Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product OPA-15406 (difamilast)

Protocol No. 271-102-00016

A Phase 3, Multicenter, Open-labeled, Uncontrolled Trial to Evaluate the Efficacy and Safety of OPA-15406 Ointment in Infants Younger Than 2 Years of Age With Atopic Dermatitis

A Long-term Trial of OPA-15406 in Infants With Atopic Dermatitis (Phase 3 Trial)

STATISTICAL ANALYSIS PLAN

VERSION: 2.0
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Confidential

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
ALT (GPT)	Alanine aminotransferase
AST (GOT)	Aspartate aminotransferase
BSA	Body surface area
CTCAE	Common terminology criteria for adverse events
EASI	Eczema Area and Severity Index
IGA	Investigator's Global Assessment
MedDRA	Medical Dictionary for Regulatory Activities ICH
OC	Observed cases
POEM	Patient-Oriented Eczema Measure
TEAE	Treatment-emergent adverse event

1 Introduction

The purpose of this statistical analysis plan (SAP) is to describe the detailed analysis methods of the planned statistical analyses to be included in the Clinical Study Report (CSR) for Trial 271-102-00016.

2 Trial Objectives

The objectives and endpoints of the trial are shown below.

Table 2-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary objective: To investigate the efficacy of 0.3% OPA-15406 ointment when administered twice daily for 4 weeks in infants younger than 2 years of age with AD	Efficacy endpoint: • Success rate in Investigator's Global Assessment (IGA) (Percentage of subjects with an IGA score of 0 or 1 with improvement by at least 2 grades)
Secondary objectives: This trial will be conducted in infants younger than 2 years of age with AD • To investigate the safety of 0.3% OPA-15406 ointment when administered twice daily for 4 weeks • To investigate the efficacy and safety of 0.3% or 1% OPA-15406 ointment when administered twice daily for 52 weeks • To investigate the pharmacokinetics of 0.3% or 1% OPA-15406 ointment when administered twice daily for 4 weeks	Efficacy endpoints: • Response rate in Eczema Area and Severity Index (EASI) 90 (improvement of ≥90% in EASI), EASI 75 (improvement of ≥75% in EASI) and EASI 50 (improvement of ≥50% in EASI) • Change from baseline in IGA score • Percent change from baseline in the total score of EASI and each clinical sign score • Change from baseline in the total score of Patient-Oriented Eczema Measure (POEM) • Change from baseline in the total affected body surface area (BSA) (%) Safety endpoints: • Adverse events (AEs) • Vital signs, body weight • Clinical laboratory tests Pharmacokinetic endpoint: • Plasma concentration of OPA-15406

3 Trial Design

3.1 Type/Design of Trial

This trial is a phase 3, multicenter, open-label, uncontrolled trial to evaluate the efficacy and safety of OPA-15406 ointment in infants younger than 2 years of age with atopic dermatitis.

1) Screening period

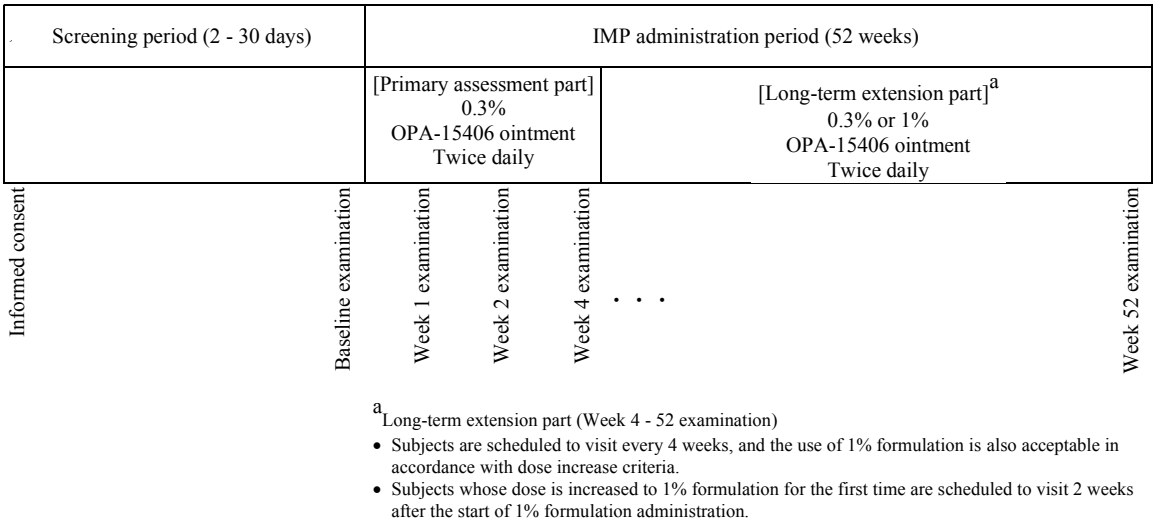
After obtaining informed consent from the subject's legal guardian, the investigator or subinvestigator will perform the screening examination. The screening period is defined as the period between the day of screening examination and the day of baseline examination (2 - 30 days).

2) IMP administration period

The IMP administration period is defined as the period between the day of baseline examination and the end of Week 52 examination (or the end of withdrawal examination). The primary assessment part is defined as the period between the baseline examination and the Week 4 examination, and the long-term extension part is defined as the period between the Week 4 examination and the Week 52 examination. Subjects who meet the inclusion and exclusion criteria at the baseline examination will be prescribed with the IMP. The IMP will be administered to the treatment area from the day of baseline examination twice daily for 52 weeks. If a subject discontinues the IMP administration between the day of baseline examination and the day of Week 52 examination, a withdrawal examination will be performed for that subject.

3) Trial period

The trial period for individual subjects is the period from the day of obtaining the written informed consent from the subject's legal guardian to the day of the Week 52 examination (or withdrawal examination). For subjects who missed the Week 52 examination (or withdrawal examination), the day of discontinuation will be the day when the investigator or subinvestigator determined that the subject was to be withdrawn from the trial. It does not include the follow-up period for AEs.



a Long-term extension part (Week 4 - 52 examination)
- Subjects are scheduled to visit every 4 weeks, and the use of 1% formulation is also acceptable in accordance with dose increase criteria.
- Subjects whose dose is increased to 1% formulation for the first time are scheduled to visit 2 weeks after the start of 1% formulation administration.

Figure 3-1 Trial Design Schematic

3.2 Dosing Methods

3.2.1 Dose, Regimen, and Treatment Period

As the starting dose, 0.3% formulation will be administered twice daily (approximately 12 hours apart between morning and night administrations) for 52 weeks.

Primary Assessment Part (Baseline Through Week 4 Examination)

- The 0.3% formulation will be administered twice daily for 4 weeks.
- Even when the affected area is relieved, IMP administration should be continued there as the treatment area.

Long-term Extension Part (Week 4 Examination through Week 52 Examination)

- If subjects meet the dose increase criteria (see Section 3.2.2.1) at each 4-weekly assessment visit following the Week 4 examination, the 1% formulation will be used.
- When subjects show an improvement in skin symptoms and use of the 1% formulation is considered unnecessary, the dosage can be reduced to the 0.3% formulation. As a general rule, formulation switching should be done after the 4-weekly assessment (the formulation may be switched before the 4-weekly assessment if prompt dose reduction is required due to AEs or for other reasons).
- If all skin symptoms have resolved, IMP administration may be suspended based on the judgment of the physician. If skin symptoms relapse after interruption, IMP administration will be restarted.

The amount of IMP (g) per dose is 10 g/m^2 BSA, which is calculated as follows.

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

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

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

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

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

3.2.2 Dose Modification of the Investigational Medicinal Product

3.2.2.1 Dose Increase

For subjects receiving the 0.3% formulation with an IGA score of 2 or greater, the dose will be increased to the 1% formulation unless a concern about unacceptable tolerability is identified at a 4-weekly assessment (in the long-term extension part) including the Week 4 examination. Even for subjects with an IGA score of less than 2, the dose can be increased if judged necessary by the investigator or subinvestigator. Dose increase will be recorded together with the reason in the source documents and eCRF.

3.2.2.2 Dose Reduction

For subjects receiving the 1% formulation, the dose can be reduced to the 0.3% formulation if judged necessary by the investigator or subinvestigator (eg, improvement in skin symptoms, occurrence of an AE) at a 4-weekly assessment after the Week 4 examination (in the long-term extension part). Dose reduction will be recorded together with the reason in the source documents and eCRF.

3.2.2.3 Interruption (Treatment Interruption)

IMP administration must not be suspended until the Week 4 examination. Interruption will be allowed if judged necessary by the investigator or subinvestigator (eg, resolution of skin symptoms, exacerbation of skin symptoms [which requires rescue medication], occurrence of an AE [excluding exacerbation of skin symptoms]) at a 4-weekly

assessment after the Week 4 examination (in the long-term extension part). Interruption will be recorded together with the reason in the source documents and eCRF. The investigator or subinvestigator should perform the specified examination/assessments during interruption, and decide on the necessity of restarting IMP administration.

3.2.2.4 Restarting IMP Administration After Interruption

Following interruption, restarting IMP administration (exacerbation of skin symptoms, improvement of skin symptoms [in cases where IMP administration was suspended to allow rescue medication], improvement of an AE [excluding exacerbation of skin symptoms]) will be recorded together with the reason in the source documents and eCRF.

3.3 Trial Population

Infants 3 months or older and younger than 2 years of age with AD and an IGA score of 2 or 3.

