J2T-DM-KGAF SAP v.2

A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial to Evaluate the Efficacy and Safety of Lebrikizumab in Patients With Moderate-to-Severe Atopic Dermatitis

NCT03443024

Approval Date: 25-FEB-2019

STATISTICAL ANALYSIS PLAN

Protocol Number: DRM06-AD01

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial to Evaluate the Efficacy and Safety of Lebrikizumab in Patients with Moderate-to-Severe Atopic Dermatitis

Development Phase of Study: 2b

Sponsor: Dermira, Inc.
Sponsor Contact: PPD

Statistical Analysis Plan based on Protocol Version: Amendment 2 - 07 March 2018

Statistical Analysis Plan Date: 25FEB2019
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Revisions to the Statistical Analysis Plan described herein must be approved through a formal written amendment with the exception of minor editorial changes to tables, figures, or listing shells, and any necessary textual clarifications for programmers that do not affect the stated analysis variables, study endpoints, or statistical methods.

TABLE OF CONTENTS

Change History:

Version	Date	Summary of Changes	Author
1.0	14AUG2018	Original document	PPD
2.0	25FEB2019	Made administrative changes and corrected typos as needed. Updated Section 6.1 to add MedDRA and WHO dictionary versions. Added new Section Visit Windowing for ADIQ as 6.1.4. Updated Section 6.1.6 to note only missing data up to the Week 16 visit will be imputed. Updated Section 6.1.7.1 to add imputation method for sensitivity analysis adjusting for subjects that use a rescue medication. Updated Section 6.1.7.2 to add imputation method for sensitivity analysis adjusting for subjects that use a rescue medication. Updated Section 6.11 Prior and Concomitant Medications to include how to handle missing dates. Updated Section 6.12 Rescue Medications to define how rescue medications will be identified. Updated Section 6.13.1 to remove the overall test. Updated Section 6.13.2 to remove the overall tests. Updated 6.13.3 to account for observed and rescue medication sensitivity analyses. Updated Section 6.13.3.2 to remove part on rescue medications. Added Section 6.13.3.3 to add sensitivity analyses adjusting for subjects that use rescue medications. Updated Section 6.14 Other Supportive Efficacy Analyses to add by time point analyses Days 2	PPD

		through 7 for Sleep-Loss and Pruritus Numerical Rating Scales. Updated Section 6.14 Other Supportive Efficacy Analyses to remove the following endpoint: Frequency and percent distributions of the dichotomized Sleep-loss NRS will be summarized at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 and time points Days 2 through 7. Updated Section 6.15.1 Extent of Exposure to clarify the definitions of missed injections and expected number of injections. Updated Section 6.15.2 Anti-Drug Antibody (ADA) Data to include NAb analysis. Updated Section 6.15.4 Adverse Events for defining treatment-emergent AEs when the start date of the AE is missing.	

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	atopic dermatitis
ADA	anti-drug antibody
ADIQ	Atopic Dermatitis Impact Questionnaire
AE(s)	adverse event(s)
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BSA	body surface area
CMH	Cochran-Mantel-Haenszel
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
g/dL	grams per deciliter
HADS	Hospital Anxiety and Depression Scale
HR	heart rate
IGA	Investigator Global Assessment
IL	interleukin
IWRS	interactive web response system
LOCF	last observation carried forward
LSMean	least square mean
max	maximum
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
mg	milligram
min	minimum
n	number of observations
N	number of subjects (sample size)
NRI	non-response imputation
NRS	numerical rating scale
PK	pharmacokinetic
POEM	Patient Oriented Eczema Measure
PP	per-protocol
PT	preferred term
Q2W	every 2 weeks

Q4W	every 4 weeks
QST	QST Consultations, Ltd.
QTcB	Q-T interval corrected for heart rate using Bazett's formula
QTcF	Q-T interval corrected for heart rate using Fridericia's formula
SAE(s)	serious adverse event(s)
SAS®	Statistical Analysis System (SAS® Institute Inc., Cary, NC)
SD	standard deviation
SOC	system organ class
TEAE(s)	treatment-emergent adverse event(s)
WHO-DDE	World Health Organization Drug Dictionary Enhanced

2. INTRODUCTION

Atopic dermatitis (AD) is a relapsing and remitting inflammatory skin disorder that affects all age groups [1]. It is chronic, incurable, and is characterized by skin-barrier disruption and immune dysregulation (largely mediated by type-2 helper T cells) [1]. Clinically, AD is characterized by xerosis, erythematous crusted eruption (dermatosis), lichenification, an impaired skin barrier, and intense pruritus [2]. AD flares are frequently triggered by exposure to environmental factors, irritants, and allergens [3].

Lebrikizumab is a humanized monoclonal immunoglobulin G4 antibody with a mutation in the hinge region for increased stability. Lebrikizumab binds specifically to soluble human interleukin (IL)-13 with high affinity, and potently inhibits IL-13 signaling through the IL-4Rα/IL-13Rα1 complex. Because lebrikizumab binds to IL-13 in a non-receptor binding domain (i.e., a portion of the molecule not involved in binding to its receptor), antibody-bound IL-13 can still bind its receptor (IL-13 Rα1), but the receptor complex is not activated.

Study DRM06-AD01 is designed to evaluate multiple dose levels of lebrikizumab and to demonstrate the dose response of lebrikizumab in the treatment of moderate-to-severe AD. The effect of lebrikizumab will be assessed as a monotherapy (without concomitant topical corticosteroids). The dose levels tested—125 mg every 4 weeks (Q4W), 250 mg Q4W, and 250 mg every 2 weeks (Q2W)—were chosen to determine the optimal dose for treatment of moderate-to-severe AD. Loading doses of lebrikizumab will be used in the active-treatment groups to allow drug to reach steady state quickly (after the first dose in the Q4W dose groups, and after the second dose in the Q2W dose group).

