as correlated by Fridericia's formula [QTcF]), and RR intervals at each timepoint will be summarized for the overall population and by treatment group using descriptive statistics. Criteria for potentially clinically significant ECG abnormalities in heart rate, PR, QRS, QT, QTcB, and QTcF intervals will be set (Table 16.1-2), and the number and percentage of subjects who meet the criteria will be provided for the overall population and by treatment group.

11 Pharmacokinetic Analyses

11.1 Pharmacokinetics Analysis Set

The pharmacokinetic analysis set consists of all subjects who have received the IMP at least once and have at least one evaluable plasma drug concentration measured.

11.2 Pharmacokinetic Endpoints

- Plasma trough concentration of OPA-15406 (predose at Week 1, Week 4, and Week 8): All subjects
- Plasma concentration of OPA-15406 (predose, and 2, 4, and 8 hours after IMP administration on Day 1 and Week 4): PK parameter assessment group (that is planned to consist of 6 subjects per group)
- Pharmacokinetic parameters of OPA-15406: C_{max}, C_{max}/Dose, t_{max}, AUC_{8h}, and AUC_{8h}/Dose on Day 1 and Week 4
- Accumulation of OPA-15406: Ratios of the C_{max}, C_{max}/Dose, AUC_{8h}, and AUC_{8h}/Dose at Week 4 to those on Day 1 [$R_{4w,ac}(AUC_{8h})$, $R_{4w,ac}(AUC_{8h}/Dose)$, $R_{4w,ac}(C_{max})$, and $R_{4w,ac}(C_{max}/Dose)$]

11.3 Method of Calculation of Pharmacokinetic Parameters and Endpoints

1) Pharmacokinetic parameters will be determined by subject using the non-compartment analysis. In subjects whose plasma concentration is below the lower limit of quantification at all the sampling points, the C_{max} and AUC_{8h} will be treated as zero (ng/mL or ng·h/mL) and the t_{max} not calculable.
2) Plasma concentration below the lower limit of quantification will be treated as zero (ng/mL) for the calculation of pharmacokinetic parameters and descriptive statistics.
3) Plasma trough concentrations will be handled as follows:

- If the time of the blood sampling was within 6 hours from the last IMP administration, the sampling point will be excluded from the analysis.
- If the treatment area (%) was changed (including non-compliance of IMP) within 3 days before the sampling point, the sampling point will be excluded from the analysis.

4) The timepoint of the blood sampling for the pharmacokinetic endpoint at withdrawal will be handled as follows: If the blood sampling at withdrawal meets neither of the exclusion criteria in (3) and falls within the allowable window shown below, the sampling point will be included in the analyses. If the sampling point at withdrawal coincides with any pharmacokinetic timepoint, the blood sampling at withdrawal will not be included in the analyses.

Timepoint	Study Day	Allowable Window (Day)		
Baseline	1		-	1
Week 1	8	4	-	22
Week 4	29	23	-	50
Week 8	57	51	-	71

5) In AUC_{8h}/Dose and C_{max}/Dose, Dose will be calculated as follows:
Dose (mg) = [Amount of administration (g) for 1% of BSA per dose just before the assessment point] × [treatment area (%)] × [formulation strength (0.3% or 1%)] × 1000

6) $R_{4w,ac}(AUC_{8h})$, $R_{4w,ac}(AUC_{8h}/Dose)$, $R_{4w,ac}(C_{max})$, and $R_{4w,ac}(C_{max}/Dose)$ will be determined by dividing the AUC_{8h}, AUC_{8h}/Dose , C_{max}, and C_{max}/Dose values at Week 4 by the AUC_{8h}, AUC_{8h}/Dose, C_{max}, and C_{max}/Dose values on Day 1, respectively.

11.4 Method of Display

1) When plotting the plasma drug concentration-time profile, arithmetic means and standard deviations will be used.

