STATISTICAL ANALYSIS PLAN

INCB018424 PHOSPHATE CREAM

INCB 18424-206/NCT03011892

A Phase 2, Randomized, Dose-Ranging, Vehicle-Controlled and Triamcinolone 0.1% Cream-Controlled Study to Evaluate the Safety and Efficacy of INCB018424 Phosphate Cream Applied Topically to Adults With Atopic Dermatitis

IND Number:	**77,101**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Protocol Version:	**15 SEP 2016**
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SAP Version:	**Original**
SAP Author:	[redacted]**, Biostatistics**
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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AD	atopic dermatitis
AE	adverse event
ANOVA	analysis of variance
BMI	body mass index
BID	twice daily
[redacted]	[redacted]
CI	confidence interval
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DB	double blind
DBP	diastolic blood pressure
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCRF	electronic case report form
FWER	family-wise error rate
IGA	Investigator's Global Assessment
IND	Investigational New Drug
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
NCI	National Cancer Institute
NRI	nonresponder imputation analysis
NRS	Numerical Rating Scale
PD	pharmacodynamics
PI	percentage improvement
[redacted]	[redacted]
PP	per protocol
PT	preferred term
QD	once daily
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure

Abbreviation	Term
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This is a randomized, vehicle- and active (triamcinolone 0.1% cream)-controlled study in subjects with mild to moderate AD. The study is double-blinded for vehicle, INCB018424 doses, and active control. Subjects will receive blinded study drug for 8 weeks followed by 4 weeks of optional open-label treatment with INCB018424 1.5% cream BID for subjects who meet Protocol-defined criteria. Section 1 of the Protocol provides a detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with INCB018424 cream. The purpose of this SAP is to define the methodology for analyzing and summarizing the data collected during the conduct of Study INCB 18424-206. The scope of this plan includes the interim and final analyses that are planned and will be executed by the Department of Biostatistics or designee [redacted]

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 18424-206 Protocol dated 15 SEP 2016, Administrative Change 1 dated 10 JAN 2017, Administrative Change 2 dated 28 MAR 2017, and Administrative Change 3 dated 19 APR 2017, and eCRFs approved 06 FEB 2017. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives

2.2.1. Primary Objective

- To establish the efficacy of each dose of INCB018424 cream QD or BID in subjects with AD compared with vehicle cream BID.

2.2.2. Secondary Objectives

2.2.2.1. Key Secondary Objective

- To establish the efficacy of each dose of INCB018424 cream QD or BID in subjects with AD compared with triamcinolone 0.1% cream BID.

2.2.2.2. Other Secondary Objective

- To evaluate the safety and tolerability of INCB018424 cream when applied QD or BID to subjects with AD.

[redacted]

2.3. Study Endpoints

2.3.1. Primary Endpoint

- Mean percentage change from baseline in EASI score at Week 4 in subjects treated with 1.5% INCB018424 cream BID compared with subjects treated with vehicle cream BID.

2.3.2. Secondary Endpoints

2.3.2.1. Key Secondary Endpoints

- Mean percentage change from baseline in EASI score at Week 4 in subjects treated with INCB018424 compared with subjects treated with vehicle cream BID.
- Mean percentage change from baseline in EASI score at Week 4 in subjects treated with INCB018424 compared with subjects treated with triamcinolone 0.1% cream BID.

2.3.2.2. Other Secondary Endpoints

- Mean percentage change from baseline in EASI score at Week 2 and Week 8.
- Proportion of subjects who achieve a $\geq$ 50% improvement from baseline in EASI (EASI-50) at Weeks 2, 4, and 8.
- Assessment of dose response based on percentage change from baseline in EASI score at Week 4.
- Time to achieve EASI-50.
- Proportion of subjects achieving an IGA score of 0 to 1 who have an improvement of $\geq$ 2 points from baseline at Weeks 2, 4, and 8.
- Mean change from baseline in the Itch NRS score at Weeks 2, 4, and 8.
- Safety and tolerability assessed by monitoring the frequency, duration, and severity of AEs; performing physical examinations; collecting vital signs; and collecting laboratory data for hematology, serum chemistry, and urinalysis.

3. STUDY DESIGN

This is a randomized, vehicle- and active (triamcinolone 0.1% cream)-controlled study in subjects with mild to moderate AD. The study is double-blinded for vehicle, INCB018424 doses, and active control. Approximately 300 subjects will be randomized 1:1:1:1:1:1 (approximately 50 subjects each) to treatment with INCB018424 1.5% BID, INCB018424 1.5% QD, INCB018424 0.5% QD, INCB018424 0.15% QD, vehicle BID, and active control (triamcinolone 0.1% cream) BID and stratified by EASI score (≤ 7 and > 7). Subjects will receive blinded study drug for 8 weeks. Subjects randomized to QD regimens will apply vehicle for the evening application. Subjects randomized to triamcinolone will apply triamcinolone 0.1% cream BID for 4 weeks and vehicle cream for 4 weeks to not exceed the allowable triamcinolone application duration.

After the DB period, a 4-week period of open-label treatment with INCB018424 1.5% cream BID will be offered to subjects who meet Protocol-defined criteria. Subjects will have follow-up assessments 1 month after the last application of study drug. The total duration of participation will be up to 20 weeks, including up to 4 weeks for screening, 8 weeks of DB treatment, 4 weeks of optional open-label treatment, and 4 weeks of safety follow-up.

3.1. Randomization

In the treatment period, approximately 300 subjects will be randomized 1:1:1:1:1:1 to the 6 treatment groups. Subjects will be stratified at randomization based on baseline EASI score of ≤ 7 or > 7.