3. STUDY OBJECTIVES

To evaluate the safety and efficacy of lebrikizumab compared with placebo in patients with moderate-to-severe AD.

To evaluate the dose-response of lebrikizumab in patients with moderate-to-severe AD.

4. STUDY DESIGN

4.1 Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group study. Approximately 275 patients with moderate-to-severe AD will be enrolled into this 32-week study.

Patients will be seen every 2 weeks and receive all study drug injections in the clinic. Patients will be evaluated for safety and efficacy through Week 16 on study. A safety follow-up visit will occur at Week 24 and a follow-up phone call will occur at Week 32.

Serum PK and anti-drug antibody (ADA) will be collected from all patients. PK samples will be collected at Baseline, Weeks 2, 4, 8, 12, 16, and 24. ADA samples will be collected at Baseline, Weeks 2, 4, 16, and 24.

Patients will be randomized 3:3:3:2 to one of 4 treatment groups, each described below.

Treatment Group 1: Lebrikizumab, 125 mg Q4W

Baseline: Loading dose of 250 mg (2 injections of 1 mL of 125 mg/mL drug product and 2 injections of 1-mL placebo)

Week 2: Four 1-mL injections of placebo

Weeks 4, 8, 12: 125 mg (one 1-mL injection of 125 mg/mL drug product and one 1-mL injection of placebo)

Weeks 6, 10, 14: Two 1-mL injections of placebo

Treatment Group 2: Lebrikizumab, 250 mg Q4W

Baseline: Loading dose of 500 mg (four 1-mL injections of 125 mg/mL drug product)

Week 2: Four 1-mL injections of placebo

Weeks 4, 8, 12: 250 mg (two 1-mL injections of 125 mg/mL drug product)

Weeks 6, 10, 14: Two 1-mL injections of placebo

Treatment Group 3: Lebrikizumab, 250 mg Q2W

Baseline and Week 2: Loading dose of 500 mg (four 1-mL injections of 125 mg/mL drug product)

Week 4, 6, 8, 10, 12, 14: 250 mg (two 1-mL injections of 125 mg/mL drug product)

Treatment Group 4: Placebo Q2W

Baseline and Week 2: Four 1-mL injections of placebo

Week 4, 6, 8, 10, 12, 14: Two 1-mL injections of placebo

4.1.1 Schedule of Visits and Assessments

The schedule of assessments can be found in Appendix 1 (Schedule of Visits and Procedures) of the protocol.

4.1.2 Method of Assigning Subjects to Treatment Groups

A randomization schedule will be generated by a member of the QST Consultations, Ltd. (QST) Statistical Services department who is not associated with the conduct or analysis of the study, using a validated system. The randomization list will not be stratified.

At the Baseline/Day 1 visit, qualified subjects will be randomized to treatment using an IWRS. The interactive web response system (IWRS) will assign a study drug kit number based on a predetermined randomization schedule. The kit number will be recorded in the electronic case report form. Approximately 225 subjects will be randomized to active treatment and approximately 50 subjects will be randomized to placebo treatment for a total of approximately 275 subjects. Subjects will be randomized to treatment groups in such a manner to balance treatment allocation in a 3:3:3:2 fashion (lebrikizumab, 125 mg Q4W: lebrikizumab, 250 mg Q4W: lebrikizumab, 250 mg Q2W: placebo Q2W).

4.1.3 Blinding

The Sponsor or designee, the Investigator, study-site personnel, and the patient will be blinded to treatment assignment. The integrity of the clinical study will be maintained by observing the treatment blind. If knowledge of a patient's treatment assignment is required for the patient's clinical care and/or safety, the Investigator will open the Code Breaking Card received with the study-drug kit. The Code-Breaking Card should be stored in a secure, locked location at the site. The Investigator should have access to the Code-Breaking Card at all times (e.g., 24/7). The Investigator should consult with the Sponsor's medical monitor prior to obtaining treatment assignment information. The Investigator must document (in the patient's medical record) the date and time the blind was broken, the names of the personnel involved, and the reason that treatment assignment information was required.

5. EFFICACY AND SAFETY ENDPOINTS

5.1 Efficacy Endpoints

For all efficacy evaluations the measurement endpoint is defined at Week 16.

5.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- The percent change in Eczema Area and Severity Index (EASI) from Baseline to Week 16.

5.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Proportion of patients with a 75% improvement from Baseline in EASI (EASI75) at Week 16.
- Proportion of patients with an Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) and a reduction ≥2 points from Baseline to Week 16.
- Proportion of patients with EASI <7 at Week 16.
- Proportion of patients achieving EASI50 and EASI90 at Week 16.
- Percent change in sleep-loss numerical rating scale (NRS) score from Baseline to Week 16.
- Percent change in pruritus NRS score from Baseline to Week 16.
- Proportion of patients with pruritus NRS change of ≥3 point improvement from Baseline to Week 16.
- Proportion of patients with pruritus NRS change of ≥4 point improvement from Baseline to Week 16.
- Absolute and percent change in Body Surface Area (BSA) involved with AD from Baseline to Week 16.
- Absolute and percent change in Atopic Dermatitis Impact Questionnaire (ADIQ) score from Baseline to Week 16.

5.2 Safety Endpoints

Safety will be assessed through adverse events (AEs), serum chemistry, hematology, urinalysis, and serology laboratory testing, electrocardiogram (ECG) testing, physical examination, vital signs, and pharmacokinetics (PK). The planned PK analysis will be included in a separate PK Analysis Plan.