11.5 Statistical Analysis Methods

1) Descriptive statistics of the plasma trough concentrations and dose(mg)-normalized plasma trough concentrations will be calculated by treatment group and pharmacokinetic timepoint.
2) Descriptive statistics of the total treatment area (%) will be calculated by treatment group and pharmacokinetic timepoint.
3) Among the subjects included in PK parameter assessment group, descriptive statistics of the plasma concentrations and pharmacokinetic parameters of OPA-15406 will be calculated by treatment group and pharmacokinetic timepoint.
4) In 1), 2), or 3) above, when the number of analyzed subjects is zero (0), only the number of subjects will be calculated; when only one (1) subject is analyzed, only the number of subjects, arithmetic mean, and geometric mean will be calculated; and when two (2) subjects are analyzed, only the number of subjects, arithmetic mean, geometric mean, and maximum and minimum values will be calculated.

11.6 Handling of Values

- Values will be rounded off the final step of calculation. Descriptive statistics will be calculated as individual values not rounded off.
- Pharmacokinetic parameters a value of "n + 1" figures will be rounded off to obtain a value of "n" figures shown below:

AUC_{8h}	3 significant figures
AUC_{8h}/Dose	3 significant figures
C_{max}	3 significant figures
C_{max}/Dose	3 significant figures
t_{max}	2 decimal places
$R_{4w,ac}(AUC_{8h})$, $R_{4w,ac}(C_{max})$	3 significant figures
$R_{4w,ac}(AUC_{8h}/Dose)$, $R_{4w,ac}(C_{max}/Dose)$	3 significant figures

- Among descriptive statistics, the number of subjects will be displayed in integers, and minimum and maximum will be displayed as it is in the same number of digits (n-digit) as that of an individual value of the target data. For arithmetic mean, geometric mean, median, and standard deviation values, a value of "n + 1" figures will be rounded off to obtain a value of "n" figures so that the number of digits will be the same number of digits (n-digit) as that of an individual value of the target data. For coefficient of variation, 2 decimal places will be rounded to obtain 1 decimal place.

12 Rationale for Target Number of Subjects

12.1 Target Number of Subjects

180 subjects

12.2 Rationale for the Number of Subjects

In the phase 2 trial outside Japan (271-12-205), the primary variable of incidence of success in IGA was 20.93% in the 1% OPA-15406 group and 2.70% in the vehicle group, respectively. In the present trial, with the assumption that the difference in incidence of success in IGA between the 1% OPA-15406 group and the vehicle 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.

13 Changes From Analysis Planned in the Protocol

13.1 Changes From the Efficacy Analyses Planned in the Protocol

- The factors/covariates included in the MMRM or ANCOVA model were described consistently. A categorical variable included in the model was described as a factor, and a continuous variable as a covariate.

  Rationale for change: To further clarify the analytical methods
- The logistic regression with incidence of success in IGA as an outcome variable will not be conducted.

  Rationale for change: In the primary analysis, the Cochran-Mantel-Haenszel test stratified by baseline IGA will be conducted. In addition, IGA data will be evaluated by sensitivity analysis based on the 3 assessments of incidence of success in IGA defined in "Section 6.3.1 Response in Investigator's Global Assessment , 2) Sensitivity Analysis," as well as the summarization of IGA scores by timepoint using MMRM and the analysis of time to response in IGA. Thus, it was considered that IGA data can be adequately evaluated by these analyses.
- The frequency distribution of incidence of success in IGA by trial site will not be provided.

  Rationale for change: Because many sites will participate in the trial and the number of subjects in each group will be limited.

13.2 Changes From the Pharmacokinetic Analyses Planned in the Protocol

The following pharmacokinetic endpoints were added.

- Pharmacokinetic parameters of OPA-15406: C_{max}/Dose and AUC_{8h}/Dose on Day 1 and Week 4
- Accumulation of OPA-15406: Ratios of the C_{max}/Dose and AUC_{8h}/Dose at Week 4 to those on Day 1 [$R_{4w,ac}(AUC_{8h}/Dose)$, $R_{4w,ac}(C_{max}/Dose)$]

  Rationale for change: The dose (mg) differs among subjects, dose-normalized parameters were added.
- The descriptive statistics of the plasma trough concentrations of OPA-15406 will not be calculated by affected BSA at baseline. The plasma trough concentrations of OPA-15406 will be normalized by dose (mg), not by affected BSA.