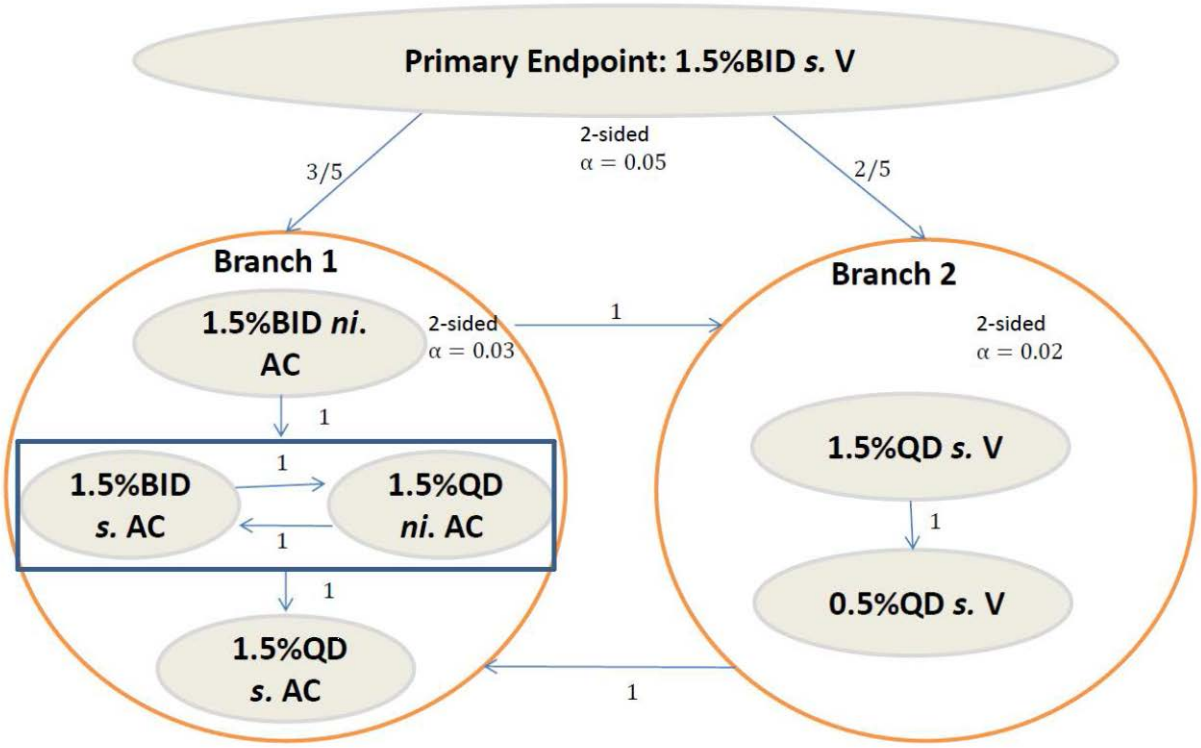
3.2. Control of Type I Error

For the primary endpoint and key secondary endpoints, the overall 2-sided Type I error rate is 0.05.

A graphical procedure with a gatekeeping testing strategy for the primary and key secondary analyses, as specified in Protocol Section 9.2.1, will be implemented to control the overall Type I error rate. The underlying procedure is derived using the methodology developed in Bretz et al (2009). This method will guarantee a strong control of the FWER.

A family of 7 elementary hypotheses, corresponding to treatment comparisons between active dose groups and vehicle (or triamcinolone) is evaluated in Figure 1 based on the percentage change from baseline to Week 4 EASI score.

Figure 1: Illustration of the Statistical Treatment Comparisons



AC = active control; s = superiority; ni = noninferiority; V = vehicle.
Note: Active control (triamcinolone 0.1% cream) BID for 4 weeks followed by vehicle cream BID for 4 weeks.

The primary endpoint will test the superiority of INCB018424 1.5% BID compared with vehicle.

The key secondary endpoint has 2 branches. Branch 1 will test whether:

- INCB018424 1.5% BID is noninferior to triamcinolone (active control)
- INCB018424 1.5% QD is noninferior to triamcinolone (active control)
- INCB018424 1.5% BID is superior to triamcinolone (active control)
- INCB018424 1.5% QD is superior to triamcinolone (active control)

Branch 2 will test whether:

- INCB018424 1.5% QD is superior to vehicle
- INCB018424 0.5% QD is superior to vehicle

3.2.1. Primary Analysis

The primary alternative hypothesis (superiority of INCB018424 1.5% BID compared with vehicle) will be tested at a 2-sided $\alpha = 0.05$ level. The test on the primary endpoint will be used as a gatekeeper for 6 statistical tests on secondary endpoints that will be grouped into 2 parallel branches (see Figure 1). The first branch (Branch 1) includes tests of INCB018424 versus the active control (triamcinolone). The second branch (Branch 2) includes tests of INCB018424 versus vehicle. The initial allocation of the overall significance level to Branch 1 and Branch 2 is 3/5 and 2/5, respectively. The weights of the level to be passed on if 1 hypothesis is rejected are specified in Figure 1.

3.2.2. Secondary Analysis

3.2.2.1. Tests in Branch 1

- **Step 1:** The first alternative hypothesis (noninferiority of INCB018424 1.5% BID compared with triamcinolone) will be tested at a 2-sided $\alpha = 0.03$ level if the primary test is significant. If the first alternative hypothesis is established, then hypotheses in Step 2 will be tested at an overall error rate of 0.03.

- **Step 2:** If Step 1 is established, then a superiority test of INCB018424 1.5% BID compared with triamcinolone and noninferiority test of INCB018424 1.5% QD compared with triamcinolone will be carried out using the Bonferroni-Holm procedure at an overall 2-sided $\alpha = 0.03$ level.

- **Step 3:** If both of the null hypotheses in Step 2 are rejected, then a superiority test of INCB018424 1.5% QD compared with triamcinolone will be carried out at a 2-sided $\alpha = 0.03$ level.

If all 4 tests in Branch 1 are significant, then the overall level ($\alpha = 0.03$) of Branch 1 will be reallocated to Branch 2, and the first alternative hypothesis in Branch 2 will be tested with start level of 2-sided 0.05. If 1 or more of the tests in Branch 1 is nonsignificant, there will be no level reallocated from Branch 1 to Branch 2, and the first alternative hypothesis in Branch 2 will be tested with start level of 2-sided $\alpha = 0.02$.

3.2.2.2. Tests in Branch 2

- Alternative hypotheses (superiority of INCB018424 1.5% QD and 0.5% QD compared with vehicle) will be tested in sequence using the alpha level decided in previous steps.

If 1 or more of the 4 tests in Branch 1 is nonsignificant, but all tests in Branch 2 are significant, then the alpha level will be reallocated to Branch 1, and Branch 1 will reopen with a start level of 2-sided $\alpha = 0.05$.

3.2.3. Noninferiority Margin

In a historical study (Beck et al 2014), the difference of percentage change from baseline to Day 29 in EASI scores between active control (placebo and glucocorticoids) and placebo was 27.1% with the derived lower limit of 95% CI 16.4%. Therefore, 27% constitutes the minimum expected benefit of triamcinolone (active control) over vehicle. Given that the result is based on 2 studies with small sample sizes, the margin is chosen to be -10%, which is between a half of the lower 95% CI (-8%) and 50% of the minimum effect (-13.5%).

Noninferiority analysis will be performed between each of the active treatment groups and triamcinolone.

3.3. Sample Size Considerations

In order to provide a large safety database and to provided adequate power for efficacy variables, the total sample size for the study is 300 subjects randomized at a 1:1:1:1:1:1 ratio (stratified by baseline EASI score) to treatment with INCB018424 1.5% BID, INCB018424 1.5% QD, INCB018424 0.5% QD, INCB018424 0.15% QD, triamcinolone (active control), and vehicle.

