J2T-MC-KGBP (Lebrikizumab) Statistical Analysis Plan Version 1

An Open-Label, 24-Week Study to Investigate the Safety and Efficacy of Lebrikizumab in Adult and Adolescent Participants with Moderate-to-Severe Atopic Dermatitis and Skin of Color

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Statistical Analysis Plan: J2T-MC-KGBP (Lebrikizumab): An Open-Label, 24-Week Study to Investigate the Safety and Efficacy of Lebrikizumab in Adult and Adolescent Participants with Moderate-to-Severe Atopic Dermatitis and Skin of Color

Lebrikizumab (LY3650150)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

[Protocol J2T-MC-KGBP]
[Phase 3b]

Statistical Analysis Plan Version 1

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1. Table of Contents

List of Abbreviations

Term	Definition
ADA	anti-drug antibodies
AD	atopic dermatitis
ADCT	Atopic Dermatitis Control Tool
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate transaminase
BMI	body mass index
BSA	body surface area
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CDLQI	Children's Dermatology Life Quality Index
CRF	case report form
CSR	clinical study report
CTR	Clinical Trial Registry
DBL	database lock
DLQI	Dermatology Life Quality Index
DSUR	Development Safety Update Report
EASI	Eczema Area and Severity Index
EASI-75	Eczema Area and Severity Index improvement of ≥75%
EASI-90	Eczema Area and Severity Index improvement of ≥90%
eCRF	electronic case report form
F-IGA	Investigator's Global Assessment of the Face
HLT	high-level term

ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
ISR	injection site reactions
Lilly	Eli Lilly and Company
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NAb	Neutralizing anti-drug antibodies
NMSC	non-melanoma skin cancer
NRS	Numeric rating scale
OI	opportunistic infection
PD	pharmacodynamic
PDS	Post-Inflammatory Dyschromia Scale
PhUSE	Pharmaceutical Users Software Exchange
PK	pharmacokinetic
POEM	Patient-Oriented Eczema Measure
PO-SCORAD	Patient-oriented SCORing Atopic Dermatitis
PROMIS	Patient-Reported Outcomes Information System
PRSQ	Participant Reported Satisfaction Question
PT	Preferred Term
Q2W	every 2 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneously
SE	standard error
SMQ	Standardized MedDRA Query
SOC	System Organ Class

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TBL	total bilirubin
TE-ADA	treatment-emergent ADA
TEAE	treatment-emergent adverse event
WHO	World Health Organization
WPAI-AD	Work Productivity and Activity Impairment Questionnaire–Atopic Dermatitis

2. Revision History

Statistical Analysis Plan Version 1 was approved prior to first database lock.

Revisions since Version 1:

Section	Action
Version 1.0	Created May 2023

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3. Study Objectives

Table KGBP.3.1 shows the protocol-defined objectives and endpoints of the study.

Table KGBP.3.1. Protocol-Defined Objectives and Endpoints

Study Primary Objective: To assess the effect of lebrikizumab 250 mg Q2W in reducing the signs and symptoms of AD at Week 16 in participants with moderate-to-severe AD and skin of color
Study Secondary Objective: To evaluate the effect of treatment with lebrikizumab in the signs and symptoms of AD at Week 16 and Week 24 in participants with moderate-to-severe AD and skin of color
Primary Endpoint: Percentage of participants achieving EASI-75 (≥75% reduction from baseline in EASI) at Week 16
Secondary Endpoints: • Percentage of participants achieving EASI-75 at Week 24 • Percentage of participants with an IGA score of 0 or 1 and a reduction ≥2 points from baseline to Weeks 16 and 24 • Percentage change in EASI total from baseline to Weeks 16 and 24 • Change in EASI total from baseline to Weeks 16 and 24 • Percentage of participants achieving EASI 90 at Weeks 16 and 24 • Percentage of participants with a Pruritus NRS of ≥4 points at baseline who achieve a 4-point reduction at Weeks 16 and 24 • Percentage of participants with a Pruritus NRS ≥3 points at baseline who achieve at least 3-point reduction at Weeks 16 and 24 • Percentage change in Pruritus NRS score from baseline to Weeks 16 and 24 • Percentage of participants with a Sleep-Loss Scale score of ≥2 points at baseline who achieve a 2-point reduction at Weeks 16 and 24 • Percentage change in Sleep-Loss Scale score from baseline to Weeks 16 and 24 • Percentage of participants with a Skin Pain NRS of ≥4 points at baseline who achieve a 4-point reduction from baseline to Weeks 16 and 24 • Change in POEM from baseline to Weeks 16 and 24 • Change in DLQI from baseline to Weeks 16 and 24 in participants ≥ 16 years of age at baseline • Change in cDLQI from baseline to Weeks 16 and 24 in participants < 16 years of age at baseline • Percentage of participants with a DLQI of ≥4 points at baseline who achieve a ≥4-point improvement in DLQI at Weeks 16 and 24 in participants ≥16 years at baseline
Exploratory Endpoints: • Change from baseline in body surface area (BSA) by visit • Percentage change in PO-SCORAD from baseline by visit • Change in Post-inflammatory Dyschromia Scale (PDS) from baseline by visit • Percentage change in ADCT from baseline by visit • Using WPAI-AD by visit, change in baseline in o absenteeism in those who are currently employed (working for pay) o presenteeism in those who are currently employed (working for pay) o overall work impairment in those who are currently employed (working for pay), and o impairment in activities (all participants) • Percentage of participants with an F-IGA score of 0 or 1 and a reduction ≥2 points from baseline by visit • Lichenification change from baseline (calculated from EASI) • Participant satisfaction change from baseline (1 question)

- Percentage of participants achieving EASI-75 by visit
- Percentage of participants with an IGA score of 0 or 1 and a reduction ≥2 points from baseline by visit
- Percentage change in EASI total by visit
- Change in EASI total by visit
- Percentage of participants achieving EASI-90 by visit
- Percentage of participants with a Pruritus NRS of ≥4 points at baseline who achieve a 4-point reduction by visit
- Percentage of participants with a Pruritus NRS of ≥3 points at baseline who achieve a 3-point reduction by visit
- Percentage change in Pruritus NRS score by visit
- Percentage of participants with a Sleep-Loss Scale score of ≥2 points at baseline who achieve a 2-point reduction by visit
- Percentage change in Sleep-Loss Scale score from baseline by visit
- Percentage of participants with a Skin Pain NRS of ≥4 points at baseline who achieve a 4-point reduction from baseline by visit
- Change from baseline in POEM by visit
- Changes from baseline in serum proteins related to AD pathogenesis

4. Study Design

4.1. Summary of Study Design

Study J2T-MC-KGBP (KGBP) is an open-label, phase 3b study, which is 24 weeks in treatment duration. The study is designed to evaluate the safety and efficacy of lebrikizumab in male and female adult and adolescent participants with skin of color and moderate-to-severe AD.