  Rationale for change: Calculation of dose-normalized plasma trough concentration was considered adequate, the concentrations will not be computed by or normalized by affected BSA.
- The descriptive statistics for age, treatment area at baseline, and amount of administration will not be calculated by the affected BSA.

  Rationale for change: These were considered not necessary for interpretation of the data.
- The descriptive statistics of total treatment area (%) will be calculated by treatment group and pharmacokinetic timepoint.

  Rationale for change: These were considered necessary for interpretation of the data.

14 References

Not applicable.

15 Revision History

Not applicable.

Table 15-1 Revision History

Version Number	Date of Revision	Section	Original Description	Revised Description	Reason for Revision
–	–	–	–	–	–

16 Appendix

16.1 Criteria for Potentially Clinically Significant

Table 16.1-1 Criteria for Potentially Clinically Significant Vital Sign Abnormalities

TEST	CRITERIA 1	CRITERIA 2
DIASTOLIC BLOOD PRESSURE(MMHG)	DIASTOLIC BLOOD PRESSURE (mmHg) < 50 AND DECREASE >= 15	DIASTOLIC BLOOD PRESSURE (mmHg) > 105 AND INCREASE >= 15
HEART RATE (BEATS/MIN)	HEART RATE (BPM) < 50 AND DECREASE >= 15	HEART RATE (BPM) > 120 AND INCREASE >= 15
SYSTOLIC BLOOD PRESSURE (MMHG)	SYSTOLIC BLOOD PRESSURE (mmHg) < 90 AND DECREASE >= 20	SYSTOLIC BLOOD PRESSURE (mmHg) > 180 AND INCREASE >= 20
TEMPERATURE (°C)	-	TEMPERATURE (°C) >= 37.8 AND INCREASE >= 1.1°C
WEIGHT (KG)	WEIGHT (kg) DECREASE >= 7%	WEIGHT (kg) INCREASE >= 7%

Table 16.1-2 Criteria for Potentially Clinically Significant ECG Abnormalities

CLASSIFICATION	CATEGORY	CRITERIA
VENT RATE OUTLIERS	NOTABLE INCREASES	25% INCREASE FROM BASELINE AND VENTRICULAR RATE > 100 BPM
VENT RATE OUTLIERS	NOTABLE DECREASES	25% DECREASE FROM BASELINE AND VENTRICULAR RATE < 50 BPM
PR OUTLIERS	NOTABLE CHANGES	>= 25% CHANGE FROM BASELINE WHEN PR > 200 MSEC
QRS OUTLIERS	NOTABLE CHANGES	>= 25% CHANGE FROM BASELINE WHEN QRS > 100 MSEC
QT	NEW ONSET (>= 450 MSEC)	NEW ONSET (>=450 MSEC) IN QT MEANS A SUBJECT WHO ATTAINS A VALUE >=450 MSEC DURING TREATMENT PERIOD BUT NOT AT EACH BASELINE
QTcB	NEW ONSET (>= 450 MSEC) IN MALE OR (>= 470 MSEC) IN FEMALE	NEW ONSET (>=450 MSEC IN MALE OR >= 470 MSEC IN FEMALE) IN QTCB MEANS A SUBJECT WHO ATTAINS A VALUE >=450 OR >=470 MSEC DURING TREATMENT PERIOD BUT NOT AT EACH BASELINE
QTcB	NEW ONSET (>= 450 MSEC) AND >= 10% INCREASE	NEW ONSET (>=450 MSEC) AND >= 10% INCREASE IN QTCB MEANS A SUBJECT WHO ATTAINS A VALUE >= 450 MSEC AND >= 10% INCREASE DURING TREATMENT PERIOD BUT NOT AT EACH BASELINE
QTcB	INCREASE 30 - 60 MSEC	INCREASE IN CHANGE FROM BASELINE VALUE >= 30 AND <= 60 MSEC
QTcB	INCREASE > 60 MSEC	INCREASE IN CHANGE FROM BASELINE VALUE > 60 MSEC
QTcF	NEW ONSET (>= 450 MSEC) IN MALE OR (>= 470	NEW ONSET (>=450 MSEC IN MALE OR >= 470 MSEC IN FEMALE) IN QTCB MEANS A SUBJECT WHO ATTAINS A VALUE >=450 OR >=470 MSEC