3.4 Handling of Time Points

The number of days from IMP administration to the endpoint measurement day will be calculated with the start day of IMP administration set as the starting point (Day 1). In determining the assessment time points for analyses, unscheduled data and withdrawal data, as well as scheduled visit data, will be included. However, unscheduled data obtained at 2 weeks after the start of 1% formulation administration and between 4 and 8 weeks after the scheduled visit will be excluded from the determination of assessment time points in analysis. The acceptable windows for time points in the analysis of safety and efficacy endpoints will be as shown in Table 3.4-1. When there are multiple non-missing measurement values in the acceptable window, the last data in the acceptable window will be adopted. Regarding efficacy and safety endpoints, the latest data among all the data obtained after the start of IMP administration will be adopted as the last time (Last Visit).

The data nearest to the start day of IMP administration among predose data including screening data will be adopted as the baseline for analysis.

Table 3.4-1 Acceptable Windows for Time Points in Analysis

Week	Trial Day Interval	
Baseline		1
Week 1	2	10
Week 2	11	21
Week 4	22	42
Week 8	43	70
Week 12	71	98
Week 16	99	126

Table 3.4-1 Acceptable Windows for Time Points in Analysis

Week	Trial Day Interval	
Week 20	127	154
Week 24	155	182
Week 28	183	210
Week 32	211	238
Week 36	239	266
Week 40	267	294
Week 44	295	322
Week 48	323	350
Week 52	351	372

For subjects receiving the 1% formulation, analysis time points with starting point of dose increase to the 1% formulation will also be defined in addition to the above-described time points in analysis. For instance, when the dose is increased to 1% at Week 4, the record corresponding to Week 4 will be defined as that at the time of increase to 1%, and Week 2 After Dose Increase will be defined as the time point specified in the CRF (2 weeks after the start of 1% formulation administration). Week 4 After Dose Increase and later are defined as shown in Table 3.4-2.

Table 3.4-2 Acceptable Windows for Time Points in Analysis Starting From the Time of Dose Increase

Week	Definition of time points
Time of increase to 1%	The time point on the same day as the day that the doctor first directed a dose increase
Week 2 After Dose Increase	2 weeks after the start of 1% formulation administration (the time point specified in the CRF)
Week 4 After Dose Increase	Analysis visits specified in Table 3.4-1 minus Week at increase to 1%
Week 8 After Dose Increase	
Week 12 After Dose Increase	
Week 16 After Dose Increase	
Week 20 After Dose Increase	
Week 24 After Dose Increase	
Week 28 After Dose Increase	
Week 32 After Dose Increase	
Week 36 After Dose Increase	
Week 40 After Dose Increase	
Week 44 After Dose Increase	
Week 48 After Dose Increase	

3.5 Handling of Endpoints

3.5.1 IGA Response

Response (improvement) is defined as an IGA score, which is the primary endpoint, of 0 or 1 with improvement of at least 2 grades from baseline. Subjects without the above improvement will be handled as non-responders. In addition, subjects with missing IGA data will be handled as non-responders.

3.5.2 EASI Response (EASI 75, EASI 90, EASI 50)

Response (improvement) in EASI 75 is defined as a decrease by ≥75% in the percent change from baseline in the total score of EASI. Subjects without the above improvement will be handled as non-responders. Response (improvement) in EASI 90 is defined as a decrease by ≥90% in the percent change from baseline in the total score of EASI. Subjects without the above improvement will be handled as non-responders. Response (improvement) in EASI 50 is defined as a decrease by ≥50% in the percent change from baseline in the total score of EASI. Subjects without the above improvement will be handled as non-responders. In addition, subjects with a missing total score of EASI will be handled as non-responders in EASI 75, EASI 90, and EASI 50.

4 Sample Size

5 Datasets for Analysis

5.1 Efficacy Analysis Set

Consists of all subjects who have received the IMP at least once.

5.2 Safety Analysis Set

Consists of all subjects who have received the IMP at least once.

5.3 Pharmacokinetic Analysis Set

Consists of all subjects who have received the IMP at least once and in whom a plasma drug concentration is determined for at least 1 time point after IMP administration.

5.4 Handling of Missing Data

Missing data are not imputed. For IGA response, EASI 75, EASI 90, and EASI 50, subjects with missing IGA or EASI scores are handled as non-responders.

6 Primary and Secondary Endpoints

6.1 Primary Endpoint (Primary Assessment Part)

- Success rate in IGA (percentage of subjects with an IGA score of 0 or 1 with improvement by at least 2 grades)

6.2 Secondary Endpoints

6.2.1 Efficacy Endpoint

- Response rate in EASI 90 (improvement of ≥90% in EASI), EASI 75 (improvement of ≥75% in EASI) and EASI 50 (improvement of ≥50% in EASI)
- Change from baseline in IGA score
- Percent change from baseline in the total score of EASI and each clinical sign score
- Change from baseline in the total score of POEM
- Change from baseline in the total affected BSA (%)

6.2.2 Safety Endpoints

- AEs
- Vital signs, body weight
- Clinical laboratory tests

6.2.3 Pharmacokinetic Endpoint

- Plasma concentration of OPA-15406

7 Subject Disposition and Demographic and Other Baseline Characteristics

Unless otherwise noted, the summarizations described below will be performed for each of the following treatment groups and for all subjects: subjects receiving only the 0.3% formulation even at 4 weeks postdose and later (hereinafter referred to as the 0.3%

formulation group) and subjects receiving the 1% formulation at least once at 4 weeks postdose or later (hereinafter, the 1% formulation [dose increase] group).

7.1 Subject Disposition

The number of subjects for whom informed consent was obtained, the number of subjects receiving IMP administration, and the frequency distribution of completed or withdrawn subjects (the number and percentage of subjects, the same applies hereinafter) will be shown. The denominator of percentage is defined as subjects receiving IMP administration. For withdrawn subjects, the frequency distribution by withdrawal reason will be shown. The frequency distribution of subjects included in each analysis set will be shown.

7.2 Demographic and Other Baseline Characteristics

In the efficacy analysis set, for age (month), sex, disease duration (month), body weight, height, body mass index (BMI), race, and AD severity, descriptive statistics or a frequency distribution will be shown depending on each characteristic. Descriptive statistics will be shown for age, disease duration, body weight, height, and BMI, and a frequency distribution will be shown for age group (<12 months, ≥12 months), sex, race, ethnicity, study country, and AD severity. By using MedDRA, medical histories/complication names will be coded by system organ class (SOC) and preferred term (PT). Medical histories/complication names will not be summarized but only listed.

In deriving the disease duration, the data will not be imputed when date data is missing. The year and month data will be used for calculation when the day is missing.

When “day, month, and year” are all available: (Administration start day, month, and year - AD onset day, month, and year + 1) / 30

When only “month and year” are available: (Administration start year × 12 + Administration start month) - (AD onset year × 12 + AD onset month) + 1

7.3 Assessment of Baseline Conditions

In the efficacy analysis set, a frequency distribution will be shown for IGA (2 or 3) at baseline, and descriptive statistics will be shown for the total EASI (Eczema Area and Severity Index) score at baseline. Affected area at baseline will be classified into the following categories, and a frequency distribution will be shown.

Categories of affected area: ≥5% and <10%, ≥10% and <20%, ≥20% and <40%, and ≥40%

7.4 Treatment Compliance

In the efficacy analysis set, compliance regarding administration frequency until 52 weeks after baseline will be classified into the following categories, and the number and percentage of subjects will be calculated. In addition, the number and percentage of treated subjects will be calculated by week (Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, and Any Exposure). Compliance regarding administration frequency will be calculated using the following equation. Treatment compliance with IMP (%) = (Actual administration frequency / directed administration frequency of the 0.3% or 1% formulation) × 100

Categories of compliance regarding administration frequency: <50%, ≥50% and <60%, ≥60% and <70%, ≥70% and <80%, ≥80% and <90%, ≥90% and <100%, ≥100% and <110%, ≥110% and <120%, and ≥120%

In addition, frequency distribution will be shown for the reasons for dose increase, dose reduction, and treatment interruption. If there are multiple reasons, the first reason will be counted.

7.5 Prior and Concomitant Medications

In the efficacy analysis set, the number and percentage of subjects receiving drugs will be calculated for drugs administered prior to the start day of IMP administration, drugs administered during the IMP administration period, and drugs administered after the end of IMP administration. Drugs will be coded by using the WHO Drug Dictionary and summarized by using ATC classification level 2 and Preferred names. Concomitant therapies will not be summarized but only listed.

7.6 Protocol Deviations

The number and percentage of subjects with a significant deviation from the protocol will be shown. In addition, the number and percentage of subjects by significant deviation category will be shown for each site.

8 Efficacy Analyses

The following analyses will be performed in the efficacy analysis set. In analyses of the primary endpoint, summarization will be performed for each of the following treatment groups: subjects secondly receiving only the 0.3% formulation even at 4 weeks postdose and later (hereinafter, the 0.3% formulation group) and subjects receiving the 1% formulation at least once at 4 weeks postdose or later (hereinafter, the 1% formulation

[dose increase] group). Unless otherwise noted, regardless of administration status (administration of the 0.3% formulation, administration of the 1% formulation, or treatment interruption), the data of the analysis time points specified in Table 3.4-1 will be summarized.

8.1 Primary Efficacy Endpoint Analysis

Response (improvement) is defined as a postdose IGA score of 0 or 1 with improvement of at least 2 grades, and the primary endpoint is the success rate in IGA at Week 4. In all subjects of the efficacy analysis set, the number of subjects with an IGA response and success rate at 4 weeks after IMP treatment and their two-sided 95% confidence intervals (Clopper-Pearson method) will be calculated. The same analysis will be performed at 1 week and 2 weeks postdose. Subjects with missing IGA data will be handled as non-responders. The success rate at each assessment time point will be graphically shown.