Study Periods

This trial has 4 study periods:

- Screening (Visit 1: ≤30 days prior to baseline)
- Treatment (Visits 2-9: 24 weeks)
- Safety follow-up (Visit 801: at Week 34 or approximately 12 weeks after last treatment)
- Continued Access (Visits 501, 502, and 503)

Participants who enroll into KGBP Protocol Addendum 3 will move directly into the Continued Access Period after completing the 24-week treatment period. Such participants will not complete Visit 801. A post-treatment follow-up visit (V901) will occur approximately 12 weeks post the last dose at the end of the Continued Access Period for the participants who do not move to commercial lebrikizumab or who discontinued early from the Continued Access Period. Please refer to KGBP Protocol Addendum 3 for more information.

Visit Types

Study visits at Week 12 (Visit 6) and Week 20 (Visit 8) will be performed virtually, that is, via telephone or telemedicine tools.

All other visits will be conducted at the clinical trial site.

Dosing

During the 24-week Treatment Period, approximately 80 participants will receive treatment:

- 500 mg subcutaneous (SC) loading dose at baseline and Week 2, followed by 250 mg SC Q2W until Week 16.
- Responders, defined as achieving IGA (0,1) or EASI-75 at Week 16, will receive Q4W dosing and will administer study intervention at Week 20.
- Inadequate responders at Week 16 will receive Q2W dosing and will administer study intervention at Weeks 18, 20, and 22.

During the Continued Access Period, eligible participants will continue lebrikizumab on the same dosing regimen (Q2W or Q4W) they were assigned at Week 16. Please refer to KGBP Protocol Addendum 3 for more information.

The study population is described in Section 5.1.1.

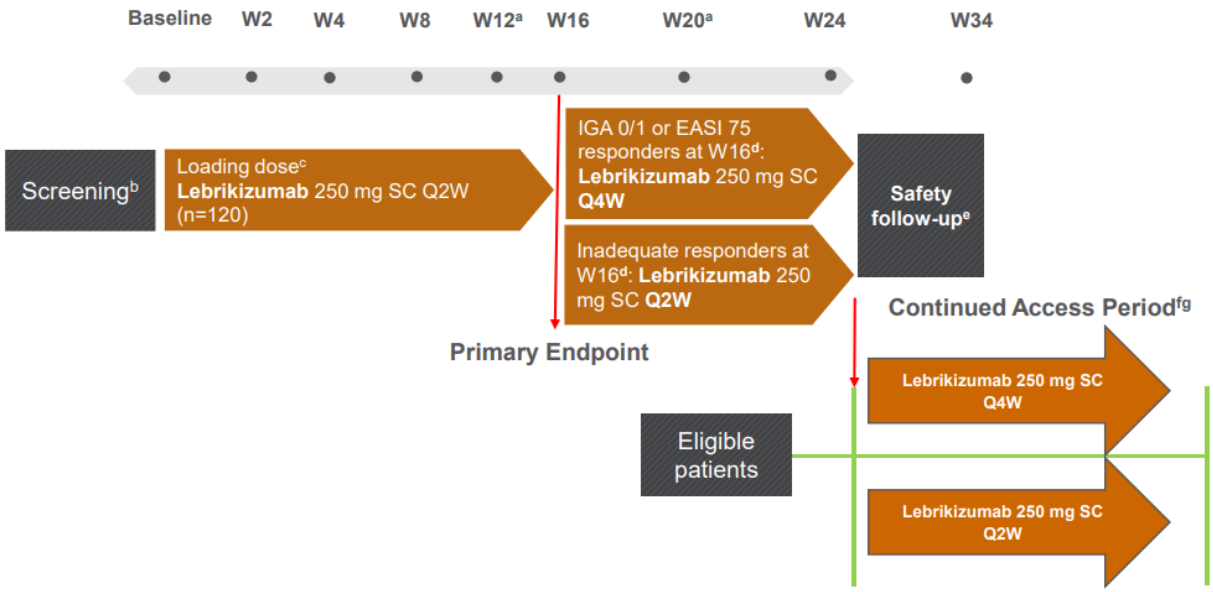
The efficacy and safety assessments are described in Sections 5.11 and 5.13 respectively.

4.1.1 Number of Participants

Approximately 80 participants will be enrolled to study intervention. Because the inclusion of Black and African American patients is historically limited in clinical trials and given the focus of skin of color in this study, the majority of the patients in this study will be of Black or African American race (approximately 55 participants). The remainder of the participants may be of any race other than White, with enrollment of up to 10% Asian participants. Patients will be evaluated for study eligibility before the baseline visit (Day 1).

4.1.2 Schema

Figure KGBP.4.1



Abbreviations: EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; n = number; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SC = subcutaneous; W = week.

[a] Weeks 12 and 20 are phone visits.

[b] 30-day screening window.

[c] Lebrikizumab loading dose of 500 mg SC will be administered at baseline and Week 2.

[d] Responders: Participants who reach IGA 0 or 1 (clear or almost clear) or a 75% reduction in the EASI score from baseline (EASI-75). Inadequate responders are participants who do not reach these criteria.

[e] The safety follow-up visit will occur approximately 12 weeks after last study intervention injection.