Table 16.1-2 Criteria for Potentially Clinically Significant ECG Abnormalities		
CLASSIFICATION	**CATEGORY**	**CRITERIA**
	MSEC) IN FEMALE	DURING TREATMENT PERIOD BUT NOT AT EACH BASELINE
QTcF	NEW ONSET (>= 450 MSEC) AND >= 10% INCREASE	NEW ONSET (>=450 MSEC) AND >= 10% INCREASE IN QTCB MEANS A SUBJECT WHO ATTAINS A VALUE >= 450 MSEC AND >= 10% INCREASE DURING TREATMENT PERIOD BUT NOT AT EACH BASELINE
QTcF	INCREASE 30 - 60 MSEC	INCREASE IN CHANGE FROM BASELINE VALUE >= 30 AND <= 60 MSEC
QTcF	INCREASE > 60 MSEC	INCREASE IN CHANGE FROM BASELINE VALUE > 60 MSEC

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CT-8.4.1.3 Incidence of Deaths due to Treatment-emergent Adverse Events by System Organ Class

CT-8.4.2.1 Incidence of Deaths due to Treatment-emergent Adverse Events by System Organ Class and Preferred Term

CT-8.4.2.2 Incidence of Deaths due to Treatment-emergent Adverse Events by System Organ Class and Preferred Term

CT-8.4.2.3 Incidence of Deaths due to Treatment-emergent Adverse Events by System Organ Class and Preferred Term

CT-8.5.1.1 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class

CT-8.5.1.2 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class

CT-8.5.1.3 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class

CT-8.5.2.1 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term

CT-8.5.2.2 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term

CT-8.5.2.3 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term

CT-8.5.3.1 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity

CT-8.5.3.2 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity

CT-8.5.3.3 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity

CT-8.5.4.1 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and CTCAE Grade

CT-8.5.4.2 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and CTCAE Grade

CT-8.5.4.3 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and CTCAE Grade

CT-8.6.1.1 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class

CT-8.6.1.2 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class

CT-8.6.1.3 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class

CT-8.6.2.1 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class and Preferred Term

CT-8.6.2.2 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class and Preferred Term

CT-8.6.2.3 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class and Preferred Term

CT-8.6.3.1 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class and Preferred Term

CT-8.6.3.2 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class and Preferred Term

CT-8.6.3.3 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class and Preferred Term

CT-8.6.4.1 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class and Preferred Term

CT-8.6.4.2 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class and Preferred Term

CT-8.6.4.3 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class and Preferred Term

CT-8.7.1.1 Incidence of Treatment-emergent Adverse Events Greater Than or Equal to 5% in Any Group by System Organ Class and Preferred Term

CT-8.7.1.2 Incidence of Treatment-emergent Adverse Events Greater Than or Equal to 5% in Any Group by System Organ Class and Preferred Term

CT-8.7.1.3 Incidence of Treatment-emergent Adverse Events Greater Than or Equal to 5% in Any Group by System Organ Class and Preferred Term

CT-8.8.1.1 Incidence of Non-Serious Treatment-emergent Adverse Events Greater Than or Equal to 5% in Any Group by System Organ Class and Preferred Term

CT-8.8.1.2 Incidence of Non-Serious Treatment-emergent Adverse Events Greater Than or Equal to 5% in Any Group by System Organ Class and Preferred Term