8.2 Key Secondary Efficacy Endpoint Analyses

In the same manner as the primary endpoint analysis in 8.1, the number of subjects with an IGA response and success rate at each assessment time point and their two-sided 95% confidence intervals (Clopper-Pearson method) will be calculated for each treatment group and all subjects.

By using OC data, the number of subjects with an IGA response and success rate at each assessment time point and the last time (Last Visit) and their two-sided 95% confidence intervals (Clopper-Pearson method) will be calculated for each treatment group and all subjects. The success rate at each assessment time point will be graphically shown.

The cumulative number and rate of subjects who improved at least once by each assessment time point with IGA response and their two-sided 95% confidence intervals (Clopper-Pearson method) will be calculated by treatment group and for all subjects. The success rate at each assessment time point will be graphically shown.

EASI 75, EASI 90, and EASI 50 will be analyzed in the same manner as IGA response.

8.3 Secondary Efficacy Endpoint Analysis

Regarding IGA score, total EASI score, EASI score of each symptom and each part, total POEM score, and total affected area (%), the descriptive statistics of actual measurements and changes from baseline at each assessment time point and the last time (Last Visit) will be calculated for each treatment group and all subjects. For the IGA score, total EASI score, EASI score of each symptom and each part, and total POEM score, the descriptive statistics will be calculated for percent change from baseline as well. For

changes in IGA from baseline, the time courses of changes in IGA score from baseline at each timepoint will be plotted with the mean and SD. As for total EASI score, the time courses of changes in total EASI score from baseline at each timepoint will be plotted with the mean and SD.

Regarding IGA score, by using OC data, the shift table at each assessment time point and the last time (Last Visit) from baseline will be shown for each treatment group and all subjects.

8.4 Subgroup Analyses

Regarding IGA response at 4 weeks after IMP administration in 8.1 and IGA response at the last time (Last Visit) in 8.2, the number of subjects with IGA response and success rate, and their two-sided 95% confidence intervals (Clopper-Pearson method) will be shown for each of the following subgroups. EASI 75, EASI 90, and EASI 50 will be analyzed in the same manner. The data at 52 weeks in 8.1 and 52 weeks (OC data) in 8.2 will also be analyzed by age.

Age: <12 months, ≥12 months

Sex: male, female

IGA score at baseline: 2 (mild), 3 (moderate)

Severity of AD: mild, moderate, severe, most severe

Total EASI score at baseline: <15, ≥15

Affected area at baseline: <20%, ≥20%

Presence of the use of anti-inflammatory drugs: present, absent

Presence of the use of topical drugs other than anti-inflammatory drugs: present, absent

By the modal dose: 0.3% OPA-15406 ointment, 1% OPA-15406 ointment

Presence of dose increase set at 4 weeks postdose: no dose increase at 4 weeks postdose, dose increase at 4 weeks postdose

By IGA score at 4 weeks postdose: 0, 1, 2, 3, 4

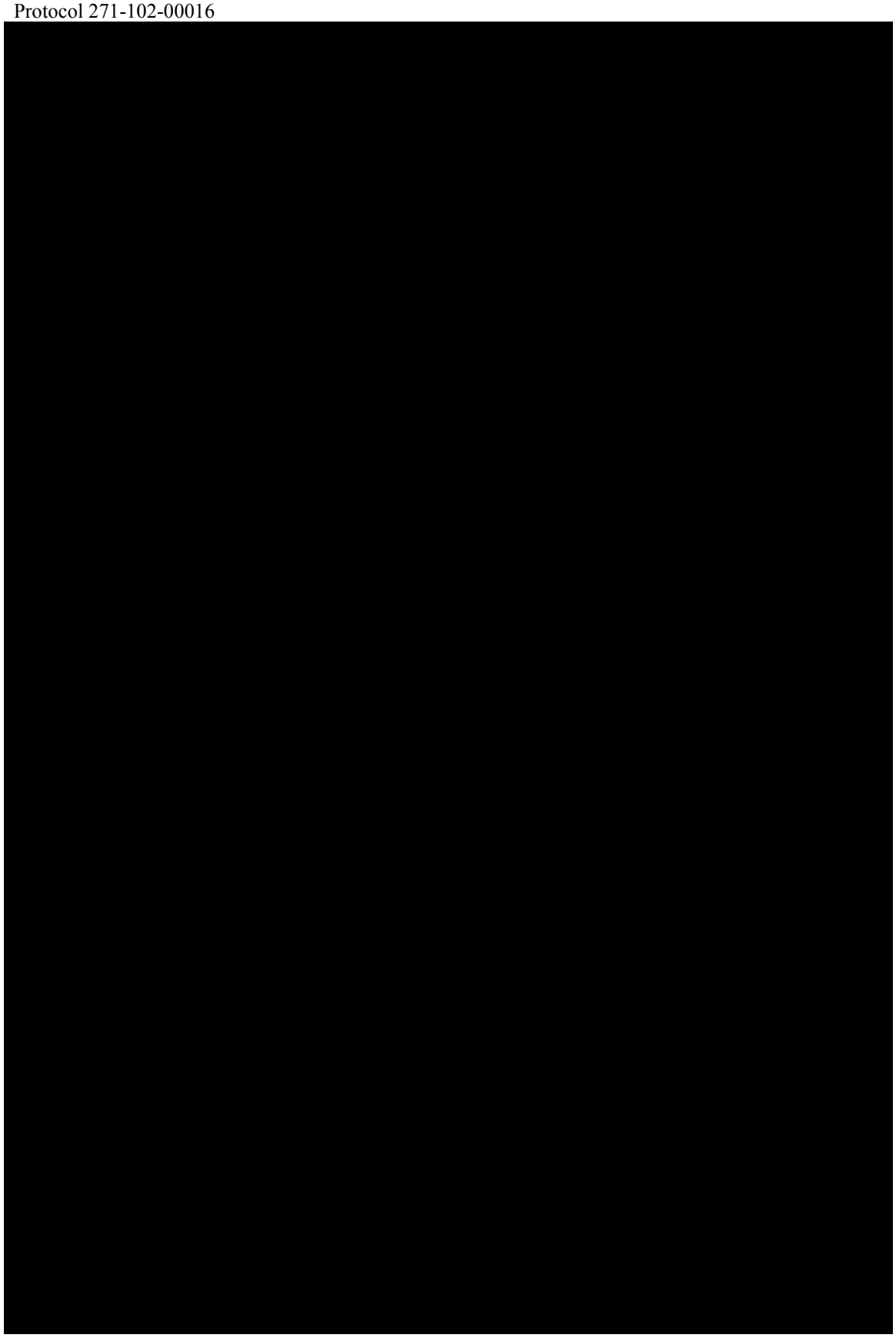
In addition, the modal dose is defined as the most frequently administered concentration during the IMP administration period. However, when frequency is the same between concentrations, the last concentration administered will be adopted as the concentration of the modal dose. Subjects using anti-inflammatory drugs are defined as subjects who used prohibited concomitant topical drugs (steroids, tacrolimus, delgocitinib, guaiazulene, ibuprofen piconol, suprofen, and enoxolone) during the IMP administration

period in the cases of medical requirements such as the worsening of symptoms. In addition, subjects using topical drugs other than anti-inflammatory drugs are defined as subjects who used topical drugs other than prohibited concomitant anti-inflammatory drugs (steroids, tacrolimus, delgocitinib, guaiazulene, ibuprofen piconol, suprofen, and enoxolone) during the IMP administration period.

Furthermore, subjects aged <12 months will be tabulated by the following categories. In the same manner as the age categories described above (<12 and ≥12 months), analysis will be performed at 4 and 52 weeks after IMP administration in 8.1, 52 weeks postdose in 8.2 (OC data), and the last time (Last Visit).

Age: <6 months, ≥6 and <12 months

8.5 Exploratory or Other Analyses



9 Safety Analysis

In the safety analysis set, the following analyses will be performed. Unless otherwise noted, the summarizations described below will be performed for each of the following treatment groups and for all subjects: subjects receiving only the 0.3% formulation even at 4 weeks postdose and later (hereinafter referred to as the 0.3% formulation group) and subjects receiving the 1% formulation at least once at 4 weeks postdose or later (hereinafter, the 1% formulation [dose increase] group).

9.1 Extent of Exposure to Investigational Medicinal Product

Descriptive statistics will be calculated for the number of days of administration (except for treatment interruption), total amount of IMP administration, and amount of administration per dose. The amount of administration is defined as the difference between the total weights of prescribed IMP and returned IMP. In addition, descriptive statistics will also be shown in the same manner for the amount with consideration of IMP concentration (0.3% OPA-15406 and 1% OPA-15406). In calculating the amount of treatment, the weight of the IMP with an unknown weight upon return will be calculated as 0 (zero) at return.

The sum of treatment duration and the descriptive statistics of treatment duration for 0.3% OPA-15406, and the sum of treatment duration and the descriptive statistics of treatment duration for 1% OPA-15406 will be calculated. The same analysis will be performed for age categories (<12 months, ≥12 months). Furthermore, for subjects aged <12 months, the same analysis will be performed by the following categories: <6 months and ≥6 and <12 months.

9.2 Adverse Events

By using MedDRA (Ver 26.1), adverse events will be coded by system organ class (SOC) and preferred term (PT).

Regarding the following treatment-emergent AEs (TEAEs), the number and percentage of subjects with an onset will be calculated. If the same event occurred multiple times in the same subject, the most severe one will be used in analyses by severity, and the one with the earliest onset will be used in analyses by onset time. For skin and subcutaneous tissue disorders, analyses by the grade classification of the Common Terminology Criteria for Adverse Events (CTCAE) will also be performed.