6. STATISTICAL AND ANALYTICAL PLANS

6.1 General Methodology

All statistical processing will be performed using SAS® unless otherwise stated. No interim analyses are planned.

Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance. The inclusion of p-values in the efficacy analyses is to assist in characterizing the therapeutic efficacy of the active medication. No adjustments will be made for multiple comparisons for the efficacy analyses. The primary analysis will be performed when all patients have completed the treatment phase at Week 16. The final time-course data analysis will be performed when all patients have finished Week 32.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of patients in each category will be presented. The denominator for percentage will be based on the number of patients appropriate for the analysis. For continuous parameters, descriptive statistics will include the number of patients (n), mean, standard deviation (SD), median, and range. Appropriate inferential statistics will be used for the primary and secondary efficacy variables.

The primary method of handling missing efficacy data will be the method of Markov Chain Monte Carlo (MCMC) multiple imputation.

The primary analysis will be performed when all patients have completed the treatment phase at Week 16.

Reported AEs, medical history terms and prior and concomitant procedures and therapies will be classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology version 20.1. Prior and concomitant medications will be classified on the basis of World Health Organization Drug Dictionary Enhanced (WHO-DDE) terminology version March 2017.

6.1.1 Statistical Analysis

All analyses will be performed by QST using SAS® Version 9.3 or later. All summary tables and data listings will be prepared utilizing SAS® software.

The standard operating procedures of QST will be followed in the creation and quality control of all data displays and analyses.

6.1.2 Baseline Definition

Baseline is defined as the last non-missing assessment prior to first dose of study drug.

6.1.3 Visit Windowing

Efficacy data will be summarized based on nominal visit indications with the exception of data captured at early termination and unscheduled visits. Efficacy data from early termination and unscheduled visits will be summarized based on mapped visit values. The analysis windows for early termination and unscheduled visits are presented in the following table.

Analysis Windows for Efficacy Assessments

Scheduled Visit	Target Study Day	Window (Days)
Week 2	15	9 to 22
Week 4	29	23 to 36
Week 6	43	37 to 50
Week 8	57	51 to 64
Week 10	71	65 to 78
Week 12	85	79 to 92
Week 14	99	93 to 106
Week 16	113	107 to 127
Week 20	141	128 to 158
Week 24	169	159 to 197
Week 32	225	198 to 239

Efficacy data collected prior to study day 9 for early termination and unscheduled visits will not be analyzed, with the exception of those identified as baseline values. Efficacy data collected at early termination and unscheduled visits after study day 239 will not be included in analyses.

The definition for the study day included in each study window is defined below:

Study Day prior to Day 1 = Visit Date – Day 1 Date

Study Day on or after Day 1 = Visit Date – Day 1 Date + 1

If an assessment's mapped visit is a visit at which the subject has data from a scheduled visit present, or if no analyses are planned for the assessment at the mapped visit, the data collected at the early termination or unscheduled visit will not be included in analyses.

In the event of multiple values from unscheduled or early termination assessments within an analysis window, the value closest to the scheduled visit target study day will be used for analyses. If two values tie as closest to the time point (for example, one value is before and the other value is after the time point), then the later value will be selected.

Safety data will be summarized based on nominal visit indications. Data captured at early termination will be assigned an Analysis Window visit based on the "Analysis Windows for Efficacy Assessments" above. Unscheduled visits will not be summarized.

Data collected at all visits will be included in the data listings with visit presented as reported by the site, except for subject reported electronic diary data. Subject reported electronic diary data listings will be presented with analysis visit, since there is no site reported visit.

6.1.4 Visit Windowing for ADIQ

ADIQ is recorded by the subjects using an electronic diary with the date of entry recorded. Since ADIQ is not captured at the clinic for a specific visit the ADIQ diary data will be windowed into the appropriate study visit for analysis as outlined below.

Baseline ADIQ

The baseline ADIQ will be identified using the definition in Section 6.1.2 Baseline Definition.

Post-baseline ADIQ

First, an ADIQ recorded on the same day as a study visit will be mapped to that study visit and flagged for analysis if occurring at a scheduled study visit. If a visit ranges over multiple days the start date of the visit will be used for mapping. Note, unscheduled and early termination visits will be mapped to planned study visits using Section 6.1.3 Visit Windowing prior to this step. All remaining ADIQ will be mapped using the analysis windows presented in the following table.

Analysis Windows

Scheduled Visit	Target Study Day	Window (Days)
Week 2	15	9 to 22
Week 4	29	23 to 36
Week 6	43	37 to 50
Week 8	57	51 to 64
Week 10	71	65 to 78
Week 12	85	79 to 92
Week 14	99	93 to 106
Week 16	113	107 to 127
Week 20	141	128 to 158
Week 24	169	159 to 197
Week 32	225	198 to 239
Note: Only visits up through week 16 will be flagged for ADIQ analysis.		

If multiple ADIQ are mapped to the same analysis visit selecting an ADIQ to be flagged for analysis will follow the following steps.

1) If the subject had the corresponding visit, the ADIQ closest to the actual visit day will be flagged. If two ADIQ are equidistant to the actual visit day the ADIQ prior to the planned study day will be flagged.

If the subject missed the corresponding visit, the ADIQ closest to the actual planned study day will be flagged. If two ADIQ are equidistant to the planned study day the ADIQ prior to the planned study day will be flagged.

6.1.5 Adjustments for Covariates

Baseline EASI will be a covariate for the primary efficacy endpoint for EASI. Baseline sleep-loss NRS will be a covariate for the secondary efficacy endpoint for sleep-loss NRS. Baseline pruritus NRS will be a covariate for the secondary efficacy endpoint for pruritus NRS. Baseline BSA involved with AD will be a covariate for the secondary efficacy endpoint for BSA involved with AD. Baseline ADIQ score will be a covariate for the secondary efficacy endpoint for ADIQ score. No other covariates are planned to be used in the analyses for this study.