CT-8.8.1.3 Incidence of Non-Serious Treatment-emergent Adverse Events Greater Than or Equal to 5% in Any Group by System Organ Class and Preferred Term

CT-8.9.1.1 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term According to Application Site

CT-8.9.1.2 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term According to Application Site

CT-8.9.1.3 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term According to Application Site

CT-8.10.1.1 Incidence of Potentially Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term According to Application Site

CT-8.10.1.2 Incidence of Potentially Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term According to Application Site

CT-8.10.1.3 Incidence of Potentially Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term According to Application Site

CT-9.1 Listing of Deaths

CT-9.2 Listing of Serious Adverse Events

CT-9.3 Listing of Study Drug Discontinuations Due to Adverse Events

CT-9.4 Incidence of Potential Hy's Law Cases

CT-9.5 Listing of Potential Hy's Law Cases - by Subject

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CT-10.1.2 Mean Change From Baseline in Laboratory Test Values: Hematology

CT-10.2.1 Shift Tables of Clinical Laboratory Test Results: Serum Chemistry

CT-10.2.2 Shift Tables of Clinical Laboratory Test Results: Hematology

CT-10.2.3 Shift Tables of Clinical Laboratory Test Results: Urinalysis

CT-11.1 Mean Change From Baseline in Vital Sign Parameters

CT-11.2 Listing of Vital Signs Abnormalities

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CT-12.3 Listing of Categorical Changes in ECG Evaluations

CT-12.4 Criteria for Categorical Changes in ECG Evaluations

CF-1.1 Incidence of Responder Rate for Overall IGA Score by Visit

CF-1.2 Incidence of Responder Rate for Overall IGA Score by Visit - Revised Responder Definition

CF-2.1.1 Least Square Means of Change from Baseline in Overall IGA Score by Visit - MMRM

CF-2.1.2 Means of Overall IGA Score by Visit - OC

CF-2.1.3 Means of Overall IGA Score by Visit - LOCF

CF-2.2.1 Least Square Means of Change from Baseline in Overall EASI Score by Visit - MMRM

CF-2.2.2 Means of Overall EASI Score by Visit - OC

CF-2.2.3 Means of Overall EASI Score by Visit - LOCF

CF-3.1 Kaplan-Meier Plot of Time to Improvement in Overall IGA Score

CF-3.2 Kaplan-Meier Plot of Time to Improvement in VRS for Pruritus Score

PKT-1.1 Individual and Summary of OPA-15406 Plasma Concentrations Following Topical Administration of 0.3% OPA-15406 Ointment to Adult Subjects With Atopic Dermatitis (Group for Which PK Parameters are Evaluated)

PKT-1.2 Individual and Summary of OPA-15406 Plasma Concentrations Following Topical Administration of 1% OPA-15406 Ointment to Adult Subjects With Atopic Dermatitis (Group for Which PK Parameters are Evaluated)

PKT-2.1 Individual and Summary of OPA-15406 Plasma Trough Concentrations Following Topical Administration of 0.3% OPA-15406 Ointment to Adult Subjects With Atopic Dermatitis

PKT-2.2 Individual and Summary of OPA-15406 Plasma Trough Concentrations Following Topical Administration of 1% OPA-15406 Ointment to Adult Subjects With Atopic Dermatitis

PKT-3 Individual and Summary of OPA-15406 Plasma Pharmacokinetic Parameters Following Topical Administration of OPA-15406 Ointment to Adult Subjects With Atopic Dermatitis

PKT-4 Individual and Summary of OPA-15406 Accumulation Parameters Following Topical Administration of OPA-15406 Ointment to Adult Subjects With Atopic Dermatitis

PKT-5.1 Individual and Summary of Normalized OPA-15406 Plasma Trough Concentrations by Dose Derived From % BSA Treated Following Topical Administration of 0.3% OPA-15406 Ointment to Adult Subjects With Atopic Dermatitis