- TEAE
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- TEAEs leading to IMP treatment interruption
- TEAEs leading to IMP dose reduction
- TEAEs by CTCAE Grade (only for skin and subcutaneous tissue disorders)
- TEAEs at treatment areas
- TEAEs by onset time (≤4 weeks, >4 and ≤12 weeks, >12 and ≤24 weeks, >24 and ≤36 weeks, >36 and ≤52 weeks, and >52 weeks)

Adverse reactions (adverse events whose relationships with the IMP cannot be ruled out) will be analyzed in the same manner as TEAEs.

Serious TEAEs, TEAEs leading to discontinuation of the IMP, TEAE leading to IMP treatment interruption, and TEAEs leading to IMP dose reduction will be summarized by severity and CTCAE Grade.

For TEAEs that developed in ≥5% of any treatment group and non-serious TEAEs that developed in ≥5% of any treatment group, the number and percentage of subjects with an onset will be calculated.

In addition, TEAEs will be summarized in regard to the following items.

- TEAEs except for events that developed during the treatment interruption period
- TEAEs that developed by 4 weeks after IMP administration (only for all subjects)
- TEAEs that developed by 8 weeks after IMP administration
- TEAEs that developed in the treatment area
- TEAEs that developed in the treatment area by 4 weeks after IMP administration

9.2.1 Subgroup Analyses of Adverse Events

The summary of adverse events and summary of adverse events (treatment area) will be tabulated by the following subgroups. TEAEs (by SOC and PT) and TEAEs by severity (by SOC and PT) will also be summarized by event. Adverse reactions will also be summarized in the same manner.

- Sex (male, female)
- Age (<12 months, ≥12 months)
- Presence of the use of anti-inflammatory drugs
- Presence of the use of topical drugs other than anti-inflammatory drugs

For the summary of adverse events that developed by 4 weeks after IMP administration and the adverse events (treatment area) that developed by 4 weeks after IMP administration, subgroup analysis will be performed by sex and age.

Furthermore, subjects aged <12 months will be tabulated by the following categories.

Age: <6 months, ≥6 and <12 months

9.2.2 Analyses of Adverse Events by Drug Concentration

Regarding the following TEAEs, the summary of adverse events and summary of adverse events (treatment area) will be tabulated. TEAEs (by SOC and PT) and TEAEs by severity (by SOC and PT) will also be summarized by event. Adverse reactions will also be summarized in the same manner.

- TEAEs that developed at administration of 0.3% OPA-15406
- TEAEs that developed at administration of 1% OPA-15406

9.3 Clinical Laboratory Data

Regarding the actual measurements and changes from baseline at each assessment time point and the last time (LOCF) for the OC data of laboratory parameters (except for urine qualitative test), the descriptive statistics will be calculated for each treatment group and all subjects. For the urine qualitative test of laboratory tests, the shift table at each

assessment time point from baseline will be prepared for each treatment group and all subjects. For the tests other than urine qualitative test, the shift table before and after administration in which values are classified into normal, high level, and low level on the basis of the reference value will be prepared for each treatment group and all subjects.

The number and percentage of subjects who meet the criteria of the abnormality of hepatic functions (Hy's Law) (Appendix 1) will be calculated for each treatment group and all subjects. In addition, the listing of the abnormality of hepatic functions will also be prepared. All the postdose data will be included in the judgment.

9.4 Vital Signs and Body Weight

Regarding body weight, body temperature, blood pressure (systolic/diastolic), and pulse rate, the descriptive statistics of the actual measurements and changes from baseline at each assessment time point and the last time (LOCF) based on the OC data will be calculated for each treatment group and all subjects.

9.5 Physical Examination

Data will not be summarized.

9.6 Electrocardiogram Data

Not applicable.

9.7 Other Safety Variables

Not applicable.

10 Pharmacokinetic Analysis

In the pharmacokinetic analysis set, descriptive statistics will be calculated as shown below.

10.1 OPA-15406 Plasma Concentrations

[redacted]

10.2 Handling of Data

- For the acceptable windows for assessment time points, the acceptable windows for assessment time points for analysis described in Table 10.2-1, rather than the time points specified in section 1.3 of the protocol, will be used. [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- Plasma OPA-15406 concentration will be noted with 3 significant digits.
- [redacted]
- The number of digits for descriptive statistics are defined as shown in Table 10.2-2.

Table 10.2-2 Number of Digits for Descriptive Statistics

Descriptive statistics to be calculated	Number of digits
Number of subjects analyzed	Integer
Number of subjects summarized	Integer
Arithmetic mean	Numerical values will be rounded off at the (n + 1) place so that their number of digits (n) will be the same as that of values in individual subjects in the target data.
Standard deviation	
Median	
Minimum	Numerical values will be displayed, as they are, in the same number of digits (n) as that of values in individual subjects in the target data.
Maximum	
Coefficient of variation	Numerical values will be rounded off to the first decimal place.

11 Pharmacodynamic Analysis

Not applicable.

12 Pharmacogenomic Analysis

Not applicable.

13 Interim Analysis

[redacted]