[f] The planned maximum duration of Continued Access treatment will vary for each participant enrolled into KGBP Protocol Addendum 3 and will end if and when the participant meets criteria for discontinuation of study intervention or discontinuation from the study. Participants may remain in the Continued Access Period as long as these criteria for discontinuation are not met and until the sponsor stops the study and addendum.

[g] Participants in the Continued Access Period will receive the same dose they were taking during Weeks 16 to 24 of the Treatment Period.

4.2. Determination of Sample Size

Based on available data, the anticipated EASI-75 response rate is approximately 50%. A total sample size of 80 enrolled participants will provide >95% probability that the half-width of the 2-sided 90% CI of the EASI-75 response rate is at most 10%.

Example point estimates for EASI-75 response rates and corresponding 2-sided 90% CIs based on the Wilson Score method for a sample size of 80 participants are summarized in the table below. The CIs are provided as reference rather than a basis of any decision criteria.

Table 4.2 Estimated 90% CI with Sample Size of 80 Participants

Example Point Estimates	Lower Bound of 90% CI	Upper Bound of 90% CI
40%	31.46%	49.19%
45%	36.16%	54.16%
50%	40.96%	59.04%
55%	45.84%	63.84%
60%	50.81%	68.54%
65%	55.87%	73.15%
70%	61.03%	77.66%

4.3. Method of Assignment to Treatment

This is an open-label study. All enrolled patients will be assigned to 250-mg lebrikizumab Q2W at the baseline visit. At Week 16, patients will be assigned to 250-mg lebrikizumab Q2W or 250-mg lebrikizumab Q4W based on their IGA or EASI score.

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5. A Priori Statistical Methods

5.1. General Considerations

Statistical analysis of this study will be the responsibility of ICON. The latest version of the MedDRA will be used.

Summaries from assessment of endpoints described in the protocol are planned to be included in a CSR. Summaries for key safety data are also planned to be included in the CSR. Results from additional efficacy summaries and other safety summaries may also be provided in the CSR as deemed appropriate.

Any change to the data analysis methods described in the protocol will require a protocol amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the CSR.

All statistical processing will be performed using SAS® 9.4 unless otherwise stated.

The schedule of visits and procedures outlined in the protocol specifies the allowable windows for assessments. Assessments performed outside these windows will not be excluded from any summaries, unless specified otherwise.

5.1.1 Analysis Populations

Analysis populations are defined in Table KGBP.5.1 along with the analyses they will be used to conduct. The number of patients included in each population will be summarized.

Table KGBP.5.1.1 Analysis Populations

Population	Description
All Entered Patients	All patients who signed informed consent. Patient flow will be summarized.
Intent-to-Treat (ITT) Population	All enrolled patients according to their planned intervention. Unless otherwise specified, efficacy and health outcomes analyses for Weeks 0 to 16 of the Treatment Period will be conducted on this population.
Safety Population	All enrolled patients who received at least 1 confirmed dose of lebrikizumab 250 mg. Safety analyses will be conducted on this population.
Treatment Period II Population	All enrolled patients who received at least 1 confirmed dose of lebrikizumab 250 mg during Weeks 16 to 24 of the Treatment Period. Unless otherwise specified, efficacy and health outcomes analyses for Weeks 16 to 24 of the Treatment Period will be conducted on this population.

5.1.2 General Considerations for Analyses

All analyses will be descriptive. Frequencies, percentages, and 90% Wilson-Score CIs for percentages will be reported for discrete efficacy endpoints. Mean, standard deviation, minimum, Q1, median, Q3, maximum, and the number of participants will be reported for continuous

efficacy endpoints. AEs, discontinuation, and other categorical safety data will be summarized using frequencies and percentages. Continuous vital signs, body weight, and other continuous safety variables including laboratory variables will be summarized descriptively as well.

Baseline

Baseline will be defined as the last available value before the first injection for efficacy and health outcome analyses. In most cases, this will be the measure recorded at the baseline visit (Day 1). If the patient does not take any injection, the last available value on or prior to treatment assignment date will be used. Change from baseline will be calculated as the visit value of interest minus the baseline value.

For Pruritus Numeric Rating Scale (NRS), Skin Pain NRS, and Sleep-Loss due to Pruritus collected via eDiary, the baseline period is the 7-day window prior to the first injection. A patient must have responses on at least 4 of 7 days to calculate a baseline weekly mean. If a patient has 3 or fewer responses, the baseline mean value will be considered missing.

For the safety analyses, the following baselines will be used. For safety analyses using a baseline period, the baseline period is defined as the time from the screening visit to the date/time of the first injection.

- TEAEs: baseline will be all results recorded during the baseline period.
- Treatment-emergent abnormal laboratory and vital signs results: baseline will be all results recorded during the baseline period.
- Change from baseline to last post-baseline observation or to each scheduled postbaseline visit for laboratory and vital signs results: baseline will be the last scheduled non-missing assessment recorded during the baseline period.

5.2 Primary and Supportive Estimands

There will be five estimands addressing different clinical questions of interest and intercurrent events for the primary and secondary endpoints.

5.2.1. Primary Estimand for the Primary Endpoint

The primary estimand for the primary endpoint represents the primary clinical question of interest: What is the intervention effect in percentage of participants achieving at least 75% improvement from baseline in Eczema Area and Severity Index (EASI) after 16 weeks of lebrikizumab 250 mg Q2W intervention in participants with skin of color and moderate-to-severe AD who remain on study treatment until Week 16?

The primary estimand for the primary endpoint is described by the following attributes:

A. Population: participants with skin of color and moderate-to-severe AD who remain on study treatment until Week 16.
B. Endpoint: whether participants achieve at least 75% improvement from baseline in EASI at Week 16.

C. Intercurrent events: There are no intercurrent events for this population since participants who initiate rescue medication are discontinued from the study and hence study treatment. Therefore, participants who stay on study treatment through Week 16 will not have an intercurrent event such as initiating rescue medication or permanently discontinuing treatment.
D. Population-level summary: percentage of participants achieving EASI-75 response at Week 16.