3.4. Schedule of Assessments

Refer to Protocol dated 15 SEP 2016 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Definitions for Day 1, Baseline, and the Last Available Value

Day 1, baseline, and last available value for the DB period and the open-label period are defined in Table 1.

Table 1: Definition of Day 1, Baseline, and Last Available Value

Study Period	Treatment Group	Day 1	Baseline	Last Available Value
DB period	INCB018424 cream 1.5% BID 1.5% QD 0.5% QD 0.15% QD Vehicle triamcinolone	Date of first application or date of randomization for subjects randomized but not treated in the DB period	The last nonmissing measurement obtained on or before the day of the first dose.	The last nonmissing measurement obtained after the first dose, and within 30 days after the last dose in the DB period or before the first dose in the extension period, whichever is earlier.
Open-label period	INCB018424 cream 1.5% BID	Date of first application in DB period	The last nonmissing measurement obtained on or before the day of the first dose in DB period	The last nonmissing measurement obtained after the first dose and within 30 days after the last dose.
	INCB018424 cream 1.5% QD 0.5% QD 0.15% QD Vehicle triamcinolone	Date of first application in open-label period	The last nonmissing measurement obtained on or before the day of the first dose in the open-label period	The last nonmissing measurement obtained after the first dose in open-label period and within 30 days after the last dose.

When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or when the first dose is not available, use the following convention to determine the baseline value:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.2. Study Day

Study Day 1 is used to calculate the study day for mapping scheduled visits. Study Day 1 is the date of the first dose of INCB018424 cream, vehicle, or triamcinolone cream in the DB treatment period.

If a visit/reporting date is on or after Study Day 1, then the study day at the visit/reporting date will be calculated as

Study Day # = (Visit/Reporting Date – Study Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Study Day # = (Visit/Reporting Date – Study Day 1 date).

A study day of -1 indicates 1 day before Study Day 1.

4.2. Variable Definitions

4.2.1. Age

Subject age will be calculated as the integer part of the number of years from date of birth to the date of signing the informed consent form, using the following formula:

Age = integer part of (date of informed consent – date of birth + 1) / 365.25

4.2.2. Body Mass Index

Body mass index will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2

4.2.3. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first application of study treatment.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first application of study treatment and is ongoing throughout the study or ends on/after the first application of study treatment.
- On/after the date of first application of study treatment and is ongoing or ends during the course of study treatment.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after the first application of study treatment. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; Version 9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of subjects in each category.

During the DB period, the safety population will be used for all safety analyses, and the ITT population will be used for all efficacy analyses. [redacted]

Interim analyses are planned for this Protocol as defined in Section 9.

5.2. Treatment Groups

This is a study in subjects with AD, with a DB, randomized, and vehicle- and active (triamcinolone 0.1% cream)-controlled treatment period followed by an optional open-label treatment period. Data will be summarized based on the treatment regimen that was initially assigned or that subjects received during the DB period.

- DB period versus open-label period:
  - INCB018424 1.5% BID
  - INCB018424 1.5% QD
  - INCB018424 0.5% QD
  - INCB018424 0.15% QD
  - TAC*
  - Vehicle BID

  *Active control (triamcinolone 0.1% cream) BID for 4 weeks followed by vehicle cream BID for 4 weeks.

Table summaries, unless otherwise indicated, will present data by treatment group. The results will be summarized and presented separately for the DB period and open-label period.

5.3. Analysis Populations

5.3.1. Double-Blind Period

5.3.1.1. Intent-to-Treat Population

All subjects who are randomized to the study constitute the ITT population in the DB period. Treatment groups for this population will be defined according to the treatment assignment at the time of randomization regardless of the actual study treatment the subject might receive during study participation. This population will be used for analyses of all efficacy data in the DB Treatment Period.

5.3.1.2. Per-Protocol Population

Subjects in the ITT population who are considered to be sufficiently compliant with the Protocol compose the PP population, which is defined for supportive sensitivity analyses for efficacy endpoints in the treatment period.

5.3.1.3. Safety Population

The safety population in the DB treatment period includes all enrolled subjects who applied at least 1 dose of INCB018424 cream, triamcinolone cream, or vehicle cream. Treatment groups for this population will be determined according to the actual treatment the subject received regardless of assigned study treatment. All safety analyses will be conducted using the safety population.

5.3.2. Open-Label Period

All analyses for the open-label period will be conducted with the open-label evaluable population, which includes all subjects who applied at least 1 dose of INCB018424 1.5% cream during the open-label period.

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

The following demographic variables will be summarized for the ITT population in the DB period, and open-label evaluable population in the open-label period: age, sex, race, ethnicity, weight, height, BMI.

The following baseline disease characteristics will be summarized for the ITT population:

- Months since first onset of AD
- Prior history of asthma (No/Yes)
- Prior allergies (food, environmental) (No/Yes)
- History of contact dermatitis (No/Yes)
- Common complications of AD
- Prior treatments for AD
- Months since onset of current AD
- Prior therapy for AD given in the past 30 days (No/Yes)
- Total BSA involvement in current AD episode
- Facial involvement (No/Yes)
- Number of AD episodes/flare-ups over the last 12 months

6.2. Disposition of Subjects

The number and percentage of subjects who were treated, randomized, and completed the DB treatment period through Week 4 and Week 8; were treated in open-label period; completed the open-label period; discontinued from the study or study treatment during the DB period; and discontinued from the study during the open-label period with a primary reason for discontinuation will be summarized for the ITT population in the DB period and open-label evaluable population in open-label period.

6.3. Protocol Deviations and Violations

Protocol deviations and violations recorded in the eCRF will be presented in the subject data listings.

6.4. Exposure

For subjects in the safety population in the DB period and in the open-label evaluable population in the open-label period, descriptive statistics will be provided by treatment group for duration of treatment, average daily dose, and total dose. Duration of treatment with INCB018424 cream, vehicle cream, or triamcinolone cream is defined as the number of days from Day 1 to the last record (defined in Table 2) of INCB018424 cream, vehicle cream, or triamcinolone cream application.

Table 2: Duration of Treatment

Study Period	Treatment Group	Day 1	Last Record
DB period	All treatment groups	Date of first application in the DB period	Date of last record in the DB period
Open-label period	INCB018424 cream 1.5% BID	Date of first application in the DB Period	Date of last record in the open-label period
	INCB018424 cream 1.5% QD 0.5% QD 0.15% QD Vehicle triamcinolone	Date of first application in the open-label period	Date of last record in the open-label period

6.5. Study Drug Compliance

Overall compliance (%) for the application of INCB018424 cream, vehicle cream, or triamcinolone cream (4 weeks) followed by vehicle cream (4 weeks) will be calculated for all subjects in the safety (DB period) and open-label evaluable (open-label period) populations as follows:

Overall compliance (%) = 100 × [total amount dispensed – total amount returned] / [intended "dose"]

- Total amount dispensed is defined as the sum of the weights of tubes dispensed before the current visit.
- Total amount returned is defined as the sum of the weights of the tubes returned before and at the current visit.
- The intended dose will be based on the earliest study day of permanent discontinuation of study drug (ie, first AE with action taken = "drug withdrawn" for AE discontinuation) or last study drug record in the database.