6.1.6 Handling of Dropouts or Missing Data

Missing 16 week efficacy data will be imputed and subsequently analyzed. The primary method of handling missing efficacy data will be the method of MCMC multiple imputation which does not rely on the assumption of data missing at random. Additionally, the pattern of missing observations in each treatment group will not influence the missing value estimation in the other because the imputation will be conducted independently for each treatment group. The mITT population analyses and summaries on EASI and IGA will use the MCMC multiple imputation method to impute missing values up to the Week 16 visit. Missing data for Post-Week 16 visits will not be imputed.

The multiple imputation process for imputing missing EASI and IGA data and subsequent analysis will involve 4 distinct phases with these principal tasks:

1. Calculate the number of missing 16 week values for each treatment group to be estimated by MCMC. Let nmiss be the maximum number of missing among the two treatment groups.
2. Create a data set of subjects, one for each treatment group, with observed values and those needing estimation by MCMC. The missing values in each data set will be filled in using the MCMC method ‘5 x nmiss’ times to generate ‘5 x nmiss’ data sets. The resulting data sets for each treatment arm will be combined into one complete data set for each imputation.
3. For each complete data set, compute the necessary derived variables. Each complete data set will be analyzed with the appropriate analysis model. See Sections 6.1.5.1.1 and 6.1.5.1.2 for details.

Analyses using the Cochran-Mantel-Haenszel (CMH) statistics will be normalized using the Wilson-Hilferty transformation [4] prior to combining them using SAS® PROC MIANALYZE.

The results from these analyses will be combined into a single inference using SAS® PROC MIANALYZE.

Per-protocol population analyses and summaries on EASI and IGA will use the last observation carried forward (LOCF) imputation method to impute missing values up to the Week 16 visit. Missing data for Post-Week 16 visits will not be imputed.

Sensitivity analyses on some of the secondary efficacy variables will use non-response imputation (NRI) to impute missing values.

6.1.6.1 MCMC Multiple Imputation

6.1.6.1.1 EASI Missing Data Imputation

A total of 4 random seeds will be needed to use PROC MCMC to impute the EASI score for the four treatment groups. Those 4 random seeds have been pre-specified by using a random number generator:

- Lebrikizumab, 125 mg Q4W: seed = 1083679005
- Lebrikizumab, 250 mg Q4W: seed = 1346533179
- Lebrikizumab, 250 mg Q2W: seed = 297484487
- Placebo Q2W: seed = 424603513

For binary responses related to EASI, the binary response variables will be calculated based on the multiply imputed datasets that have been created.

6.1.6.1.2 IGA Missing Data Imputation

A total of 4 random seeds will be needed to impute IGA for the four treatment groups. Those 4 random seeds have been pre-specified by using a random number generator:

- Lebrikizumab, 125 mg Q4W: seed = 1975600090
- Lebrikizumab, 250 mg Q4W: seed = 1260832817
- Lebrikizumab, 250 mg Q2W: seed = 2036512379
- Placebo Q2W: seed = 202520365

For binary responses related to IGA, the binary response variables will be calculated based on the multiply imputed datasets that have been created. Because the MCMC algorithm is based on the multivariate normal model, imputed values for IGA will not generally be one of the discrete values used in IGA scoring (0, 1, 2, 3, or 4). Therefore, to derive the binary IGA response variable, standard rounding rules will be applied to the imputed values. For example, if a patient has an IGA score imputed as 1.4 (and assuming a Baseline IGA score of 3), the imputed value

would be rounded down to 1, and the minimum change from Baseline of 2 would have been met. This patient would be considered a responder.

After imputing with PROC MCMC, the dichotomous success rate (clear or almost clear with at least a 2-point change from Baseline) will be computed. Each complete data set will be analyzed with a CMH and a logistic regression with a factor of treatment group. The results from these analyses will be combined using SAS® PROC MIANALYZE.

6.1.7 Non-Responder Imputation

6.1.7.1 EASI Missing Data Imputation

The sensitivity analysis for the secondary dichotomized EASI score success will use NRI to impute missing values. Specifically, any patient with a missing EASI75 value at Week 16 will be treated as a non-responder for analysis purposes.

The sensitivity analysis adjusting for patients with Rescue Medication use for the dichotomized EASI score success will use NRI to impute missing values. Specifically, any patient with Rescue Medication use (defined in Section 6.12) or discontinued treatment before the Week 16 study drug administration will be treated as a non-responder. Other missing values before Week 16 will use the LOCF method. Subjects that completed treatment, but have a missing dichotomized EASI score success will use the LOCF method.

6.1.7.2 IGA Missing Data Imputation

The sensitivity analysis for the dichotomized IGA success will use NRI to impute missing values. Specifically, any patient with a missing IGA value at Week 16 will be treated as a non-responder for analysis purposes.

The sensitivity analysis adjusting for patients with Rescue Medication use for the dichotomized IGA success will use NRI to impute missing values. Specifically, any patient with Rescue Medication use (defined in Section 6.12) or discontinued treatment before the Week 16 study drug administration will be treated as a non-responder. Other missing values before Week 16 will use the LOCF method. Subjects that completed treatment, but have a missing dichotomized IGA success will use the LOCF method.

6.2 Interim Analyses and Data Monitoring

No interim analysis or data monitoring is planned for this study.

6.3 Multicenter Studies

The study will be conducted at multiple study centers in the United States. Pooling of investigational sites will not be performed for the results for analysis.

6.4 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity will be made.