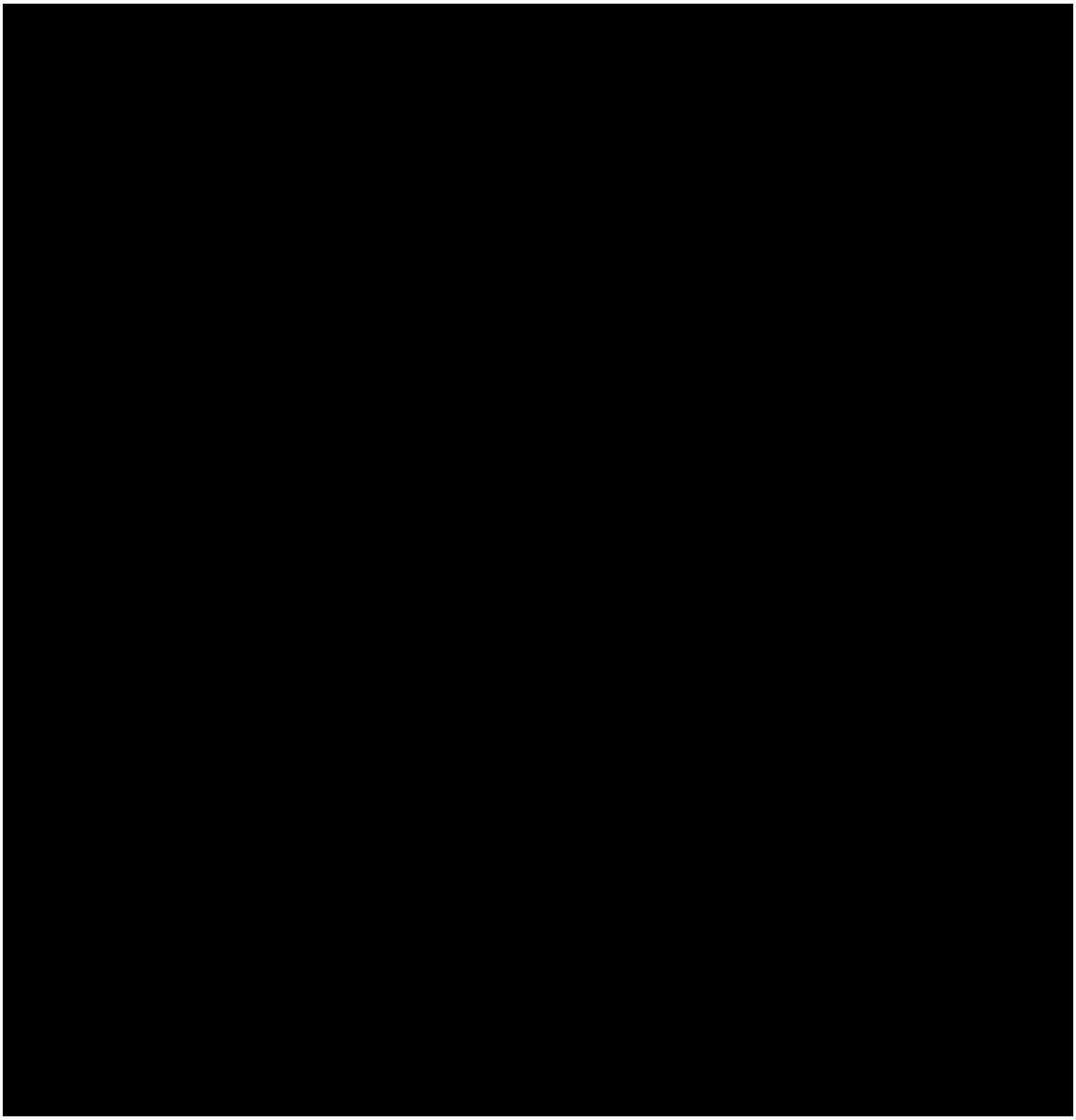
14 Changes from Planned Analysis Plan

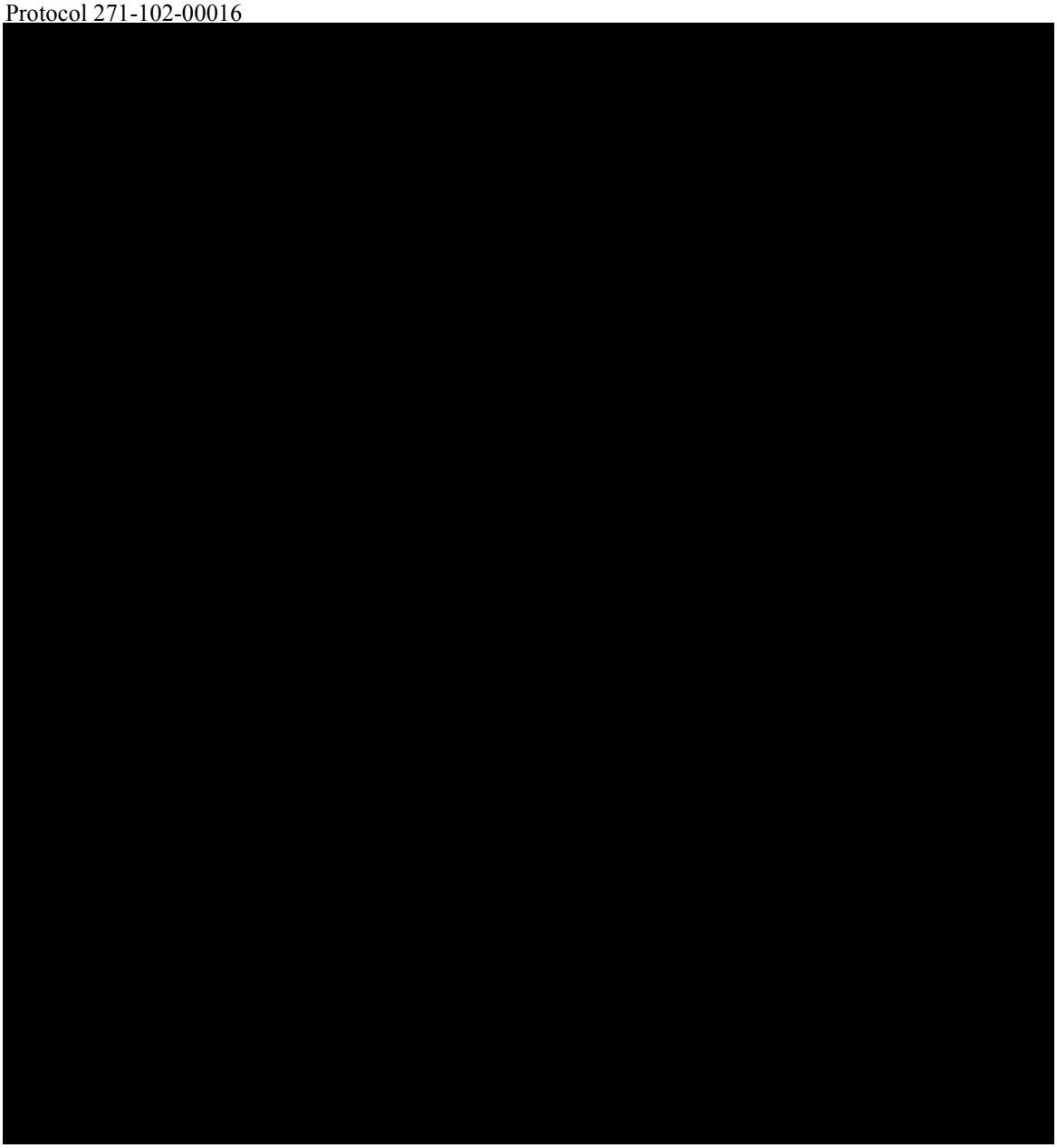
Not applicable.

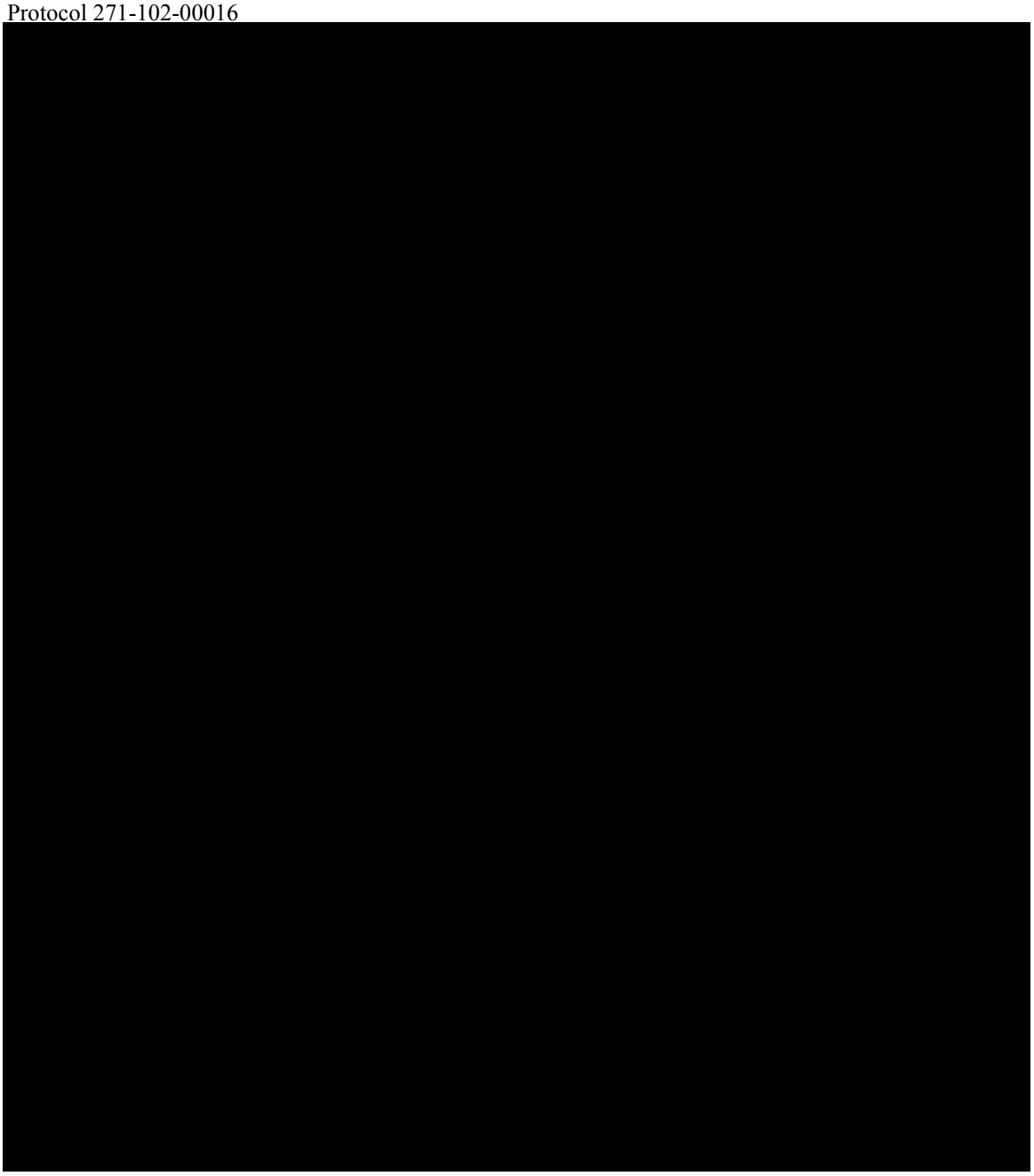
15 References

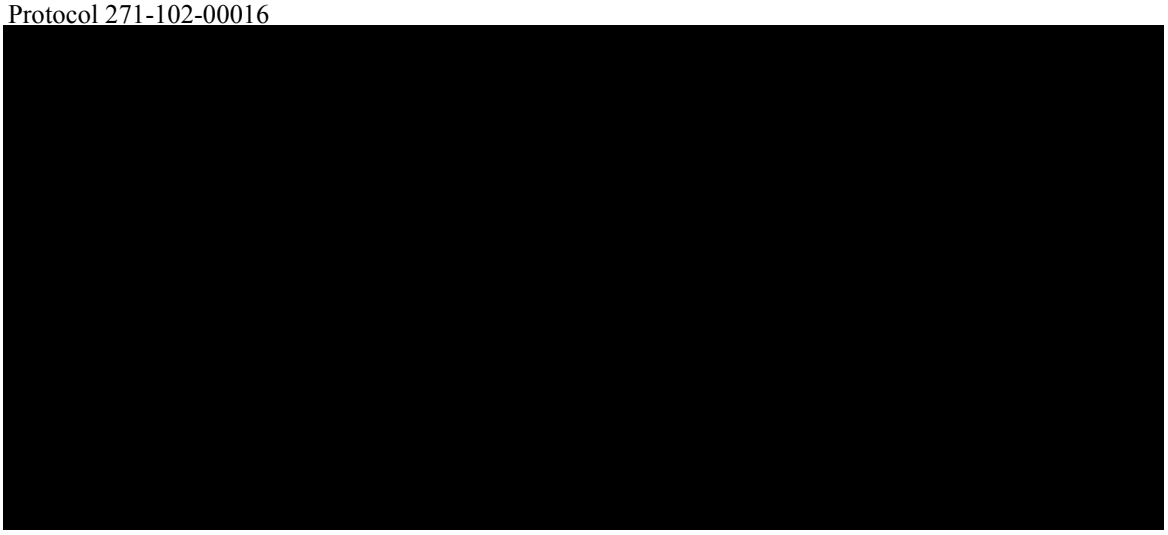
Not applicable.