5.2.2. Supportive Estimands for the Primary Endpoint

There are two supportive estimands for the primary endpoint. The first is a hybrid estimand representing the following clinical question of interest: What is the intervention effect in percentage of participants achieving at least 75% improvement from baseline in Eczema Area and Severity Index (EASI) after 16 weeks of lebrikizumab 250 mg Q2W intervention in participants with skin of color and moderate-to-severe AD if all participants adhered to treatment except those who discontinued due to lack of efficacy?

This estimand is described by the following attributes:

A. Population: participants with skin-of-color and moderate-to-severe AD.
B. Endpoint: whether participants achieve at least 75% improvement from baseline in EASI at Week 16.
C. Intercurrent events (ICEs): One ICE, permanent treatment discontinuation, is considered by this estimand as follows:
    a. Participants who discontinue treatment due to lack of efficacy prior to Week 16 will be considered as treatment failures, i.e. non-responders, after the ICE. Therefore, a composite strategy is used for this type of ICE.
    b. For participants who discontinue treatment due to reasons other than lack of efficacy prior to Week 16, a hypothetical strategy will be used to estimate what the treatment effect would have been if subjects continued with treatment. Therefore, a hypothetical strategy is used for this type of ICE.
D. Population-level summary: percentage of participants achieving EASI-75 response at Week 16.

The second supportive estimand for the primary endpoint is a hypothetical estimand representing the following clinical question of interest: What is the intervention effect in percentage of participants achieving at least 75% improvement from baseline in Eczema Area and Severity Index (EASI) after 16 weeks of lebrikizumab 250 mg Q2W intervention in participants with skin of color and moderate-to-severe AD if all participants adhered to treatment?

This estimand is described by the following attributes:

A. Population: participants with skin of color and moderate-to-severe AD.
B. Endpoint: whether participants achieve at least 75% improvement from baseline in EASI at Week 16.
C. Intercurrent events (ICEs): One ICE, permanent treatment discontinuation, is considered by this estimand as follows:

   a. For participants who discontinue treatment prior to Week 16, a hypothetical strategy will be used to estimate what the treatment effect would have been if all subjects continued with treatment. Therefore, a hypothetical strategy is used for this type of ICE.

D. Population-level summary: percentage of participants achieving EASI-75 response at Week 16.

5.2.3. Estimands for Secondary Endpoints at Week 16

The primary estimand for the primary endpoint will be applied to all secondary endpoints at Week 16. The supportive estimands for the primary endpoint will also be applied to all secondary endpoints at Week 16.

5.2.4. Estimands for Secondary Endpoints at Week 24

The primary estimand for the primary endpoint will be applied to all secondary endpoints at Week 24. There are two supportive estimands for secondary endpoints at Week 24. The first is a hybrid estimand representing the following clinical question of interest: What is the intervention effect in successful responses or means after 24 weeks of lebrikizumab intervention in participants with skin of color and moderate-to-severe AD if all participants adhered to treatment except those who discontinued due to lack of efficacy?

This estimand is described by the following attributes:

A. Population: Treatment Period II population as described in Section 5.1.1.
B. Endpoint: apply to all secondary endpoints at Week 24.
C. Intercurrent events (ICEs): One ICE, permanent treatment discontinuation, is considered by this estimand as follows:
   a. Participants who discontinue treatment due to lack of efficacy after Week 16 will be considered as treatment failures, i.e. non-responders, after the ICE. Therefore, a composite strategy is used for this type of ICE.
   b. For participants who discontinue treatment due to reasons other than lack of efficacy after Week 16, a hypothetical strategy will be used to estimate what the treatment effect would have been if subjects continued with treatment. Therefore, a hypothetical strategy is used for this type of ICE.
D. Population-level summary: percentage of successful responses or means at Week 24.

The second supportive estimand for secondary endpoints at Week 24 is a hypothetical estimand representing the following clinical question of interest: What is the intervention effect in successful responses or means after 24 weeks of lebrikizumab 250 mg Q2W intervention in participants with skin of color and moderate-to-severe AD if all participants adhered to treatment?

This estimand is described by the following attributes:

A. Population: Treatment Period II population as described in Section 5.1.1.

B. Endpoint: apply to all secondary endpoints at Week 24.
C. Intercurrent events (ICEs): One ICE, permanent treatment discontinuation, is considered by this estimand as follows:
    a. For participants who discontinue treatment after Week 16, a hypothetical strategy will be used to estimate what the treatment effect would have been if all subjects continued with treatment. Therefore, a hypothetical strategy is used for this type of ICE.
D. Population-level summary: Population-level summary: percentage of successful responses or means at Week 24.

Because participants who initiate rescue medication are required to discontinue from the study and hence permanently discontinue study treatment, the supportive estimands for the primary and secondary endpoints only consider permanent treatment discontinuation as an ICE.

Analytical details on how missing data including those as a result of intercurrent events will be handled can be found in Section 5.4. The following table (Table KGBP.5.3) summarizes the analytical strategies that will be conducted on the intercurrent events for the five estimands.

Table KGBP.5.3 Description of Primary and Supportive Estimands

Estimand	Population	Analysis Strategy for the ICE of Permanent Treatment Discontinuation		Missing Data Imputation Method
		Due to lack of efficacy	Due to any other reasons, including initiation of rescue medication	
Primary Estimand for the Primary Endpoint and Secondary Endpoints	ITT Population who remained on treatment	Not applicable	Not applicable	Primary analysis: as observed
Supportive Estimand for the Primary Endpoint and Secondary Endpoints at Week 16 (Hybrid)	ITT Population	Composite: Set to baseline	Hypothetical: Set to missing	MCMC-MI
Supportive Estimand for the Primary Endpoint	ITT Population	Hypothetical: Set to missing	Hypothetical: Set to missing	LOCF

and Secondary Endpoints at Week 16 (Hypothetical)				
Supportive Estimand for Secondary Endpoints at Week 24 (Hybrid)	Treatment Period II Population	Composite: Set to baseline	Hypothetical: Set to missing	MCMC-MI
Supportive Estimand for Secondary Endpoints at Week 24 (Hypothetical)	Treatment Period II Population	Hypothetical: Set to missing	Hypothetical: Set to missing	LOCF

Abbreviations: ICE = intercurrent event; LOCF = last observation carried forward; MCMC = Markov chain Monte Carlo.