6.5 Use of an Efficacy Subset of Subjects

Subjects randomized to study drug who received at least one dose of study medication and completed the Week 16 evaluation without any significant protocol violations will form the Per Protocol (PP) Population. The major protocol deviations will be defined at the time of evaluability evaluation, the time between the database soft lock and hard lock before unblinding.

Excluding subjects who have major protocol deviations will decrease the variability in treatment response and will allow for a better determination of dose-response relationship of study drug.

6.6 Examination of Subgroups

Not applicable to this study.

6.7 Disposition of Subjects

The number of subjects included in each analysis population (randomized, modified intent-to-treat [mITT], safety, and PP) will be summarized by treatment group and by overall. The number of subjects completed and discontinued (including the primary reason for discontinuation) will be summarized for each treatment group and by overall. Additionally, the number of subjects that discontinued study at or prior to Week 16 will be summarized for each treatment group and by overall.

Subjects who are excluded from an analysis population will be summarized by the reasons for exclusion. Reasons subjects were not randomized will be summarized for subjects who did not enroll in the study.

6.8 Protocol Deviations

Protocol deviations will not be entered into the database. Only deviations leading to exclusion from analysis populations will be identified and summarized.

6.9 Data Sets Analyzed

Subjects will be presented/summarized based on the reason(s) for exclusion.

6.9.1 Randomized Population

All subjects who are randomized to study treatment will be included in the randomized population and will be analyzed according to the treatment group they were randomized.

Listings and summaries will be provided for all randomized subjects. Listing will also include screen failure subjects.

6.9.2 Modified Intent-to-Treat Population

All subjects in the randomized population who received least one dose of study drug will be included in the mITT population and analyzed according to the treatment group they were randomized. All efficacy analyses will be presented using the mITT population.

6.9.3 Safety Population

All subjects who were randomized and had at least one dose of study drug will be included in the safety population and analyzed according to the treatment group they received. All safety analyses will be performed using the safety population.

6.9.4 Per-Protocol Population

All subjects in the safety population who complete the Week 16 evaluation without any significant protocol violations will be included in the PP population and analyzed according to the treatment group they received. The PP population will include subjects in the safety population who do not meet any of the following criteria:

- Violated the inclusion/exclusion criteria;
- Have taken any interfering concomitant medication;
- Did not attend the Week 16 visit;
- Missed more than 1 post-baseline study visit prior to Week 16;
- Did not receive at least 75% of the expected injections of study drug during participation in the study;
- Out of visit window at the Week 16 visit by ±3 days;

Subjects who discontinue from the study due to an AE related to study treatment will be included in the PP population. Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

All efficacy analyses will be performed on the PP population.

6.9.5 Pharmacokinetic Population

All PK analyses will be performed using the PK population. All subjects who are enrolled and have a pre-dose sample and at least one post-dose analyzable sample will be included in the PK population.

6.10 Demographic and Other Baseline Characteristics

All demographic and baseline summaries will be done on the mITT, PP, safety, and PK populations.

Sex, race, and ethnicity will be summarized by counts and percentages. Age, height (cm), weight (kg), and BMI (kg/m^2) will be summarized with descriptive statistics (n, mean, SD, median, min, and max).

EASI, BSA, ADIQ, Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), and Hospital Anxiety and Depression Scale (HADS) will be summarized with descriptive statistics (n, mean, SD, median, min, and max). IGA, Pruritus NRS, Sleep-loss NRS will be summarized by counts and percentages.

AD history, including number of years since onset, anatomical areas affected and prior AD treatments, will be summarized by counts and percentages. If only the year is known for start of AD the number of years since onset will be calculated by using January for month and "01" as day. If only the year and month are known for start of AD then onset will be calculated by using "01" as day.

Medical histories will be coded using the MedDRA dictionary and presented in a by-subject listing.

6.11 Prior and Concomitant Medications

Concomitant medications will be coded to preferred name and Anatomical Therapeutic Chemical (ATC) classification of ingredients using the WHO-DDE.

Counts and percentages will be provided to summarize the use of medications other than the study drug reported throughout the study. The number and percent of subjects who took other therapy will be shown by ATC level 2 term and preferred name. Medications which start prior to first dose will be considered prior medications. Ongoing medications and medications ending after the date of first dose will be considered concomitant medications. Medications that start on the date of first dose will be considered concomitant medications. Medications that end on the date of first dose will be considered prior medications. Medications which are both prior and concomitant will be included in both summaries. Incomplete or missing start and end dates which could be either prior to first dose or after first dose will be considered prior to first dose.

A by-subject listing of all prior and concomitant medications will be presented.

6.12 Rescue Medications

Corticosteroids for Systemic Use (ATC Level 2: CORTICOSTEROIDS FOR SYSTEMIC USE) or Topical Corticosteroids (ATC Level 2: CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS for Route=Topical and an atopic dermatitis indication) that were started after