6.6. Medical History

For subjects in the ITT population in the DB period, medical history will be summarized by assigned treatment groups. This summary will include the number and percentage of subjects with medical history for each body system/organ class as documented in the eCRF.

6.7. Prior and Concomitant Medication

For subjects in the safety population in the DB period and the open-label evaluable population in the open-label period, prior medications and concomitant medications will be coded using the WHO Drug Dictionary and summarized by WHO drug class and WHO drug term. Results will be summarized as number and percentage of subjects with prior and concomitant medications by PT and WHO drug class.

Prior medication information for AD will also be used to identify medication received by subjects before enrollment into the study in the treatment periods. Prior medications for AD will be summarized by treatment group as well as listed.

7. EFFICACY

7.1. General Considerations

For continuous measurements, summary statistics will include sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. For all continuous variables, both the actual value and change and/or percentage from baseline (if available) will be analyzed.

For categorical measurements, summary statistics will include sample size, frequency, and percentages.

All by-visit analyses will include the follow-up period if the data are available.

7.1.1. Handling of Dropouts or Missing Data

In general, for continuous endpoints on primary and secondary endpoints, any subject who discontinues from the study before the timepoint of interest may have missing data imputed using the imputation techniques, such as MMRM under the missing-at-random assumption. MMRM model implicitly adjusts for missing data through a variance-covariance structure.

For response endpoints, all nonresponders, as well as all subjects who discontinue study treatment at any time before the timepoint of interest or discontinue from the study for any reason, will be defined as nonresponders for the NRI analysis.

For other endpoints, missing observations will be handled as detailed in the specific sections addressing each analysis.

7.2. Efficacy Measures

7.2.1. Primary Efficacy Measures

Atopic dermatitis will be assessed using the EASI scoring system, which is a validated disease measurement for clinical studies (Hanifin et al 2001). The severity strata for the EASI are as follows: 0 = clear; 0.1 to 1.0 = almost clear; 1.1 to 7.0 = mild; 7.1 to 21.0 = moderate; 21.1 to 50.0 = severe; and 50.1 to 72.0 = very severe (Leshem et al 2015).

The EASI score (Table 3) examines 4 areas of the body and weights them for subjects 8 years of age and older as follows:

Head/Neck (H) = 0.1, Upper limbs (UL) = 0.2, Trunk (T) = 0.3, and Lower limbs (LL) = 0.4.

The percentage of area involved for each of the 4 body regions is weighted as follows: 0 = no eruption, 1 = some to < 10%, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, and 6 = 90% to 100%.

Each of the 4 body regions is assessed separately for erythema (E), induration/papulation/edema (I), excoriations (Ex), and lichenification (L) for an average degree of severity of each sign in each region with: 0 = none, 1 = mild, 2 = moderate, and 3 = severe, with half-step allowed.

Table 3: EASI Score Calculation

Body Region	EASI Score
Head/Neck (H)	(E + I + Ex + L) × Area score × 0.1
Upper limbs (UL)	(E + I + Ex + L) × Area score × 0.2
Trunk (T)	(E + I + Ex + L) × Area score × 0.3
Lower limbs (LL)	(E + I + Ex + L) × Area score × 0.4
EASI total	Sum of the above 4 body region scores

Missing values will not be imputed. An EASI total score is calculated as the sum of the nonmissing scores and will only be calculated when all subscores are nonmissing.

The PI in EASI score from baseline will be computed as follows:

PI = 100 × (baseline EASI score - observed EASI score) / baseline EASI score

A positive score denotes improvement, and a negative score denotes worsening.

7.2.2. Other Efficacy Measures

- **EASI-50**

  The categorical variable EASI-50 will be equal to 1 for percentage improvement from baseline in EASI score of 50% or greater and will be equal to 0 for percentage improvement of less than 50%. This definition is introduced for the purpose of identifying subjects who respond to the treatment (1 = responder, 0 = nonresponder).

- **Time to EASI-50**

  Time to EASI-50 is defined as the interval between the time of randomization and the time of achieving at least 50% improvement in EASI score.

- **Investigator's Global Assessment**

  The IGA score is based on a 5-point scale comparing evaluations at postbaseline visits to baseline photographs (0, clear; 1, almost clear; 2, mild disease; 3, moderate disease; 4, severe disease; 5, very severe disease).

- **Investigator's Global Assessment Responder**

  This categorical variable is defined to be equal to 1 (ie, responder) for a subject achieving an IGA score of 0 to 1 with an improvement of at least 2 from baseline and 0 (ie, nonresponder) otherwise.