16 Amendment History









Appendix 1 Criteria for Potential Hy's Law

The potential Hy's Law Cases are defined as subjects with the following criteria: ALT > = 3xULN (OR SCREENING VALUE) OR AST > = 3xULN (OR SCREENING VALUE) AND BILIRUBIN > = 2xULN (OR SCREENING VALUE)

Appendix 2 List of Tables and Figures

CT-5.6.2 Analysis of Baseline and Percent Change from Baseline in Overall IGA Score

CT-5.7.1 Analysis of Baseline and Change from Baseline in Overall EASI Score

CT-5.7.2 Analysis of Baseline and Percent Change from Baseline in Overall EASI Score

CT-5.7.3 Analysis of Baseline and Change from Baseline in Overall EASI Score, Erythema

CT-5.7.4 Analysis of Baseline and Percent Change from Baseline in Overall EASI Score, Erythema

CT-5.7.5 Analysis of Baseline and Change from Baseline in Overall EASI Score, Induration/Papulation

CT-5.7.6 Analysis of Baseline and Percent Change from Baseline in Overall EASI Score, Induration/Papulation

CT-5.7.7 Analysis of Baseline and Change from Baseline in Overall EASI Score, Excoriation

CT-5.7.8 Analysis of Baseline and Percent Change from Baseline in Overall EASI Score, Excoriation

CT-5.7.9 Analysis of Baseline and Change from Baseline in Overall EASI Score, Lichenification

CT-5.7.10 Analysis of Baseline and Percent Change from Baseline in Overall EASI Score, Lichenification

CT-5.7.11 Analysis of Baseline and Change from Baseline in Overall EASI Score, HEAD/NECK

CT-5.7.12 Analysis of Baseline and Percent Change from Baseline in Overall EASI Score, HEAD/NECK

CT-5.7.13 Analysis of Baseline and Change from Baseline in Overall EASI Score, UPPER LIMBS

CT-5.7.14 Analysis of Baseline and Percent Change from Baseline in Overall EASI Score, UPPER LIMBS

CT-5.7.15 Analysis of Baseline and Change from Baseline in Overall EASI Score, TRUNK

CT-5.7.16 Analysis of Baseline and Percent Change from Baseline in Overall EASI Score, TRUNK

CT-5.7.17 Analysis of Baseline and Change from Baseline in Overall EASI Score, LOWER LIMBS

CT-5.7.18 Analysis of Baseline and Percent Change from Baseline in Overall EASI Score, LOWER LIMBS

CT-5.8.1 Analysis of Baseline and Change from Baseline in POEM Score

CT-5.8.2 Analysis of Baseline and Percent Change from Baseline in POEM Score

CT-5.9 Analysis of Baseline and Change from Baseline in Overall Percentage Affected Body Surface Area

CT-6.1.1 Subgroup Analysis of Responder Rate for Overall IGA Score by Age

CT-6.1.2 Subgroup Analysis of Responder Rate for Overall IGA Score by Sex

CT-6.1.3 Subgroup Analysis of Responder Rate for Overall IGA Score by IGA Score at Baseline

CT-6.1.4 Subgroup Analysis of Responder Rate for Overall IGA Score by Severity of Atopic Dermatitis

CT-6.1.5 Subgroup Analysis of Responder Rate for Overall IGA Score by Total EASI Score at Baseline (<15, 15<=)

CT-6.1.6 Subgroup Analysis of Responder Rate for Overall IGA Score by Affected Body Surface Area

CT-6.1.7 Subgroup Analysis of Responder Rate for Overall IGA Score by Topical Anti-Inflammatory Agents

CT-6.1.8 Subgroup Analysis of Responder Rate for Overall IGA Score by Topical Medications Excluding Anti-Inflammatory Agents

CT-6.1.9 Subgroup Analysis of Responder Rate for Overall IGA Score by Modal Dose

CT-6.1.10 Subgroup Analysis of Responder Rate for Overall IGA Score by IMP Increase from Week 4

CT-6.1.11 Subgroup Analysis of Responder Rate for Overall IGA Score by IGA Score at Week 4

CT-6.1.12 Subgroup Analysis of Responder Rate for Overall IGA Score by Age (Subjects Under 12 Months of Age)

CT-6.2.1 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by Age

CT-6.2.2 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by Sex

CT-6.2.3 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by IGA Score at Baseline

CT-6.2.4 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by Severity of Atopic Dermatitis

CT-6.2.5 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by Total EASI Score at Baseline (<15, 15<=)

CT-6.2.6 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by Affected Body Surface Area

CT-6.2.7 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by Topical Anti-Inflammatory Agents

CT-6.2.8 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by Topical Medications Excluding Anti-Inflammatory Agents

CT-6.2.9 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by Modal Dose

CT-6.2.10 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by IMP Increase from Week 4

CT-6.2.11 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by IGA Score at Week 4

CT-6.2.12 Subgroup Analysis of 75% Over Responder Rate for Overall EASI Score by Age (Subjects Under 12 Months of Age)

CT-6.3.1 Subgroup Analysis of 90% Over Responder Rate for Overall EASI Score by Age

CT-6.3.2 Subgroup Analysis of 90% Over Responder Rate for Overall EASI Score by Sex

CT-6.3.3 Subgroup Analysis of 90% Over Responder Rate for Overall EASI Score by IGA Score at Baseline

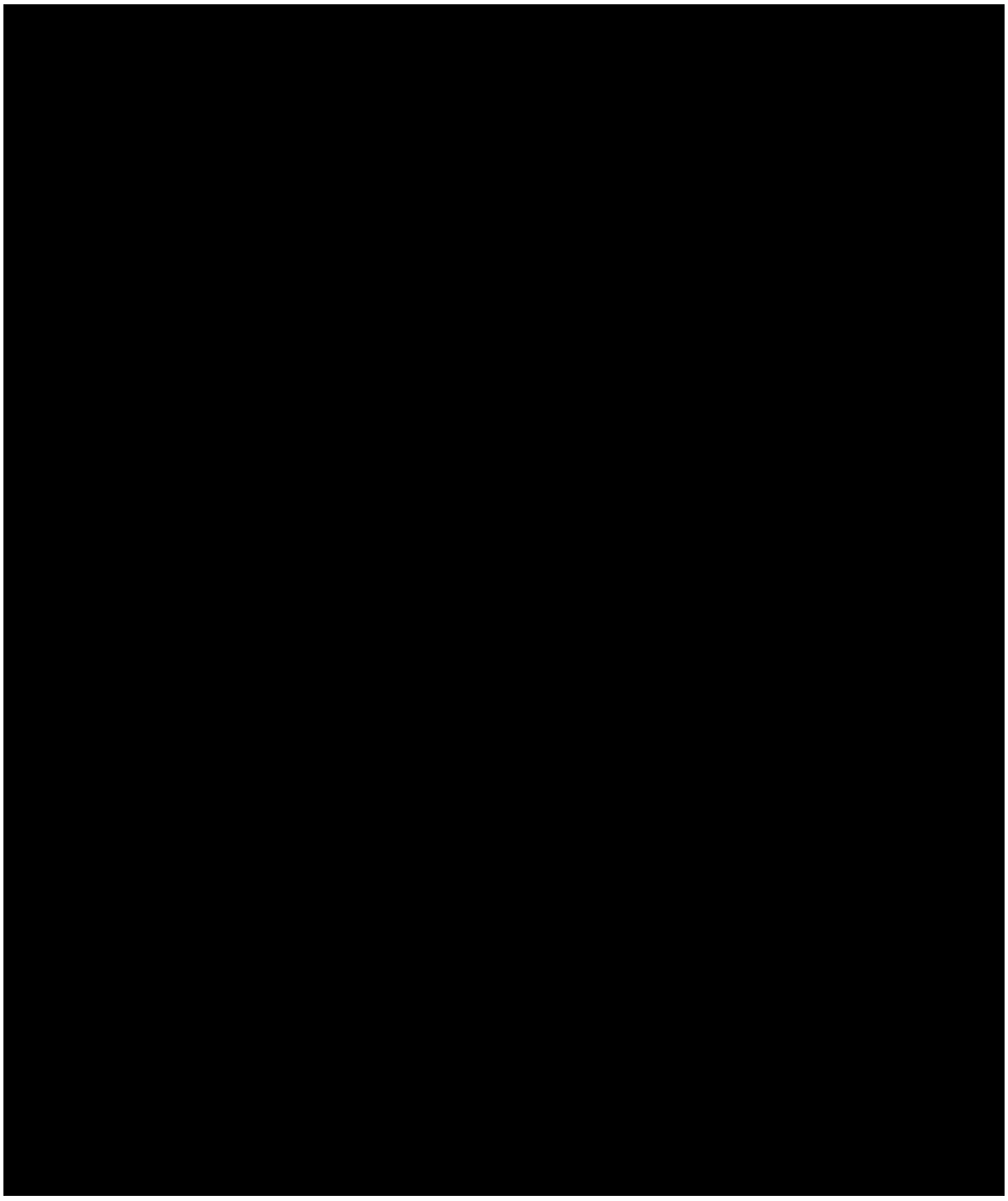
CT-6.3.4 Subgroup Analysis of 90% Over Responder Rate for Overall EASI Score by Severity of Atopic Dermatitis