5.3 Adjustments for Covariates

No statistical tests will be performed.

5.4 Handling of Dropouts or Missing Data

Intercurrent events, as per the ICH guideline (ICH E9R1), are events which occur after the treatment initiation and make it impossible to measure a variable or influence how it should be interpreted. Examples of such events include treatment discontinuation due to death or AEs, rescue treatment, and loss to follow-up.

This section describes missing data imputation methods handling intercurrent events, which will be implemented in this study. For efficacy analyses relative to the primary estimand for primary and secondary endpoints, the method of handling missing data will be the "as observed" strategy described in Section 5.4.1.

For efficacy analyses relative to the supportive hypothetical estimands for primary and secondary endpoints, missing data including those because of intercurrent events will be imputed using the Last Observation Carried Forward (LOCF) strategy described in Section 5.4.2.

For efficacy analyses relative to the supportive hybrid estimands for primary and secondary endpoints, missing data including those because of intercurrent events will be imputed using Markov Chain Monte Carlo Multiple Imputation (MCMC-MI) as described in Section 5.4.3.

5.4.1 As Observed Analysis

The "as observed" strategy is used in so-called "observed cases" or "completers" analysis ubiquitous in the literature but is not one of the recommended strategies in the ICH E9(R1). For this analysis, only data from completers at the visit are relevant. All efficacy data will be

summarized using an "as observed" analysis and summaries based on observed data at each postbaseline visit will be provided.

5.4.2 Last Observation Carried Forward

In this analysis, all missing values will be imputed using last observation carried forward (LOCF). Baseline values will be used for imputation if there is no postbaseline observation.

5.4.3. Markov chain Monte Carlo - Multiple Imputation (MCMC-MI)

The method of handling missing efficacy data relative to the supportive hybrid estimands for the primary and secondary endpoints at Week 16 will be based on Markov Chain Monte Carlo Multiple Imputation (MCMC-MI). For patients who discontinue treatment due to lack of efficacy prior to Week 16, set to the patient's baseline value subsequent to this time through Week 16. MCMC-MI will be used to handle the remaining missing data.

The method of handling missing efficacy data relative to the supportive hybrid estimand for secondary endpoints at Week 24 will be based on MCMC-MI. For patients who discontinue treatment due to lack of efficacy after Week 16, set to the patient's baseline value subsequent to this time through Week 24. MCMC-MI will be used to handle the remaining missing data. Imputation will be conducted within each treatment group independently so that the pattern of missing observations in one treatment group cannot influence missing value imputation in another.

For each imputation process, 25 datasets with imputations will be calculated. The initial seed values are given in Table KGBP.5.3. The response rates and their associated SEs will be computed for each data set using SAS PROC FREQ with the riskdiff option specified for the appropriate column in the TABLES statement. The response rates and SEs from the resulting output will be combined across the 25 imputed datasets using SAS PROC MIANALYZE.

For binary responses related to EASI and 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.

For derivation of an EASI-75 and EASI-90 response, no rounding will be performed. The imputed EASI value will be compared directly to the observed baseline EASI value to determine whether a reduction of at least 75% or 90% was achieved at each visit.

For derivation of the following Pruritus NRS, Skin Pain NRS, Sleep-Loss Scale, and DLQI responses, no rounding will be performed. The imputed Pruritus NRS, Skin Pain NRS, and Sleep-Loss Scale values will be compared directly to the observed mean baseline values to

determine whether a response was achieved. The imputed DLQI values will be compared directly to the observed baseline values to determine whether a response was achieved.

- Proportion of patients with a Pruritus NRS of ≥3 points at baseline achieving at least a 3-point reduction by visit.
- Proportion of patients with a Pruritus NRS of ≥4 points at baseline achieving at least a 4-point reduction by visit.
- Proportion of patients with a Skin Pain NRS of ≥4 points at baseline achieving at least a 4-point reduction by visit.
- Proportion of patients with a Sleep-Loss Scale of ≥2 points at baseline achieving at least a 2-point reduction by visit.
- Proportion of patients with DLQI of ≥4 points at baseline achieving at least a 4-point reduction by visit.

Note that the estimate and 90% confidence interval bounds output by this SAS PROC MIANALYZE are percents (i.e, they are in terms of the response rate). To obtain the number of responders, the estimated percent is multiplied by the number of individuals in the analysis population and rounded to the nearest integer.

Imputation of continuous data will parallel that of binary variables. IGA, EASI, Sleep-Loss, Skin Pain NRS, Pruritus NRS, DLQI, CDLQI, and POEM will be summarized using an MCMC-MI analysis.

Table KGBP.5.5. Seed Values for MCMC-Multiple Imputation

Analysis	Seed Values for Weeks 0-16 of the Treatment Period; LEB 250mg Q2W	Seed Values for Weeks 16-24 of the Treatment Period; LEB 250mg Q2W or Q4W
Proportion of patients achieving IGA of 0 or 1 with a ≥2 point improvement from baseline by visit.	661769200	893745627
Percent change from baseline in EASI score by visit. EASI-75 and EASI-90 will leverage imputation from EASI and therefore use the same seed numbers.	153233047	345987238
Change from baseline in Pruritis NRS Score by visit. Proportion of patients with a Pruritus NRS Score of ≥3 or ≥4 points at baseline achieving at least a 3-point or 4-point reduction will leverage imputation from Pruritis NRS Score and therefore use the same seed numbers.	502899349	302781834
Change from baseline in Sleep-Loss Scale by visit. Proportion of patients with a Sleep-Loss Scale of ≥2 points at baseline who achieve at least a 2-point reduction at each visit will leverage imputation from Sleep-Loss Scale and therefore use the same seed numbers.	691405299	999692612
Change from baseline in Skin Pain NRS from baseline by visit. Proportion of patients with a Pruritus NRS Score of ≥4 points at baseline achieving at least a 4-point reduction will leverage imputation from Pruritis NRS Score and therefore use the same seed numbers.	81969226	20532741
Change from baseline in DLQI by visit. Proportion of patients with DLQI ≥4 points at baseline achieving at least a 4-point reduction will leverage imputation from DLQI and therefore use the same seed numbers.	66350098	60458640
Change from baseline in cDLQI by visit.	93794488	34792747
Change from baseline in POEM by visit.	90372455	71154458

Abbreviations: CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index ; EASI = Eczema Area and Severity Index; EASI-75 = Eczema Area and Severity Index improvement of ≥75%; EASI-90 = Eczema Area and Severity Index improvement of ≥90%; IGA = Investigator's Global Assessment for Atopic Dermatitis; LEB = lebrikizumab; MCMC = Markov chain Monte Carlo; NRS = Numeric Rating Scale; POEM = Patient-Oriented Eczema Measure; Q2W = every 2 weeks; Q4W = every 4 weeks.