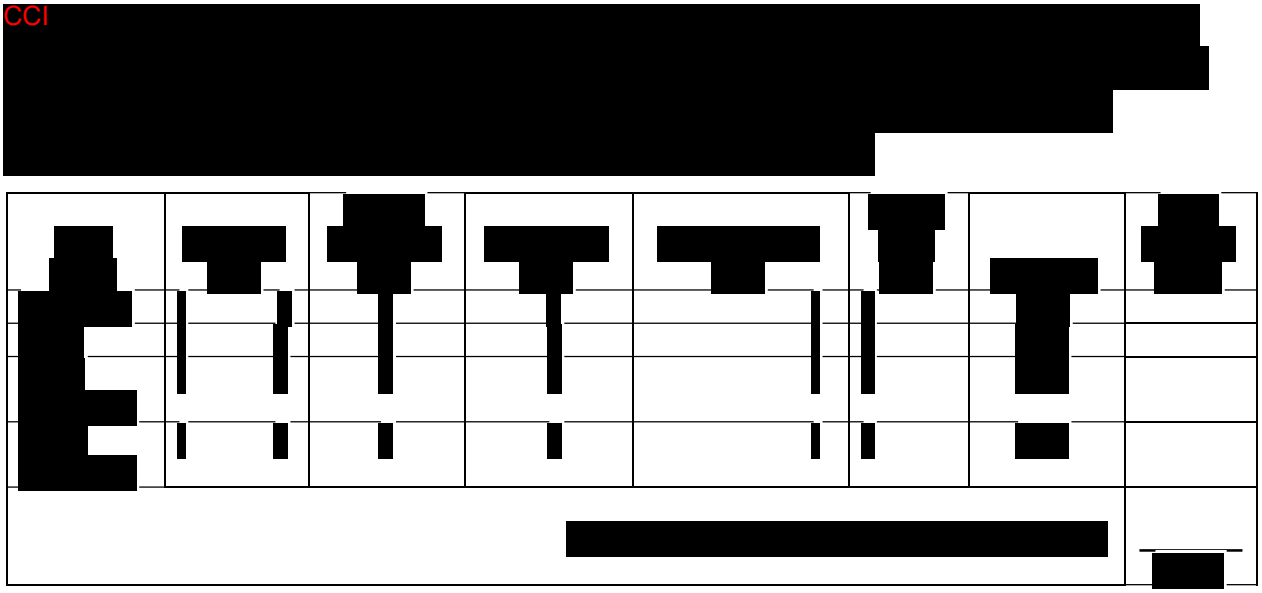
the first study drug administration and prior to Week 16 are considered Rescue Medications. Incomplete or missing start dates which could be either prior to Week 16 or after Week 16 will be considered prior to Week 16.

Counts and percentages will be provided to summarize the use of rescue medications reported throughout the study. The number and percent of subjects who took rescue medications will be shown by ATC level 2 term and preferred name.

A by-subject listing of all rescue medications will be presented.

6.13 Analysis of Efficacy

6.13.1 Primary Efficacy Analysis



Percent change from baseline to Week 16 in EASI score will be analyzed using an analysis of covariance (ANCOVA) with factor of treatment and the Baseline EASI score as a covariate. The least squares means (LSMean) will be presented along with the observed means. Pairwise comparisons will be performed of active treatments to placebo from contrasts in the overall model.

The primary efficacy analysis will be presented on both the mITT and PP populations.

6.13.2 Secondary Efficacy Analysis

The proportion of subjects who are dichotomized to success (75% improvement from baseline in EASI [EASI75]) at Week 16 will be analyzed using a CMH tests. Pairwise comparisons will be performed of each active treatment group to placebo.

The proportion of subjects who are dichotomized to success (minimum 2-grade improvement from baseline in IGA and an IGA score of 0 [clear] or 1 [almost clear]) at Week 16 will be

analyzed using a CMH tests. Pairwise comparisons will be performed of each active treatment group to placebo.

The proportion of subjects who are dichotomized to success (EASI less than 7) at Week 16 will be analyzed using a CMH tests. Pairwise comparisons will be performed of each active treatment group to placebo.

The proportion of subjects who are dichotomized to success (50% improvement from baseline in EASI [EASI50]) at Week 16 will be analyzed using a CMH tests. Pairwise comparisons will be performed of each active treatment group to placebo.

The proportion of subjects who are dichotomized to success (90% improvement from baseline in EASI [EASI90]) at Week 16 will be analyzed using a CMH tests. Pairwise comparisons will be performed of each active treatment group to placebo.

Absolute and Percent change from baseline to Week 16 in sleep-loss NRS will be analyzed using the same ANCOVA method described for the primary endpoint.

Absolute and Percent change from baseline to Week 16 in pruritus NRS will be analyzed using the same ANCOVA method described for the primary endpoint.

The proportion of subjects who are dichotomized to success (pruritus NRS greater than or equal to 3 point improvement) at Week 16 will be analyzed using a CMH tests. Pairwise comparisons will be performed of each active treatment group to placebo.

The proportion of subjects who are dichotomized to success (pruritus NRS greater than or equal to 4 point improvement) at Week 16 will be analyzed using a CMH tests. Pairwise comparisons will be performed of each active treatment group to placebo.

Absolute and percent change from baseline to Week 16 in body surface area (BSA) will be analyzed using the same ANCOVA method described for the primary endpoint.

Absolute and percent change from baseline to Week 16 in ADIQ score will be analyzed using the same ANCOVA method described for the primary endpoint. The ADIQ score is calculated by summing the score of each of the 14 questions resulting in a maximum of 56 and a minimum of 0.

The secondary efficacy analysis will be presented on both the mITT and PP populations.

6.13.3 Sensitivity Efficacy Analysis

The sensitivity efficacy analysis will be presented on both the mITT and PP populations, except for sensitivity on observed data and sensitivity adjusting for subjects that use a rescue medication which will only be presented with the mITT population.

6.13.3.1 Sensitivity Using Non-Response Imputation

Sensitivity analyses will use NRI to impute missing values. The secondary endpoints of IGA and EASI75 at Week 16 will be analyzed using the same method as their corresponding secondary endpoint.

6.13.3.2 Repeated Measures Analyses on Observed Data

The second set of sensitivity analyses will be performed on observed data. The primary endpoint of percent change from baseline in EASI score at Week 16 will be analyzed with a repeated measures ANCOVA, with treatment, visit (Weeks 4, 8, 12, and 16), and treatment by visit interaction as factors, and a covariate of baseline EASI score.