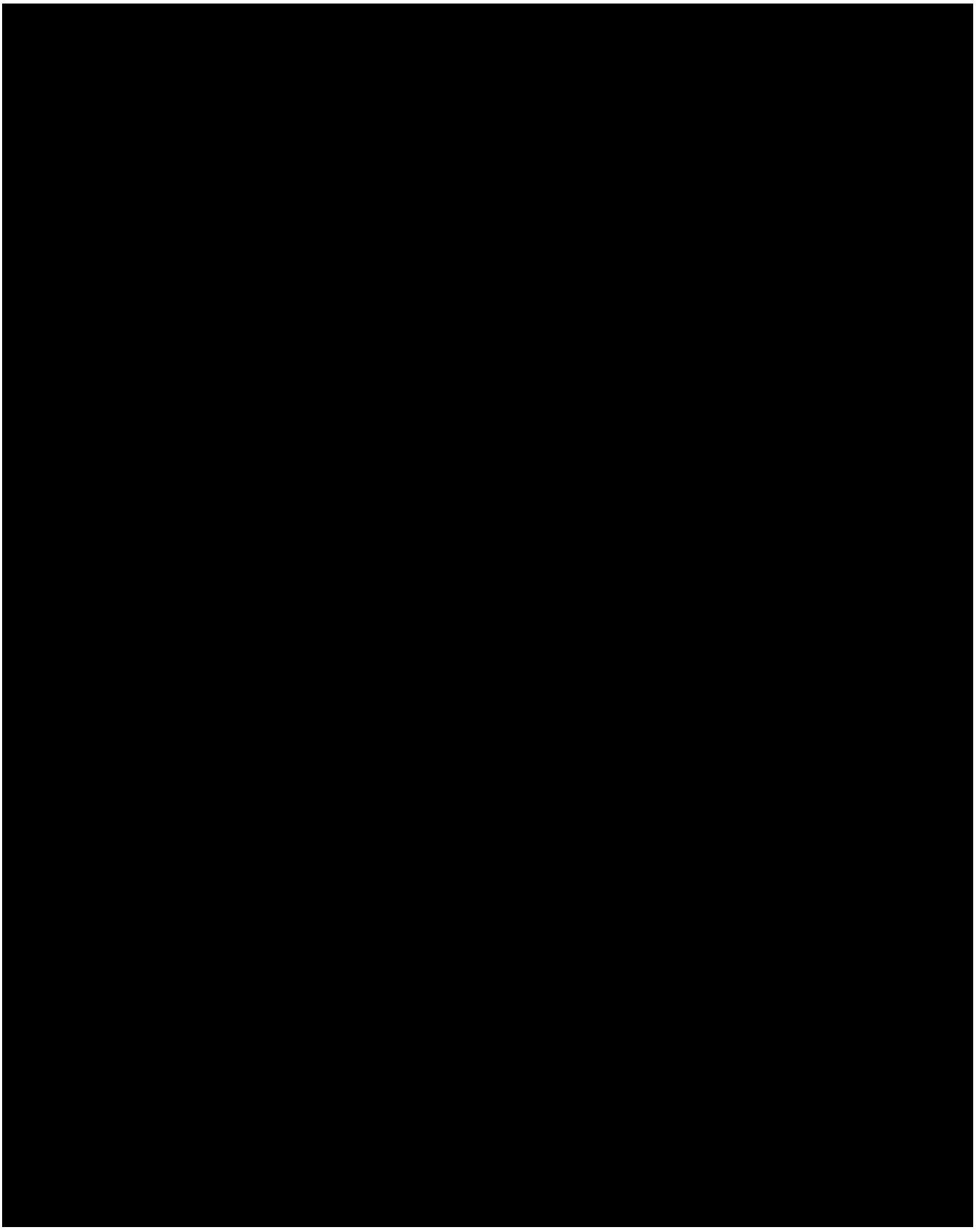
[redacted]

- **Itch Numerical Rating Scale Score**

  The Itch NRS is a once-per-24 hours ("daily") patient-reported measure of itch intensity assessed using an 11-point scale (0 = no itch to 10 = worst imaginable itch). Subjects will be asked to record their highest (worst) level of itch over the 24-hour recall period.

  The Itch NRS score for baseline and postbaseline visits will be determined by averaging the 7 daily NRS scores before the actual measurement date (inclusive) at the visit. If 4 or more daily scores are missing (out of the 7), the Itch NRS score at the visit will be set to missing.

  The categorical NRS is defined as 0 = None, 1 to 3 = Mild, 4 to 6 = Moderate, and 7 to 10 = Severe.



7.3. Analysis of the Primary Efficacy Parameter

7.3.1. Primary Efficacy Analysis

An MMRM will be fitted for the comparisons between INCB018424 1.5% BID and vehicle cream based on percentage change from baseline in EASI scores to Week 2 and Week 4. The MMRM will include the fixed effect of treatment (the 4 dose levels of INCB018424 cream, active control, and vehicle cream), the randomization stratification factor (baseline EASI score of ≤ 7 or > 7), the visit, and treatment by visit interaction. The variance-covariance matrix of the within-subject errors in MMRM will be modeled as unstructured.

A test for superiority between INCB018424 1.5% BID and vehicle cream will be performed using the least squares mean estimate of the percentage change from baseline in EASI at Week 4 from the MMRM specified above. Superiority will be established if the p-value of the difference (INCB018424 1.5% BID minus vehicle) is less than 0.05.

The MMRM implicitly adjusts for missing data through a variance-covariance structure.

7.3.2. Subgroup Analyses

Subgroups will be formed based on the following baseline variables for those subjects whose data are available:

- EASI score (0 to 7 and > 7 to 72);
- Baseline facial involvement (No/Yes)
- Serum IgE (> 200 kU/L, < 200 kU/L)

7.3.3. Sensitivity and Supportive Analyses for Primary Endpoint

A fixed-effect ANOVA model will also be performed for the comparisons between INCB018424 1.5% BID and vehicle cream based on percentage change from baseline in EASI scores to Week 4. Missing observations will be imputed by the last observations carrying forward in the ITT. The ANOVA model will include the fixed effects of treatment and randomization stratification factor.

The primary endpoint will be analyzed using the PP population as a sensitivity analysis to the ITT population in the DB period.

If the proportion of subjects with missing values for the primary endpoint is greater than 5% of the ITT population, extended models based on missing not at random assumption may be conducted for sensitivity analysis in ITT population.

7.4. Analysis of the Secondary [redacted] Efficacy Parameters

Secondary efficacy analyses will be conducted for the ITT population in the DB period.

7.4.1. Efficacy Analysis for Key Secondary Endpoints

The efficacy analysis for key secondary endpoints includes the 6 comparisons if the primary null hypothesis is rejected. Each comparison will be analyzed using a similar MMRM to that specified for the primary analysis. The graphical approach as specified in Figure 1 will be used to control the FWER.

Four tests for superiority of 1 of the INCB018424 doses to active control or vehicle cream will be performed using the least squares mean estimate of the percentage change from baseline in EASI at Week 4 from the MMRM model specified above. Superiority will be established if the p-value of the difference (INCB018424 minus the reference group, either active control or vehicle) is less than the alpha level determined by the graphical procedure.

For noninferiority, tests comparing each of 2 INCB018424 treatment groups (1.5% BID and 1.5% QD) to the active control group will be performed using the least squares mean estimate of the percentage change from baseline in EASI at Week 4. Noninferiority will be established if the lower limit of a 2-sided CI for the difference (INCB018424 minus active control) is higher than or equal to -10%. The level of the corresponding CI will be determined by the graphical procedure. In addition, a CI with the usual 95% level will be reported.

7.4.2. Efficacy Analysis for Other Secondary Endpoints

There will be no adjustment for multiple comparisons for secondary endpoints other than the key secondary endpoints.

Mean, change from baseline, and percentage change from baseline of EASI scores to Week 2, Week 4, and Week 8 may be analyzed with the similar MMRM for the primary endpoint. EASI scores at visits other than those covered by the primary and key secondary endpoints will be summarized by treatment and visit using descriptive statistics.

Categorical endpoints, including the percentage of subjects achieving EASI-50 and the percentage of IGA responders at postbaseline visits, will be summarized by treatment and visit using descriptive statistics and may be analyzed by logistic regression with stratification factor of randomization (ie, EASI ≤ 7 or > 7). All nonresponders in the DB period, as well as all subjects who discontinue study treatment at any time before the timepoint of interest, or discontinue from the study for any reason, will be defined as nonresponders for the NRI analysis.