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5.5 Multicenter Studies

This study will be conducted by multiple investigators at multiple sites.

5.6 Multiple Comparisons/Multiplicity

No statistical tests will be performed in this study so no need to account for multiple comparisons.

5.7 Patient Disposition

The following patient disposition summaries will be provided (details of the analysis populations can be found in Section 5.1.1):

- The total number and percentage of patients entering each statistical analysis population is defined in Section 5.1.1 (analysis population: all entered patients).
- The number and percentage of patients who entered the study, were treated, and screen failed will be provided overall and by screen fail reason (analysis population: all entered patients).
- The number and percentage of patients who completed Week 16, and the number and percentage of patients who discontinued the treatment at any time before Week 16, by primary reason for discontinuation of treatment (analysis populations: ITT).
- The number and percentage of patients who completed Week 24, and the number and percentage of patients who discontinued the treatment at any time before Week 24, by primary reason for discontinuation of treatment (analysis populations: Treatment Period II).
- The number and percentage of patients who were treated and completed the study, and the number and percentage of patients who discontinued the study at any time, by primary reason for discontinuation (analysis population: ITT).

All enrolled participants (that is, in the ITT population) who discontinued from study treatment will be listed together with the discontinuation reason, and the timing of discontinuation from the study will be reported.

Patient allocation by center/site will be summarized with the number of patients who entered the study, number of ITT patients, number of patients discontinued from study treatment, and number of patients discontinued from the study.

5.8 Patient Characteristics

5.8.1 Demographics and Baseline Characteristics

Patient demographic variables and baseline characteristics will be summarized for the ITT and Treatment Period II populations. The continuous variables will be summarized using descriptive statistics (mean, median, standard deviation, and range [minimum and maximum]), and the categorical variables will be summarized using frequency counts and percentages.

The following demographic information will be included:

- age
- sex (male, female)
- Fitzpatrick skin phototype
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Multiple, or Other)
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, or Unknown)
- weight (kg)
- weight category (40-<60 kg, ≥60 to <100 kg, or ≥100 kg)
- height (cm)
- BMI (kg/m^2), and
- BMI category (Underweight [<18.5 kg/m^2], Normal [≥18.5 and <25 kg/m^2], Overweight [≥25 and <30 kg/m^2], Obese [≥30 and <40 kg/m^2], or Extreme obese [≥40 kg/m^2]).

By-patient listings of basic demographic information for the ITT population will be provided.

The following baseline disease/clinical characteristics will be included:

- age at onset (years): calculated as the difference between date of onset of AD and the date of birth collected on the CRF
- duration since AD onset (years): calculated as the difference between date of informed consent and the date of onset of AD collected on the CRF
- duration since AD onset category (0 to <2 years, 2 to <5 years, 5 to <10 years, or ≥10 years)
- anatomical area affected by AD:
    - head/neck
    - trunk (internal/medial axillae and groin)
    - upper extremities (includes external axillae)
    - lower extremities (includes buttocks and feet), and
    - at least 2 areas
- AD treatment used in the past:
    - none
    - topical corticosteroids
    - topical calcineurin inhibitors
    - Topical JAK inhibitors
    - Topical phosphodiesterase-4 inhibitors (crisaborole)

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- immunosuppressive/immunomodulating drugs: systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, azathioprine, methotrexate, and other biologics (eg, B-cell depleting biologics)
- Oral JAK inhibitors
- phototherapy
- photochemotherapy

The following efficacy instruments will be included:

- IGA
- F-IGA
- EASI score including separate exploratory analysis of lichenification component of EASI
- BSA
- PDS
- PO-SCORAD
- POEM
- Pruritus NRS
- Sleep-Loss Scale
- Skin Pain NRS
- DLQI/CDLQI
- ADCT
- Participant-Reported Satisfaction Question
- WPAI-AD
- Fitzpatrick Skin Phototype Assessment

5.8.2 Medical History

Medical histories are defined as the conditions/events recorded on the *Pre-existing Conditions and Medical History* eCRF with a start date prior to the first study drug injection. Notice if a medical history worsens in severity on or after the date of first injection, it will be recorded as an AE on the *Adverse Event* eCRF with the date of worsening as the start date.

The number and percentage of patients with medical histories will be summarized for the ITT population using the MedDRA Preferred Term (PT) nested within System Organ Class (SOC).

The number and percentage of patients with specific medical history events of interest prespecified on the *Prespecified Medical History* eCRF will be summarized for the ITT population.

5.8.3 Prespecified Clinical Events

The number and percentage of patients with prespecified clinical events (including Follicular/Perifollicular accentuation of atopic dermatitis, Allergic shiner(s), Pityriasis alba, Prurigo, Eczema nummular, Eczema facial, and Hand eczema) on the *Prespecified Clinical Events* eCRF at baseline and Week 24 will be summarized. For those who reported a prespecified clinical event at baseline and who remained on treatment until Week 24, the number and percentage of patients shifting from a higher severity at baseline to a lower severity or no event at Week 24 (e.g., severe at baseline to moderate, mild, or no event at Week 24) will be reported. The number and percentage of patients shifting from a lower severity or no event at baseline to a higher severity at Week 24 (e.g., no event at baseline to mild, moderate, or severe at Week 24) will also be reported.