The two dichotomized secondary endpoints of IGA and EASI75 at Week 16 will each be analyzed with a repeated measures logistic regression model (generalized estimating equations), with the dichotomized endpoint as the dependent variable and treatment, visit (Weeks 4, 8, 12, and 16), and treatment by visit interaction as factors.

6.13.3.3 Repeated Measures Analyses Adjusting for Rescue Medications

Sensitivity analyses adjusting for rescue medications will use NRI and LOCF to impute missing values (defined in Sections 6.1.7.1 and 6.1.7.2). The secondary endpoints of IGA and EASI75 at Week 16 will be analyzed using the same method as their corresponding repeated measures analyses on observed data.

6.14 Other Supportive Efficacy Analyses

Descriptive statistics will be presented for the following parameters by treatment group for both the mITT and PP populations:

- Descriptive statistics will be used to summarize EASI at each evaluation from Baseline through Week 24.
- Descriptive statistics will be used to summarize the absolute and percent change in EASI will be summarized at Weeks 4, 8, 12, 16, 20, and 24.
- Frequency and percent distributions of the dichotomized EASI score will be summarized at Weeks 4, 8, 12, 16, 20, and 24.
- Frequency and percent distributions of the IGA score will be summarized at each evaluation from Baseline through Week 24.
- Frequency and percent distributions of the dichotomized IGA scores will be summarized at Weeks 4, 8, 12, 16, 20, and 24.

- Descriptive statistics will be used to summarize Sleep-loss NRS will be summarized at each visit from Baseline through Week 16 and time points Days 2 through 7. Baseline (Day 1) – Day 7 are nominal study days from the date of first study drug injection (Day 1).
- Descriptive statistics will be used to summarize absolute and percent change in Sleep-loss NRS will be summarized at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 and time points Days 2 through 7. Baseline (Day 1) – Day 7 are nominal study days from the date of first study drug injection (Day 1).
- Descriptive statistics will be used to summarize Pruritus NRS will be summarized at each visit from Baseline through Week 16 and time points Days 2 through 7. Baseline (Day 1) – Day 7 are nominal study days from the date of first study drug injection (Day 1).
- Descriptive statistics will be used to summarize absolute and percent change in Pruritus NRS will be summarized at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 and time points Days 2 through 7. Baseline (Day 1) – Day 7 are nominal study days from the date of first study drug injection (Day 1).
- Frequency and percent distributions of the dichotomized Pruritus NRS will be summarized at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 and time points Days 2 through 7. Baseline (Day 1) – Day 7 are nominal study days from the date of first study drug injection (Day 1).
- Descriptive statistics will be used to summarize BSA will be summarized at each evaluation from Baseline through Week 24.
- Descriptive statistics will be used to summarize absolute and percent change in BSA will be summarized at Weeks 4, 8, 12, 16, and 24.
- Descriptive statistics will be used to summarize ADIQ score will be summarized at each visit from Baseline through Week 16.
- Descriptive statistics will be used to summarize absolute and percent change in ADIQ score will be summarized at Weeks 2, 4, 6, 8, 10, 12, 14, and 16.
- Descriptive statistics will be used to summarize POEM score at Baseline, Week 16, and change from baseline at Week 16. The POEM score is calculated by summing the score of each question resulting in a maximum of 28 and a minimum of 0.

  The scoring of each question is as follows:

No days	Scored 0
1-2 days	Scored 1
3-4 days	Scored 2
5-6 days	Scored 3

Every day	Scored 4

The percentage of patients with POEM Score Change from Baseline >=4 (Clinically Meaningful Difference) will be summarized for Week 16.

- Descriptive statistics will be used to summarize DLQI score at Baseline, Week 8, Week 16, and change from baseline at Weeks 8 and 16. Frequency and percent distributions of the dichotomized DLQI score to success (achieving total DLQI score of 0 or 1 – "No effect at all on patient's life") will be summarized at Weeks 8 and 16. The DLQI score is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0.

  The scoring of each question is as follows:

Very much	Scored 3
A lot	Scored 2
A little	Scored 1
Not at all	Scored 0
Not relevant	Scored 0
Question 7, 'prevented work or studying'	Scored 3

  The percentage of patients with DLQI Score Change from Baseline >=4 (Clinically Meaningful Difference) will be summarized for Weeks 8 and 16.

- Descriptive statistics will be used to summarize HADS depression and anxiety scores will be summarized at each visit from Baseline, Week 8, Week 16, and change from baseline at Weeks 8 and 16. The HADS depression and anxiety scores are calculated as the sum of each corresponding depression and anxiety question. Frequency and percent distributions of the HADS depression and anxiety scores at Weeks 8 and 16 using the following score ranges:

  0-7 = Normal

  8-10 = Borderline abnormal

  11-21 = Abnormal

- Frequency and percent distributions of the Global Assessment of Change–AD will be summarized at Week 16.

- Descriptive statistics will be used to summarize the Global Assessment of Change–AD at Week 16.

6.15 Safety Evaluation

Safety analyses will be conducted on the safety population. No imputation will be made for missing safety data.

6.15.1 Extent of Exposure

The extent of exposure to study drug in each treatment group will be summarized by total number of days of exposure, total number of injections, number of missed injections, and number and percentage of subjects who are compliant. A subject will be considered compliant with the dosing regimen if the subject had at least 75% of the expected number of injections while enrolled in the study.

Missed injections are defined as the total number of missed or interrupted injections. If the subject discontinues the study early missed injections will also include any injections that should have been administered prior to the subject's date of treatment discontinuation.

Days of exposure = Date of last study injection – Date of first study injection + 1

The total number of injections taken is as follows:

The total number of recorded injections from the first injection until last injection.