An E_{max} model will be fit for assessment of the dose-response relationship on percentage change from baseline of EASI scores at Week 4, which will provide estimates of the maximum and minimum response levels; ED_{50} (the concentration where the response is the midpoint between the maximum and minimum); and the slope parameter. The 5 dose levels of INCB018424 cream in the model fitting will be vehicle, 0.15% QD, 0.5% QD, 1.5% QD, and 1.5% BID (equivalent to 3% QD).

The Kaplan-Meier product limit method will be used to estimate time to EASI-50. Treatment comparisons may be performed using the log-rank test stratified by randomization stratification factor, if applicable.

Daily Itch NRS scores will be summarized by treatment and visit using descriptive statistics as a continuous endpoint. Itch NRS scores for baseline and Weeks 2, 4, 8, 10, and 12 will be determined by averaging the daily NRS for the days from the start to the end of window as described in Section 7.2.2. In addition, daily NRS Itch scores, from Day -7 to Week 4 will be summarized by treatment group and presented graphically.

8. SAFETY AND TOLERABILITY

8.1. General Considerations

The analyses in this section will be provided for the safety population in the DB period and for the open-label evaluable population in the open-label period. Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few subjects. Unless otherwise stated, table summaries will be limited to AEs occurring within 30 days of the last application of study treatment or the first application in the open-label period (if available) of the study, whichever is earlier.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first application of study treatment. Adverse events will be considered treatment-emergent if they first occurred or worsened in severity after the first application of study treatment and on or before the date of the last visit of the period. Maximum severity from previous period(s) will be considered as the baseline severity for TEAEs.

Treatment-emergent AEs will be allocated to the study period (DB or open-label) according to the rules specified in Table 5.

Table 5: Allocation of Treatment-Emergent Adverse Events to Study Period

Study Period	Treatment Group	First Application Date	Last Visit	Identification of Maximum Severity
DB period	All groups	Date of first application	Date of last visit in DB period	Maximum severity from baseline
Open-label period	INCB018424 cream 1.5% BID	Date of first application in DB period	Date of last visit in open-label period	Maximum severity from baseline
	INCB018424 cream 1.5% QD 0.5% QD 0.15% QD Vehicle triamcinolone	Date of first application in the open-label period	Date of last visit in open-label period	Maximum severity from baseline and DB period

Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study treatment.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be described and graded using the NCI CTCAE v4.03. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

Adverse events will be tabulated by the MedDRA PT and SOC. A grading (severity) scale is provided for each AE term as follows: (1) mild, (2) moderate, (3) severe.

The subset of AEs considered by the investigator to be related to study treatment (INCB018424 cream, vehicle cream, or triamcinolone cream) will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study medication, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, SAEs will be tabulated.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing values will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment emergent.

8.2.2. Adverse Event Summaries

An overall summary of AEs by treatment group will include:

- Number (%) of subjects reporting any TEAEs
- Number (%) of subjects reporting any treatment-related TEAEs
- Number (%) of subjects reporting any SAEs
- Number (%) of subjects reporting any Grade 3 or 4 TEAEs
- Number (%) of subjects who temporarily interrupted study treatment because of TEAEs
- Number (%) of subjects who permanently discontinued study treatment because of TEAEs
- Number (%) of subjects who had a fatal TEAE

The following summaries will be produced by MedDRA term (if 2 or fewer subjects appear in a table, a listing may be appropriate):

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of TEAEs by SOC, PT, and maximum severity
- Summary of treatment-related AEs by SOC and PT
- Summary of treatment-related AEs by PT in decreasing order of frequency
- Summary of treatment-related AEs by SOC, PT, and maximum severity
- Summary of TEAEs leading to death by SOC and PT
- Summary of treatment-emergent SAEs by SOC and PT
- Summary of treatment-related SAEs by SOC and PT
- Summary of TEAEs leading to interruption of study treatment by SOC and PT
- Summary of TEAEs leading to discontinuation of study treatment by SOC and PT
- Summary of TEAEs requiring concomitant medications by SOC and PT
- Summary of treatment-emergent non-SAE by SOC and PT

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

All laboratory assessments will be performed using a central laboratory except for urine pregnancy tests (as applicable). Laboratory values and change from baseline values will be summarized descriptively by visit, and non-numeric test values will be tabulated when necessary.

The baseline value will be determined using the nonmissing values collected before the first application, prioritizing scheduled assessments for baseline identification over unscheduled visits. The last record before administration in the highest priority will be considered the baseline record. For baseline laboratory candidates with the same date and time in the same priority category, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

8.3.2. Laboratory Value Summaries

Clinical laboratory tests, including hematology and serum chemistry, will be performed at the Protocol-specified visits. If specific safety issues arise, additional unscheduled laboratory tests/analyses may be performed at the discretion of the investigator.

All test results and associated normal ranges from central laboratories will be reported in SI units. All tests with numeric values will have a unique unit per test. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units.

When there are multiple laboratory nonmissing values for a subject's particular test within a visit window, the laboratory value with the smallest laboratory sequence number will be used in by-visit summaries.

8.4. Vital Signs

Values at each scheduled visit, change, and percent change from baseline for vital signs, including SBP, DBP, pulse, respiration rate, and body temperature will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 6. The abnormal values for subjects exhibiting clinically notable vital sign abnormalities will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined range and percentage change greater than 25%. The abnormal values for subjects exhibiting alert vital sign abnormalities will be listed.

Table 6: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	Raw Value	Percent Change From Baseline
SBP	90-150 mmHg	± 25%
DBP	50-90 mmHg	± 25%
Pulse	45-100 beats/min	± 25%
Respiration rate	8-20 breaths/min	± 25%
Temperature	35.5°C-38.0°C	± 25%

9. INTERIM ANALYSES

An interim analysis will be conducted when at least half of the randomized subjects reach Week 4. The interim analysis will not include any testing for futility.

Sites will remain blinded to study treatment, but some Incyte personnel who do not have direct contact with the study sites will be unblinded. An internal committee at Incyte will be charged with evaluating the unblinded interim results based on both efficacy and safety analyses. Dose-response relationships may be examined using a dose-response curve and may provide information in planning Phase 3 studies. As there are no plans for stopping early for efficacy, no adjustments of alpha or final p-values for repeated testing are necessary.

For analysis of the primary endpoint, a cutoff for clinical data used in the interim analysis will be based on the earliest date that the first 150 subjects complete the Week 4 visit or discontinue the study. All visits occurring on or before this date for these 150 subjects will be included in the analysis.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 7.

Table 7: Statistical Analysis Plan Versions

SAP Version	Approval Date
Original	27 APR 2017

10.1. Changes to Protocol-Defined Analyses

Not applicable.

10.2. Changes to the Statistical Analysis Plan

Not applicable.

11. REFERENCES

Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014;371:130-139.

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009;28:586-604.

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol 2001;10:11-18.

Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. Br J Dermatol 2015;172:1353-1357.

APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings for the Clinical Study Report. Standard tables will follow the conventions in the Standard Safety Tables initial version. In-text tables are identical in structure and content as appendix tables, but follow a Rich Text Format.

The list of tables, figures, and the shells are to be used as a guideline. Modifications of the list or shells that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables for Double-Blind Period

Table No.	Title	Population	In-Text
Baseline Demographic and Characteristic			
1.1.1.1	Analysis Populations	All	
1.1.1.2	Summary of Subject Disposition	ITT	X
1.1.1.3	Summary of Number of Subjects Enrolled by Site		
1.1.2.1	Summary of Demographics	ITT	X
1.1.3.1	Summary of Baseline Characteristics	ITT	X
1.1.3.2	Summary of Medical History	ITT	
1.1.4.1	Summary of Prior Medications	ITT	
1.1.4.2	Summary of Prior Medications for Atopic Dermatitis	ITT	X
1.1.4.3	Summary of Concomitant Medications	ITT	
1.1.5.1	Summary of Drug Compliance	ITT	
Efficacy			
EASI			
2.1.1.1	Summary of EASI Score at Week 4 (Primary Endpoint)	ITT	X
2.1.1.2	Summary of EASI Score at Week 4	PP	X
2.1.1.3	Summary and Analysis of EASI Score by Visit from Baseline to Week 8	ITT	X
2.1.1.4	Summary and Analysis of EASI Score by Visit from Baseline to Week 8 by Baseline EASI Score ≤ 7 and > 7	ITT	X
2.1.1.5	Summary and Analysis of EASI Score by Visits from Baseline to Week 8 by Baseline Face Involvement	ITT	X
EASI Response			
2.1.2.1	Summary of Subjects Achieving ≥ 50%, ≥ 75%, and ≥ 90% Reduction in EASI Score by Visits from Baseline to Week 8	ITT	X
2.1.2.2	Summary of Subjects Achieving ≥ 50%, ≥ 75%, and ≥ 90% Reduction in EASI Score by Visits from Baseline to Week 8 by Baseline EASI Score ≤ 7 and > 7	ITT	
2.1.2.3	Summary of Subjects Achieving ≥ 50%, ≥ 75%, and ≥ 90% Reduction in EASI Score by Visits from Baseline to Week 8 by Baseline Face Involvement	ITT	

Table No.	Title	Population	In-Text
IGA			
2.1.3.1	Summary of IGA Responders by Visit from Baseline to Week 8	ITT	X
2.1.3.2	Summary of IGA Responders by Visit from Baseline to Week 8 by Baseline EASI Score ≤ 7 and > 7	ITT	
2.1.3.3	Summary of IGA Responders by Visit from Baseline to Week 8 by Baseline Face Involvement	ITT	
2.1.3.4	Shift Summary of IGA at Week 4	ITT	X
2.1.3.5	Summary of IGA Improvement from Baseline by Visit	ITT	
Itch NRS Score			
2.1.4.1	Summary of Itch NRS score by Visit from Baseline to Week 8	ITT	X
2.1.4.2	Summary of Categorical Itch NRS Score by Visit from Baseline to Week 8	ITT	
2.1.4.3	Shift Summary of Categorical NRS Score at Week 4	ITT	X
[redacted]			
Exposure, Adverse Events, Laboratory, and Vital Signs			
3.1.1.1	Summary of Study Drug Exposure	Safety	X
3.1.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety	X
3.1.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	
3.1.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.1.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	
3.1.2.6	Summary of Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	
3.1.2.7	Summary of Treatment-Related Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	
3.1.2.8	Summary of Treatment-Related Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	
3.1.2.10	Summary of Treatment-Emergent Adverse Events Leading to Death by MedDRA System Organ Class and Preferred Term	Safety	
3.1.2.11	Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.1.2.12	Summary of Non-Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	
3.1.2.13	Summary of Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	
3.1.2.14	Summary of Treatment-Emergent Adverse Events Leading to Interruption of Study Drug by MedDRA System Organ Class and Preferred Term	Safety	
3.1.2.15	Summary of Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term	Safety	

Table No.	Title	Population	In-Text
3.1.2.16	Summary of Treatment-Emergent Adverse Events Requiring Concomitant Medications by MedDRA System Organ Class and Preferred Term	Safety	
3.1.3.1	Summary of Laboratory Values - Hematology	Safety	
3.1.3.5	Summary of Laboratory Values - Chemistry	Safety	
3.1.4.1	Summary of Systolic Blood Pressure	Safety	
3.1.4.2	Summary of Diastolic Blood Pressure	Safety	
3.1.4.3	Summary of Pulse	Safety	
3.1.4.4	Summary of Body Temperature	Safety	
3.1.4.5	Summary of Respiration Rate	Safety	

Tables for Open-Label Period

Table No.	Title	Population	In-Text
Baseline Demographic and Characteristic			
1.2.1.2	Summary of Subject Disposition in Open-Label Period	Open-Label Evaluable	X
1.2.4.3	Summary of Concomitant Medications in Open-Label Period	Open-Label Evaluable	
1.2.5.1	Summary of Drug Compliance in Open-Label Period	Open-Label Evaluable	
Efficacy			
EASI			
2.2.1.3	Summary of EASI Score in Open-Label Period	Open-Label Evaluable	X
2.2.1.4	Summary of EASI Score by Baseline EASI Score ≤ 7 and > 7 in Open-Label Period	Open-Label Evaluable	
2.2.1.5	Summary of EASI Score by Baseline Face Involvement in Open-Label Period	Open-Label Evaluable	
EASI Response			
2.2.2.1	Summary of Subjects Achieving ≥ 50%, ≥ 75%, and ≥ 90% Reduction in EASI Score in Open-Label Period	Open-Label Evaluable	X
2.2.2.2	Summary of Subjects Achieving ≥ 50%, ≥ 75%, and ≥ 90% Reduction in EASI Score by Baseline EASI Score ≤ 7 and > 7 in Open-Label Period	Open-Label Evaluable	
2.2.2.3	Summary of Subjects Achieving ≥ 50%, ≥ 75%, and ≥ 90% Reduction in EASI Score by Baseline Face Involvement in Open-Label Period	Open-Label Evaluable	
IGA			
2.2.3.2	Summary of IGA Responders by Baseline EASI Score ≤ 7 and > 7 in Open-Label Period	Open-Label Evaluable	
2.2.3.3	Summary of IGA Responders by Baseline Face Involvement in Open-Label Period	Open-Label Evaluable	
2.2.3.5	Summary of IGA Improvement in Open-Label Period	Open-Label Evaluable	
Itch NRS			
2.2.4.1	Summary of Itch NRS in Open-Label Period	Open-Label Evaluable	X
2.2.4.2	Summary of Categorical Itch NRS in Open-Label Period	Open-Label Evaluable	X
[redacted]			