5.9 Treatment Compliance

Beginning Week 4 (Visit 4) the participant/caregiver will be encouraged to administer the study intervention while in the clinic or at home. Participants may choose to continue to receive study drug injections administered by trained clinic staff for any visit occurring in the clinic. Home dosing must be self-administered or given by a caregiver that has received proper injection technique training.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned injection supplies, and documented in the source documents.

Treatment compliance with investigational product will be summarized for patients who receive at least 1 confirmed dose of lebrikizumab (ie, the Safety Population) during the Treatment Period. Treatment compliance for each patient will be calculated as:

$$Treatment\ compliance\ (\%) = 100\ \times \frac{Total\ number\ of\ injections\ administered}{Total\ number\ of\ injections\ expected}$$

- The number of injections expected can be derived from the study drug dispense dataset.
- The total number of injections administered will be based on the *Exposure as Collected* eCRF page and on the *Exposure as Collected: Missed Injections at Home* eCRF page.

A patient will be considered compliant if he or she received ≥75% of the expected number of injections while enrolled in the study. Descriptive statistics for percent compliance will be summarized. Subintervals of interest, such as compliance between visits, may also be presented.

5.10 Prior and Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary. Medication start and stop dates will be compared to the date of first dose of treatment during Weeks 0-16 of the Treatment Period and Weeks 16-24 of the Treatment Period to be classified as concomitant for each treatment period.

Prior medications are those medications that start and stop prior to the date of first dose of study treatment. *Concomitant medications* are those medications that start before, on, or after the first day of study treatment of the defined study period (that is, Weeks 0-16 or Weeks 16-24 of the Treatment Period) and continue into that period. Concomitant medications are assigned to the study period in which they are actually ongoing. For example, if a participant is receiving a concomitant medication during Weeks 0-16 but has a stop date prior to Week 16, the same medication would not be listed as a concomitant medication for Weeks 16-24 unless the patient has a new start date.

Prior medication will be summarized by drug class and PT for the ITT population. Concomitant medication used during Weeks 0-16 and Weeks 16-24 will be presented separately for the ITT and Treatment Period II populations.

Rescue medications used during Weeks 0-16 and Weeks 16-24 will be presented separately for the ITT and Treatment Period II populations. This will include: (1) topical therapy and (2) systemic therapy (e.g., systemic corticosteroids, phototherapy, cyclosporin, etc.). More information on the definition of rescue medications can be found in Appendix 1.

5.11 Efficacy Analyses

Table KGBP.5.4 includes the description and derivation of the efficacy measures and endpoints.

For categorical parameters, the number and percentage of patients in each category will be presented, as well as a 90% Wilson-Score confidence interval for the percentage. For continuous parameters, descriptive statistics will include n (number of patients), mean, standard deviation, Q1, median, Q3, minimum, and maximum. These summaries will be provided for the data as-observed and after implementation of LOCF and MCMC-MI imputation as described in Sections 5.4.2 and 5.4.3.

The IGA, F-IGA, EASI, BSA, Pruritus NRS, Skin Pain NRS, and Sleep-Loss Scale will be reported by clinic visit.

Table KGBP.5.4. Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints

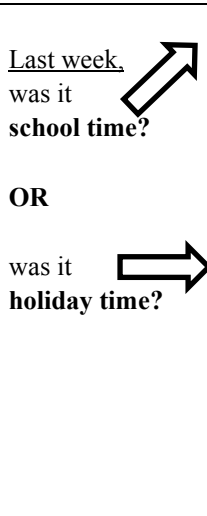
Measure	Description	Variable	Derivation/Comment	Imputation Approach if Missing Components
Investigator's Global Assessment (IGA)	The IGA is a static assessment and rates the severity of a patient's AD. The IGA is comprised of a 5-point scale ranging from 0 (clear) to 4 (severe), and a score is selected using descriptors that best describe the overall appearance of the lesions at a given time point.	IGA score	Single item. Range: 0-4 0 represents "clear" 4 represents "severe"	Single item, missing if missing
		• IGA (0,1) with ≥2-point improvement[a]	• Observed score of 0 or 1 and change from baseline ≤-2	Missing if baseline or observed value is missing
		IGA (0)	Observed score of 0	Single item, missing if missing
Face-Investigator's Global Assessment (F-IGA)	The F-IGA is a static assessment and rates the severity of a patient's AD on the face. The F-IGA is comprised of a 5-point scale ranging from 0 (clear) to 4 (severe), and a score is selected using descriptors that best describe the overall appearance of the lesions at a given time point.	F-IGA Score	Single item. Range: 0-4, 0 represents "clear", 4 represents "severe"	Single item, missing if missing
		F-IGA (0,1)	Observed score of 0 or 1	Missing if baseline or observed value is missing
		F-IGA (0)	Observed score of 0	Single item, missing if missing
Eczema Area and Severity Index (EASI)	The EASI scoring system uses a defined process (Steps 1-5 below) to grade the severity of the signs of eczema and the extent affected. The extent of disease (percentage of skin affected: 0 = 0%; 1 = 1-9%; 2 = 10-29%; 3 = 30-49%; 4 = 50-69%; 5 = 70-89%; 6 = 90-100%) and the severity of 4 clinical signs (erythema, edema/papulation, excoriation, and lichenification) each on a scale of 0-3 (0 = none, absent; 1 = mild; 2 = moderate; 3 = severe) at 4	EASI score	Derive EASI region score for each of head and neck, trunk, upper limbs, and lower limbs as follows: $EASI_{region}$ = (erythema + edema/papulation + excoriation + lichenification)*(value from percentage involvement), where erythema, edema/papulation, excoriation, and lichenification are evaluated on a scale of 0 to 3, and value from percentage involvement is on a scale of 0 to 6. Then total EASI score is as follows:	NA: partial assessments cannot be saved.