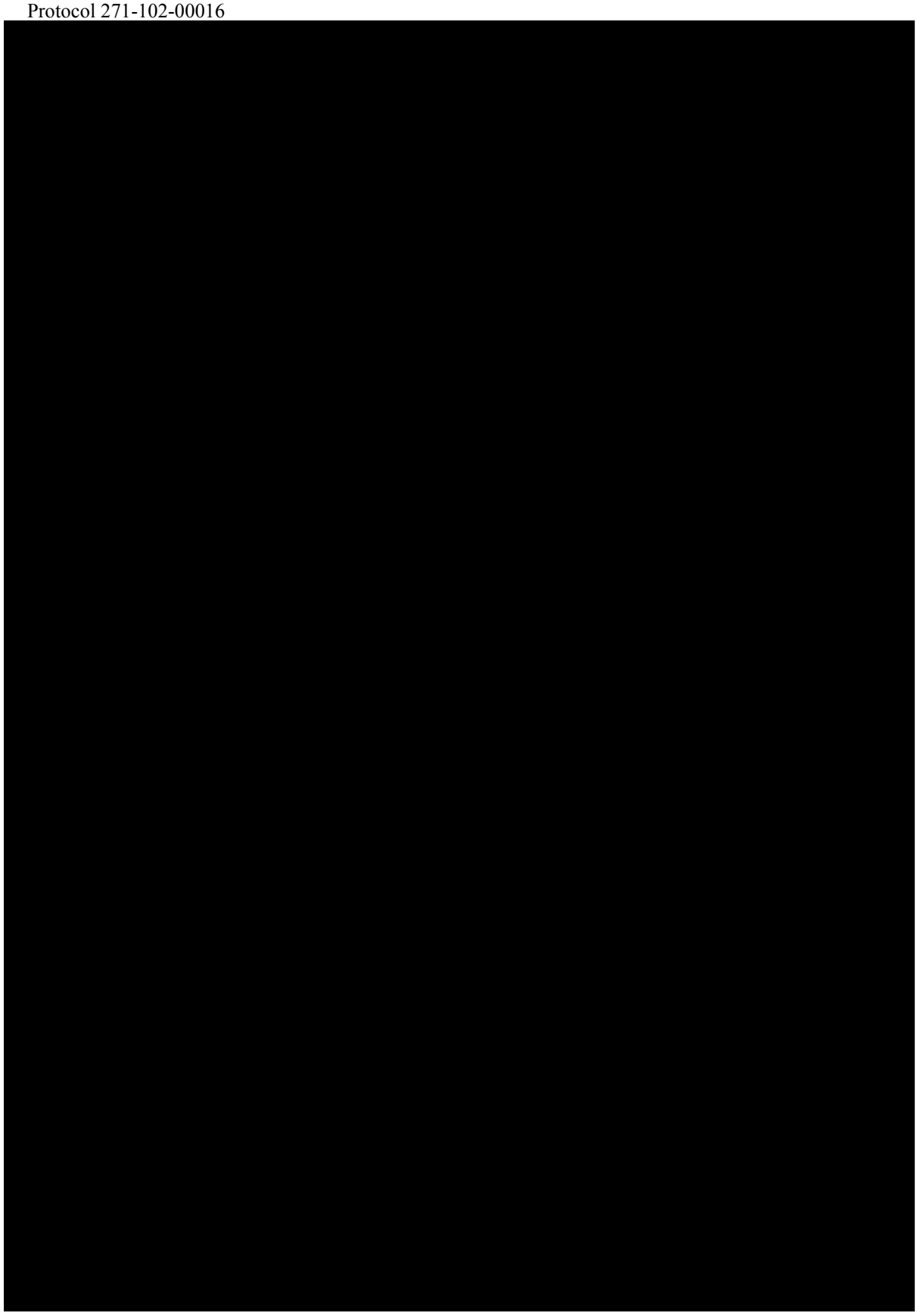
CT-6.3.5 Subgroup Analysis of 90% Over Responder Rate for Overall EASI Score by Total EASI Score at Baseline (<15, 15<=)

CT-6.4.10 Subgroup Analysis of 50% Over Responder Rate for Overall EASI Score by IMP Increase from Week 4

CT-6.4.11 Subgroup Analysis of 50% Over Responder Rate for Overall EASI Score by IGA Score at Week 4

CT-6.4.12 Subgroup Analysis of 50% Over Responder Rate for Overall EASI Score by Age (Subjects Under 12 Months of Age)





CT-7.1 Summary of Treatment Compliance for Number of Administrations

CT-7.2 Extent of Exposure to Trial Medication

CT-7.3.1 Summary of Reason for Dose Increased

CT-7.3.2 Summary of Reason for Dose Reduced

CT-7.3.3 Summary of Reason for Treatment Interrupted

CT-7.4 Summary of Treatment Period

CT-7.5 Summary of Exposure to Trial Medication

CT-7.6.1 Summary of Total Exposure to Trial Medication

CT-7.6.2 Summary of Total Exposure to Trial Medication by Age

CT-7.6.3 Summary of Total Exposure to Trial Medication by Age (Subjects Under 12 Months of Age)

CT-8.1.1.1 Adverse Events

CT-8.1.1.2 Adverse Events - Sex: Male

CT-8.1.1.3 Adverse Events - Sex: Female

CT-8.1.1.4 Adverse Events - Age: Less Than 12 Months

CT-8.1.1.5 Adverse Events - Age: Greater Than or Equal to 12 Months

CT-8.1.1.6 Adverse Events - With Topical Anti-Inflammatory Agents

CT-8.1.1.7 Adverse Events - Without Topical Anti-Inflammatory Agents

CT-8.1.1.8 Adverse Events - With Topical Medications Excluding Anti-Inflammatory Agents

CT-8.1.1.9 Adverse Events - Without Topical Medications Excluding Anti-Inflammatory Agents

CT-8.1.1.10 Adverse Events - Onset Timing of Administration of 0.3% OPA-15406

CT-8.1.1.11 Adverse Events - Onset Timing of Administration of 1% OPA-15406

CT-8.1.1.12 Adverse Events - Age: Less Than 6 Months (Subjects Under 12 Months of Age)

CT-8.1.1.13 Adverse Events - Age: Greater Than or Equal to 6 Months (Subjects Under 12 Months of Age)

CT-8.1.2.1 Adverse Events (Between Baseline and Week 4)

CT-8.1.2.2 Adverse Events (Between Baseline and Week 4) - Sex: Male

CT-8.1.2.3 Adverse Events (Between Baseline and Week 4) - Sex: Female

CT-8.1.2.4 Adverse Events (Between Baseline and Week 4) - Age: Less Than 12 Months

CT-8.1.2.5 Adverse Events (Between Baseline and Week 4) - Age: Greater Than or Equal to 12 Months

CT-8.1.2.6 Adverse Events (Between Baseline and Week 4) - Age: Less Than 6 Months (Subjects Under 12 Months of Age)

CT-8.1.2.7 Adverse Events (Between Baseline and Week 4) - Age: Greater Than or Equal to 6 Months (Subjects Under 12 Months of Age)

CT-8.1.3 Adverse Events (Between Baseline and Week 8)

CT-8.2.1.1 Adverse Events According to Application Site

CT-8.2.1.2 Adverse Events According to Application Site - Sex: Male

CT-8.2.1.3 Adverse Events According to Application Site - Sex: Female

CT-8.2.1.4 Adverse Events According to Application Site - Age: Less Than 12 Months

CT-8.2.1.5 Adverse Events According to Application Site - Age: Greater Than or Equal to 12 Months

CT-8.2.1.6 Adverse Events According to Application Site - With Topical Anti-Inflammatory Agents

CT-8.2.1.7 Adverse Events According to Application Site - Without Topical Anti-Inflammatory Agents

CT-8.2.1.8 Adverse Events According to Application Site - With Topical Medications Excluding Anti-Inflammatory Agents

CT-8.2.1.9 Adverse Events According to Application Site - Without Topical Medications Excluding Anti-Inflammatory Agents

CT-8.2.1.10 Adverse Events According to Application Site - Onset Timing of Administration of 0.3% OPA-15406

CT-8.2.1.11 Adverse Events According to Application Site - Onset Timing of Administration of 1% OPA-15406

CT-8.2.1.12 Adverse Events According to Application Site - Age: Less Than 6 Months (Subjects Under 12 Months of Age)

CT-8.2.1.13 Adverse Events According to Application Site - Age: Greater Than or Equal to 6 Months (Subjects Under 12 Months of Age)

CT-8.2.2.1 Adverse Events According to Application Site (Between Baseline and Week 4)

CT-8.2.2.2 Adverse Events According to Application Site (Between Baseline and Week 4) - Sex: Male

CT-8.2.2.3 Adverse Events According to Application Site (Between Baseline and Week 4) - Sex: Female

CT-8.2.2.4 Adverse Events According to Application Site (Between Baseline and Week 4) - Age: Less Than 12 Months

CT-8.2.2.5 Adverse Events According to Application Site (Between Baseline and Week 4) - Age: Greater Than or Equal to 12 Months

CT-8.2.2.6 Adverse Events According to Application Site (Between Baseline and Week 4) - Age: Less Than 6 Months (Subjects Under 12 Months of Age)

CT-8.2.2.7 Adverse Events According to Application Site (Between Baseline and Week 4) - Age: Greater Than or Equal to 6 Months (Subjects Under 12 Months of Age)

CT-8.3.1 Adverse Events Occurring on Treatment

CT-8.4.1.1 Treatment-emergent Adverse Events on Treatment by System Organ Class, Preferred Term and Period of Onset

CT-8.4.1.2 Drug-related Treatment-emergent Adverse Events on Treatment by System Organ Class, Preferred Term and Period of Onset

CT-8.4.1.3 Treatment-emergent Adverse Events on Treatment by System Organ Class, Preferred Term and Period of Onset (CTD Format)

CT-8.5.1.1.1 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term

CT-8.5.1.1.2 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Sex: Male

CT-8.5.1.1.3 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Sex: Female

CT-8.5.1.1.4 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Age: Less Than 12 Months

CT-8.5.1.1.5 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Age: Greater Than or Equal to 12 Months

CT-8.5.1.1.6 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - With Topical Anti-Inflammatory Agents

CT-8.5.1.1.7 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Without Topical Anti-Inflammatory Agents

CT-8.5.1.1.8 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - With Topical Medications Excluding Anti-Inflammatory Agents

CT-8.5.1.1.9 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Without Topical Medications Excluding Anti-Inflammatory Agents

CT-8.5.1.1.10 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Onset Timing of Administration of 0.3% OPA-15406

CT-8.5.1.1.11 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Onset Timing of Administration of 1% OPA-15406