PKT-5.2 Individual and Summary of Normalized OPA-15406 Plasma Trough Concentrations by Dose Derived From % BSA Treated Following Topical Administration of 1% OPA-15406 Ointment to Adult Subjects With Atopic Dermatitis

PKF-1.1 Mean OPA-15406 Plasma Trough Concentrations Following Topical Administration of OPA-15406 Ointment to Adult Subject With Atopic Dermatitis

PKF-1.2 Mean Normalized OPA-15406 Plasma Trough Concentrations by Dose Derived From % BSA Treated Following Topical Administration of OPA-15406 Ointment to Adult Subjects With Atopic Dermatitis

PKF-2 Mean OPA-15406 Plasma Concentrations Following Topical Administration of OPA-15406 Ointment to Adult Subject With Atopic Dermatitis (Group for Which PK Parameters are Evaluated)

PKF-3 Individual OPA-15406 Plasma Concentrations Following Topical Administration of OPA-15406 Ointment to Adult Subject With Atopic Dermatitis (Group for Which PK Parameters are Evaluated)

PDATA-1.1 Inclusion and Exclusion Criteria

PDATA-1.2 Subject Disposition

PDATA-2.1 Medical History

PDATA-2.2 History of Atopic Dermatitis

PDATA-3.1 Concomitant Medications: Medications Taken Prior to Start of Study Therapy

PDATA-3.2 Concomitant Medications: Medications Taken During Study Therapy

PDATA-3.3 Concomitant Medications: Medications Taken After Study Therapy

PDATA-4.1 Exposure to Trial Medication

PDATA-4.2 Listing of Trial Medication by Subject

PDATA-5.1 Physical Examination

PDATA-6 Adverse Events

PDATA-7 Vital Signs

PDATA-8 Electrocardiogram Results

PDATA-9 Blood Sampling for Pharmacokinetics

PDATA-10 Screening Failures

PDATA-11 Protocol Deviations (Major) - CRF

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PDATA-13 Eczema Area and Severity Index

PDATA-14 Visual Analog Scale for Pruritus

PDATA-15 Verbal Rating Scale

PDATA-16 Overall Investigator's Global Assessment of Disease Severity

PDATA-17 Patient-Oriented Eczema Measure

PDATA-18 Affected Body Surface Area

PDATA-19 Treatment Area

PDATA-20 Dermatology Life Quality Index

DREAS-1 Discontinued Subjects and Reasons for Discontinuations

DEMOG-1 Demographic Characteristics

DEMOG-2 Informed Consent

AE-1 Adverse Events

SMED-1 Investigational Medicinal Product Compliance

SMED-2 Actual Exposure to Study Medication

SMED-3 Investigational Medicinal Product Compliance for Number of Administrations

EFF-1 Change from Baseline in IGA Score and Response with Overall IGA Score

EFF-2 Change from Baseline in Total EASI Score

EFF-3 Change from Baseline in EASI Score, Erythema

EFF-4 Change from Baseline in EASI Score, Induration/Papulation

EFF-5 Change from Baseline in EASI Score, Excoriation

EFF-6 Change from Baseline in EASI Score, Lichenification

EFF-7 Change from Baseline in EASI Score, HEAD/NECK

EFF-8 Change from Baseline in EASI Score, UPPER LIMBS

EFF-9 Change from Baseline in EASI Score, TRUNK

EFF-10 Change from Baseline in EASI Score, LOWER LIMBS

EFF-11 Change from Baseline in VAS Score

EFF-12 Change from Baseline in Overall Percentage Affected Body Surface Area

EFF-13 Change from Baseline in POEM Score

EFF-14 Change from Baseline in VRS Score

EFF-15 Change from Baseline in DLQI Score

LAB-1 Laboratory Test Results: Serum Chemistry

LAB-2 Laboratory Test Results: Hematology

LAB-3 Laboratory Test Results: Urinalysis

PDEV-1 Summary of Subjects with Major Protocol Deviations by Type of Deviation

SUBEX-1 Subjects Excluded From Analysis Set