Table No.	Title	Population	In-Text
Exposure, Adverse Events, Laboratory, and Vital Signs			
3.2.1.1	Summary of Study Drug Exposure in Open-Label Period	Open-Label Evaluable	X
3.2.2.1	Overall Summary of Treatment-Emergent Adverse Events in Open-Label Period	Open-Label Evaluable	X
3.2.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Open-Label Period	Open-Label Evaluable	
3.2.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in Open-Label Period	Open-Label Evaluable	X
3.2.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity in Open-Label Period	Open-Label Evaluable	
3.2.2.6	Summary of Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term in Open-Label Period	Open-Label Evaluable	
3.2.2.7	Summary of Treatment-Related Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in Open-Label Period	Open-Label Evaluable	
3.2.2.8	Summary of Treatment-Related Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity in Open-Label Period	Open-Label Evaluable	
3.2.2.10	Summary of Treatment-Emergent Adverse Events Leading to Death by MedDRA System Organ Class and Preferred Term in Open-Label Period	Open-Label Evaluable	
3.2.2.11	Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term in Open-Label Period	Open-Label Evaluable	X
3.2.2.12	Summary of Non-Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Open-Label Period	Open-Label Evaluable	
3.2.2.13	Summary of Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term in Open-Label Period	Open-Label Evaluable	
3.2.2.14	Summary of Treatment-Emergent Adverse Events Leading to Interruption of Study Drug by MedDRA System Organ Class and Preferred Term in Open-Label Period	Open-Label Evaluable	
3.2.2.15	Summary of Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term in Open-Label Period	Open-Label Evaluable	
3.2.2.16	Summary of Treatment-Emergent Adverse Events Requiring Concomitant Medications by MedDRA System Organ Class and Preferred Term in Open-Label Period	Open-Label Evaluable	
3.2.3.1	Summary of Laboratory Values - Hematology in Open-Label Period	Open-Label Evaluable	
3.2.3.5	Summary of Laboratory Values - Chemistry in Open-Label Period	Open-Label Evaluable	
3.2.3.8	Shift Summary of Chemistry Values in CTC Grade - To the Worst Abnormal Value (Two-Directional CTC Grade) in Open-Label Period	Open-Label Evaluable	
3.2.4.1	Summary of Systolic Blood Pressure in Open-Label Period	Open-Label Evaluable	
3.2.4.2	Summary of Diastolic Blood Pressure in Open-Label Period	Open-Label Evaluable	
3.2.4.3	Summary of Pulse in Open-Label Period	Open-Label Evaluable	
3.2.4.4	Summary of Body Temperature in Open-Label Period	Open-Label Evaluable	
3.2.4.5	Summary of Respiration Rate in Open-Label Period	Open-Label Evaluable	

Figures

Figure No.	Title	Double-Blind Period	Open-Label Period
2.x.1.1	EASI Score by Visit and Treatment Group	x = 1 ITT	x = 2 Open-Label Evaluable
2.x.1.2	Mean Change From Baseline in EASI Score by Visit and Treatment Group	x = 1 ITT	x = 2 Open-Label Evaluable
2.x.1.3	Percentage Change From Baseline in EASI Score by Visit and Treatment Group	x = 1 ITT	x = 2 Open-Label Evaluable
2.1.1.4	EASI Score by Visit and Treatment Group	PP	
2.1.1.5	Mean Change From Baseline in EASI Score by Visit and Treatment Group	PP	
2.1.1.6	Percent Change From Baseline in EASI Score by Visit and Treatment Group	PP	
2.x.2.1	Proportion of Subjects with a ≥ 50% Reduction in EASI Score by Visit and Treatment Group	x = 1 ITT	x = 2 Open-Label Evaluable
2.x.2.2	Proportion of Subjects with a ≥ 75% Reduction in EASI Score by Visit and Treatment Group	x = 1 ITT	x = 2 Open-Label Evaluable
2.x.2.3	Proportion of Subjects with a ≥ 90% Reduction in EASI Score by Visit and Treatment Group	x = 1 ITT	x = 2 Open-Label Evaluable
2.1.2.4	Kaplan-Meier Curve of the Time to First ≥ 50% Improvement From Baseline in EASI Score	ITT	
2.1.2.5	Kaplan-Meier Curve of the Time to First ≥ 75% Improvement From Baseline in EASI Score	ITT	
2.1.2.6	Kaplan-Meier Curve of the Time to First ≥ 90% Improvement From Baseline in EASI Score	ITT	
2.x.3.1	Proportion of Subjects with IGA Response by Visit and Treatment Group	x = 1 ITT	x = 2 Open-Label Evaluable
[redacted]	[redacted]	[redacted]	
2.x.4.1	Itch NRS Score by Visit and Treatment Group	x = 1 ITT	x = 2 Open-Label Evaluable
2.x.4.2	Mean Change in Itch NRS Score by Visit and Treatment Group	x = 1 ITT	x = 2 Open-Label Evaluable
2.x.4.3	Mean Percent Change in Itch NRS Score by Visit and Treatment Group	x = 1 ITT	x = 2 Open-Label Evaluable

Listings

Listing No.	Title
Baseline Demographic and Characteristic	
1.1.1	Subject Enrollment and Disposition Status
1.1.2	Subject Inclusion and Exclusion Criteria
1.1.3	Protocol Deviations
1.2.1	Demographic
1.2.2	Baseline Characteristics
1.3	Medical History
1.4.1	Prior and Concomitant Medications
1.4.2	Prior and Concomitant Medications for Atopic Dermatitis
1.5	Study Drug Compliance

Listing No.	Title
Efficacy	
2.1.1	EASI Scores
2.1.2	Time to EASI-50
2.3.1	IGA Scores
[redacted]	[redacted]
2.4	Itch NRS
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Adverse Events (and Exposure)	
3.1	Study Drug Administration
3.2.1	Adverse Events
3.2.2	Adverse Events Leading to Discontinuation
3.2.3	Serious Adverse Events
3.2.4	Fatal Adverse Events
3.2.5	Treatment Related Adverse Events
3.2.6	Adverse Events Leading to Interruption of Drug
3.2.7	Adverse Events Requiring Concomitant Medications
Laboratory Data	
3.3.1	Clinical Laboratory Values - Hematology
3.3.2	Clinical Laboratory Values - Serum Chemistry
3.3.4	Abnormal Clinical Laboratory Values - Hematology
3.3.5	Abnormal Clinical Laboratory Values - Serum Chemistry
[redacted]	[redacted]
3.3.7	Central Laboratory Collection Times
Vital Signs	
3.4.1	Vital Signs
3.4.2	Abnormal Vital Sign Values
3.4.3	Alert Vital Sign Values

Signature Manifest

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