The total number of injections expected is as follows:

- If completed/discontinued after at or after week 4 then:

  8 + 2*(Last Study Visit Number Where Study Drug is Planned to be Administered – 3).

- If discontinued prior to week 4 then:

  4*(Last Study Visit Number Where Study Drug is Planned to be Administered – 1).

The last study visit number where study drug is planned to be administered is as follows:

- If the date of treatment completion/discontinuation is on the same day as an actual subject visit or within window of a planned subject visit the last planned study visit is the visit prior. Otherwise, if the date of treatment completion/discontinuation is between visits windows, the visit prior to the study day of the date of treatment completion/discontinuation will be the last planned study visit.

Example 1: For a subject that completes treatment through Week 14 (Visit 9) the total number of expected injections would be 8 + 2*(9 - 3) = 20 injections.

Example 2: For a subject that discontinues between Week 8 (Visit 6) and Week 10 (Visit 7) the total number of expected injections would be 8 + 2*(6 - 3) = 14 injections.

Example 3: For a subject that discontinues between Week 2 (Visit 3) and Week 4 (Visit 4) and the date of discontinuation is prior to the minimum of the visit window for week 4 then the total number of expected injections would be 4*(3 - 1) = 8 injections.

Compliance will be calculated as a percentage as 100 times the total number of injections taken divided by the total number of injections expected.

6.15.2 Anti-Drug Antibody (ADA) and NAb Data

ADA and NAb results will be summarized with descriptive statistics at Baseline, Weeks 2, 4, 16, and 24.

6.15.3 Pharmacokinetic Data

Plasma concentration data will be tabulated and summarized (n, n_{quant}, geometric mean, arithmetic mean, minimum, maximum, SD, and % coefficient of variation) by treatment group at Baseline, Weeks 2, 4, 8, 12, 16, and 24. Additionally the plasma concentrations will displayed graphically on linear and semi-logarithmic scales by treatment group and by subject.

6.15.4 Adverse Events

All AEs that occur during the study will be recorded and classified on the basis of MedDRA terminology. Treatment-emergent AEs (TEAEs) are defined as AEs with an onset on or after the date of the first study drug injection. If the start date for an adverse event is a partial date or missing and it cannot be determined as prior to or on/after first dose then the AE will be considered treatment-emergent. AE(s) noted prior to the first study drug administration that worsen after baseline will also be reported as AEs and included in the summaries.

Treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting a TEAE, system organ class (SOC), preferred term (PT), severity, relationship to study drug (causality), and seriousness. When summarizing AEs by severity and relationship, each subject will be counted once within a SOC or a PT by using the event with the highest severity and greatest relationship within each classification.

No statistical inference between treatments will be performed on AE(s).

Listings will be presented for all AE(s) as well as for serious AE(s), and AE(s) leading to discontinuation from the study.

6.15.5 Clinical Laboratory Evaluation

Hematology, chemistry, urinalysis, and serology laboratory test results will be summarized with descriptive statistics at Baseline, Weeks 4, 8, 12, 16, and 24. Additionally for hematology, chemistry, and numeric urinalysis shifts from Baseline to Weeks 4, 8, 12, 16, and 24 in laboratory test results based on normal ranges will be summarized with frequency counts and percentages. Individual laboratory test results will be presented in a by-subject listing.

Laboratory values will be assigned a Severity Grade based on the Rheumatology Common Toxicity Criteria v2.0 [5]. Laboratory values with Severity Grade of 3 or 4 will be summarized at Baseline, Weeks 4, 8, 12, 16, and 24 with frequency counts and percentages. The Severity Grade of 3 or 4 will be included in by-subject listing.

6.15.6 Other Observations Related to Safety

6.15.6.1 ECG Measurements

Descriptive statistics by treatment group and visit will be provided for the following ECG parameters: heart rate (HR), PR duration, RR duration, QRS duration, QT duration, QT interval corrected for heart rate using Bazett's formula (QTcB), and QT interval corrected for heart rate using Fridericia's formula (QTcF). Change from Baseline in ECG abnormalities will be summarized using shift tables at the Week 16 visit. Shift tables will be based on the following categories:

- PR Interval: < 100 msec, 100 – 220 msec, and > 220 msec;
- QRS Interval: < 50 msec, 50 – 110 msec, and > 110 msec;
- QTcF Interval: < 450 msec, 450 – 500 msec, and > 500 msec.

The following treatment-emergent ECG abnormalities will be summarized for subjects in the safety population with at least one post-application ECG:

- PR Interval
- > 220 msec;
- > 220 msec and Change from Baseline > 25%;
- QRS Interval
- > 110 msec;
- > 110 msec and Change from Baseline > 25%;
- QTcF Interval
- > 450 – 480 msec;
- > 480 – 500 msec;
- > 500 msec;
- Change from Baseline > 30 - 60 msec;
- Change from Baseline > 60 msec;
- > 450 - 480 msec and Change from Baseline > 30 - 60 msec;
- > 450 - 480 msec and Change from Baseline > 60 msec;
- > 480 - 500 msec and Change from Baseline > 30 - 60 msec;
- > 480 - 500 msec and Change from Baseline > 60 msec;

- > 500 msec and Change from Baseline > 30 - 60 msec;
- > 500 msec and Change from Baseline > 60 msec.

6.15.6.2 Vital Signs

Vital signs will be presented by treatment group and visit as observed values and changes from Baseline using descriptive statistics.

6.15.6.3 Physical Examination

Physical examination data will be presented in a by-subject listing.

7. DETERMINATION OF SAMPLE SIZE

The sample size for this study was based mainly on clinical considerations.

8. CHANGES IN THE PLANNED ANALYSES

There are no planned changes to the analyses.

9. REFERENCES

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