CT-8.5.1.1.12 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Age: Less Than 6 Months (Subjects Under 12 Months of Age)

CT-8.5.1.1.13 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Age: Greater Than or Equal to 6 Months (Subjects Under 12 Months of Age)

CT-8.5.2.1.1 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity

CT-8.5.2.1.2 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Sex: Male

CT-8.5.2.1.3 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Sex: Female

CT-8.5.2.1.4 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Age: Less Than 12 Months

CT-8.5.2.1.5 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Age: Greater Than or Equal to 12 Months

CT-8.5.2.1.6 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - With Topical Anti-Inflammatory Agents

CT-8.5.2.1.7 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Without Topical Anti-Inflammatory Agents

CT-8.5.2.1.8 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - With Topical Medications Excluding Anti-Inflammatory Agents

CT-8.5.2.1.9 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Without Topical Medications Excluding Anti-Inflammatory Agents

CT-8.5.2.1.10 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Onset Timing of Administration of 0.3% OPA-15406

CT-8.5.2.1.11 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Onset Timing of Administration of 1% OPA-15406

CT-8.5.2.1.12 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Age: Less Than 6 Months (Subjects Under 12 Months of Age)

CT-8.5.2.1.13 Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Age: Greater Than or Equal to 6 Months (Subjects Under 12 Months of Age)

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

CT-8.6.1.1.1 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term

CT-8.6.1.1.2 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Sex: Male

CT-8.6.1.1.3 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Sex: Female

CT-8.6.1.1.4 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Age: Less Than 12 Months

CT-8.6.1.1.5 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Age: Greater Than or Equal to 12 Months

CT-8.6.1.1.6 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - With Topical Anti-Inflammatory Agents

CT-8.6.1.1.7 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Without Topical Anti-Inflammatory Agents

CT-8.6.1.1.8 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - With Topical Medications Excluding Anti-Inflammatory Agents

CT-8.6.1.1.9 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Without Topical Medications Excluding Anti-Inflammatory Agents

CT-8.6.1.1.10 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Onset Timing of Administration of 0.3% OPA-15406

CT-8.6.1.1.11 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Onset Timing of Administration of 1% OPA-15406

CT-8.6.1.1.12 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Age: Less Than 6 Months (Subjects Under 12 Months of Age)

CT-8.6.1.1.13 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term - Age: Greater Than or Equal to 6 Months (Subjects Under 12 Months of Age)

CT-8.6.2.1.1 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity

CT-8.6.2.1.2 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Sex: Male

CT-8.6.2.1.3 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Sex: Female

CT-8.6.2.1.4 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Age: Less Than 12 Months

CT-8.6.2.1.5 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Age: Greater Than or Equal to 12 Months

CT-8.6.2.1.6 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - With Topical Anti-Inflammatory Agents

CT-8.6.2.1.7 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Without Topical Anti-Inflammatory Agents

CT-8.6.2.1.8 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - With Topical Medications Excluding Anti-Inflammatory Agents

CT-8.6.2.1.9 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Without Topical Medications Excluding Anti-Inflammatory Agents

CT-8.6.2.1.10 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Onset Timing of Administration of 0.3% OPA-15406

CT-8.6.2.1.11 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Onset Timing of Administration of 1% OPA-15406

CT-8.6.2.1.12 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Age: Less Than 6 Months (Subjects Under 12 Months of Age)

CT-8.6.2.1.13 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity - Age: Greater Than or Equal to 6 Months (Subjects Under 12 Months of Age)

CT-8.6.3.1 Incidence of Drug-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term and CTCAE Grade

CT-8.7.1.1 Incidence of Deaths due to Treatment-emergent Adverse Events by System Organ Class and Preferred Term

CT-8.8.1.1 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term

CT-8.8.2.1 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Severity

CT-8.8.3.1 Incidence of Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and CTCAE Grade

CT-8.9.1.1 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class and Preferred Term

CT-8.9.2.1 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class, Preferred Term and Severity

CT-8.9.3.1 Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation from Study by System Organ Class, Preferred Term and CTCAE Grade

CT-8.10.1.1 Incidence of Treatment-emergent Adverse Events Resulting in Reduction of IMP by System Organ Class and Preferred Term

CT-8.10.2.1 Incidence of Treatment-emergent Adverse Events Resulting in Reduction of IMP by System Organ Class, Preferred Term and Severity

CT-8.10.3.1 Incidence of Treatment-emergent Adverse Events Resulting in Reduction of IMP by System Organ Class, Preferred Term and CTCAE Grade

CT-8.11.1.1 Incidence of Treatment-emergent Adverse Events Resulting in Interruption of IMP by System Organ Class and Preferred Term

CT-8.11.2.1 Incidence of Treatment-emergent Adverse Events Resulting in Interruption of IMP by System Organ Class, Preferred Term and Severity

CT-8.11.3.1 Incidence of Treatment-emergent Adverse Events Resulting in Interruption of IMP by System Organ Class, Preferred Term and CTCAE Grade

CT-8.12.1 Incidence of Treatment-emergent Adverse Events Greater Than or Equal to 5% in Any Group by System Organ Class and Preferred Term

CT-8.13.1 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-8.14.1 Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term According to Application Site

CT-8.15.1 Incidence of 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

CT-10.1.1 Mean Change From Baseline in Laboratory Test Values: Serum Chemistry

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

CF-1.1 Incidence of Responder Rate for Overall IGA Score at Week 4

CF-1.2.1 Incidence of Responder Rate for Overall IGA Score by Visit - OC

CF-1.2.2 Incidence of Responder Rate for Overall IGA Score by Visit - Cumulative

CF-2.1 Incidence of 75% Over Response Rate for Overall EASI Score at Week 4

CF-2.2.1 Incidence of 75% Over Response Rate for Overall EASI Score by Visit - OC

CF-2.2.2 Incidence of 75% Over Response Rate for Overall EASI Score by Visit - Cumulative

CF-3.1 Incidence of 90% Over Response Rate for Overall EASI Score at Week 4

CF-3.2.1 Incidence of 90% Over Response Rate for Overall EASI Score by Visit - OC

CF-3.2.2 Incidence of 90% Over Response Rate for Overall EASI Score by Visit - Cumulative

CF-4.1 Incidence of 50% Over Response Rate for Overall EASI Score at Week 4

CF-4.2.1 Incidence of 50% Over Response Rate for Overall EASI Score by Visit - OC

CF-4.2.2 Incidence of 50% Over Response Rate for Overall EASI Score by Visit - Cumulative

CF-5.1 Means of Change from Baseline in Overall IGA Score by Visit

CF-6.1 Means of Change from Baseline in Overall EASI Score by Visit

CF-6.2 Means of Percent Change from Baseline in Overall EASI Score by Visit

PKT-1.1 Individual and Summary of OPA-15406 Plasma Concentrations Following Multiple Topical Administrations of 0.3% OPA-15406 Ointment to Pediatric Patients With Atopic Dermatitis

PKT-1.2 Individual and Summary of OPA-15406 Plasma Concentrations Following Multiple Topical Administrations of 1% OPA-15406 Ointment to Pediatric Patients With Atopic Dermatitis

PKT-2.1 Individual and Summary of OPA-15406 Plasma Concentrations Normalized by Dose Derived From Treated Body Surface Area Following Multiple Topical Administrations of 0.3% OPA-15406 Ointment to Pediatric Patients With Atopic Dermatitis

PKT-2.2 Individual and Summary of OPA-15406 Plasma Concentrations Normalized by Dose Derived From Treated Body Surface Area Following Multiple Topical Administrations of 1% OPA-15406 Ointment to Pediatric Patients With Atopic Dermatitis

PKF-1 Mean OPA-15406 Plasma Concentrations Following Multiple Topical Administrations of OPA-15406 Ointment to Pediatric Patient With Atopic Dermatitis

PKF-2 Mean OPA-15406 Plasma Concentrations Normalized by Dose Derived From Treated Body Surface Area Following Multiple Topical Administrations of OPA-15406 Ointment to Pediatric Patients With Atopic Dermatitis

Appendix 3 List of Subject Data Listings

PDATA-1 Inclusion and Exclusion Criteria Not Met

PDATA-2 Subject Disposition

PDATA-3.1 Medical History

PDATA-3.2 History of Atopic Dermatitis

PDATA-4.1 Concomitant Medications: Medications Taken Prior to Start of Study Therapy

PDATA-4.2 Concomitant Medications: Medications Taken During Study Therapy

PDATA-4.3 Concomitant Medications: Medications Taken After Study Therapy

PDATA-4.4 Concomitant Medications: Therapy

PDATA-5.1 Exposure to Trial Medication

PDATA-5.2 Listing of Trial Medication by Subject

PDATA-6 Physical Examination

PDATA-7 Vital Signs

PDATA-8 Blood Sampling for Pharmacokinetics

PDATA-9 Screening Failures

PDATA-10 Protocol Deviations (Major) - CRF

PDATA-11 Eczema Area and Severity Index

PDATA-12 Overall Investigator's Global Assessment of Disease Severity

PDATA-13 Patient-Oriented Eczema Measure

PDATA-14 Affected Body Surface Area

PDATA-15 Treatment Area

PDATA-16 Patch Application and Removal

PDATA-17 Treatment Tracking

DREAS-1 Discontinued Subjects and Reasons for Discontinuations

DEMOG-1 Demographic Characteristics

DEMOG-2 Informed Consent

AE-1 Adverse Events

SMED-1 Actual Exposure to Study Medication

SMED-2 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 Overall Percentage Affected Body Surface Area

EFF-12 Change from Baseline in POEM Score

EFF-13 Efficacy Outcome

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