	body sites (head and neck, trunk, upper limbs, and lower limbs). Half scores are allowed between severities 1, 2, and 3. Each body site will have a score that ranges from 0-72, and the final EASI score will be obtained by weight-averaging these 4 scores. Hence, the final EASI score will range from 0-72 for each time point.		EASI = $0.1*EASI_{\text{head and neck}} + 0.3*EASI_{\text{trunk}} + 0.2*EASI_{\text{upper limbs}} + 0.4*EASI_{\text{lower limbs}}$	
		• Change from baseline in EASI score Percent change from baseline EASI score[a]	Change from baseline: observed EASI score – baseline EASI score % change from baseline: $100 \times \frac{Observed\ score - Baseline}{Baseline}$	Missing if baseline or observed value is missing
		EASI-75[a]	% improvement in EASI score from baseline ≥75%: % change from baseline ≤-75	Missing if baseline or observed value is missing
		EASI-90[a]	% improvement in EASI score from baseline ≥90%: % change from baseline ≤-90	Missing if baseline or observed value is missing
Body Surface Area (BSA) Affected by AD	The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. BSA will be determined by the investigator or designee using the patient palm = 1% rule.	BSA score	BSA Total = $BSA_{\text{head and neck}} + BSA_{\text{trunk}} + BSA_{\text{upper limbs}} + BSA_{\text{lower limbs}}$	NA: partial assessments cannot be saved.
		Change from baseline in BSA score[a]	Change from baseline: observed BSA score - baseline BSA score	Missing if baseline or observed value is missing.
Dermatology Life Quality Index (DLQI)	The DLQI is a validated, dermatology-specific, patient-reported measure that evaluates a patient's HRQoL. This questionnaire has 10 items that are grouped in 6 domains, including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week". Response categories and corresponding scores are:	DLQI total score	A DLQI total score is calculated by summing all 10 question responses and has a range of 0-30 (less to more impairment) (Finlay and Khan 1994; Basra et al. 2008).	Score of 1 unanswered question = 0; If 2 or more questions are missing, the total score is missing. Note: #7B could be a valid missing while #7A is not "No." That is, #7 should be considered as 1 question.
		DLQI (0,1)	A DLQI (0,1) response is defined as a postbaseline DLQI total score of 0 or 1. A DLQI total score of 0-1 is considered as having no effect on a patient's HRQoL (Khilji et al. 2002; Hongbo et	Missing if DLQI total score is missing

	Very much = 3 A lot = 2 A little = 1 Not at all = 0 Not relevant = 0 Scores range from 0-30, with higher scores indicating greater impairment of QoL. A DLQI total score of 0-1 is considered as having no effect on a patient's HRQoL (Hongbo et al. 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Basra et al. 2015).		al. 2005).	
		4-point improvement[a]	Change from baseline ≤-4	Missing if baseline is missing or observed value is missing.
		DLQI total score and domain scores change from baseline[a]	Calculated as: observed DLQI (total score or domain scores) - baseline DLQI (total score or domain scores)	Missing if baseline or observed value is missing
		DLQI symptoms and feelings domain	Sum of responses of questions 1 and 2: 1. How itchy, sore, painful or stinging has your skin been? 2. How embarrassed or self-conscious have you been because of your skin?	If 1 question in a domain is missing, that domain is missing.
		DLQI daily activities domain	Sum of responses of questions 3 and 4: 3. How much has your skin interfered with you going shopping or looking after your home or garden? 4. How much has your skin influenced the clothes you wear?	If 1 question in a domain is missing, that domain is missing.
		DLQI leisure domain	Sum of responses of questions 5 and 6: 5. How much has your skin affected any social or leisure activities?	If 1 question in a domain is missing, that domain is missing.

			6. How much has your skin make it difficult for you to do any sport?	
		DLQI work and school domain	Sum of responses of questions 7A and 7B: 7A. Has your skin prevented you from working or studying? 7B. If No: how much has your skin been a problem at work or studying?	If the answer to question 7A is missing, this domain is missing. If 7A is No, and 7B is missing, this domain is missing.
		DLQI personal relationships domain	Sum of responses of questions 8 and 9: 8. How much has your skin created problems with your partner or any of your close friends or relatives? 9. How much has your skin caused any sexual difficulties?	If 1 question in a domain is missing, that domain is missing.
		DLQI treatment domain	Response of question 10: 10. How much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	If 1 question in a domain is missing, that domain is missing.
Children's Dermatology Life Quality Index (CDLQI)	The CDLQI is designed to measure the impact of any skin disease on the lives of children. Patients ≤16 years will complete the CDLQI and should continue to complete the CDLQI for the duration of the study. The scoring of each question is: • Very much = 3 • Quite a lot = 2 • Only a little = 1 • Not at all = 0 • Question unanswered = 0 • Question 7: 'Prevented school' (text-only questionnaire) = 3	CDLQI total score	A CDLQI total score is calculated by summing all 10 question responses and has a range of 0-30 (less to more impairment) (Waters A et al. 2010).	Score of 1 unanswered question = 0; If 2 or more questions are missing, the total score is missing.
		CDLQI (0,1)	A CDLQI (0,1) response is defined as a postbaseline CDLQI total score of 0 or 1.	Missing if CLQI total score is missing
		4-point improvement[a]	Change from baseline ≤-4	Missing if baseline or observed value is missing
		CDLQI total score and domain scores change from baseline[a]	Calculated as: observed CDLQI (total score or domain scores) - baseline CDLQI (total score or domain scores)	Missing if baseline or observed value is missing
		CDLQI symptoms and feelings domain	Sum of responses of questions 1 and 2: 1. Over the last week, how itchy, "scratchy", sore or painful has your	If 1 question in a domain is missing, that domain is missing.

			skin been? 2. Over the last week, how embarrassed or **self conscious**, **upset** or **sad** have you been because of your skin?	
		CDLQI sleep domain	Response of question 9 9. Over the last week, how much has your **sleep** been affected by your skin problem?	Single item, missing if missing
		CDLQI leisure domain	Sum of responses of questions 4, 5, and 6: 4. Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin? 5. Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**? 6. Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	If 1 question in a domain is missing, that domain is missing.
		CDLQI school or holiday domain	Responses of questions 7: If select 'Prevented school', score = 3	Single item, missing if missing

				
		CDLQI personal relationships domain	Sum of responses of questions 3 and 8: 3. Over the last week, how much has your skin affected your **friendships**? 8. Over the last week, how much trouble have you had because of your skin with other people **calling you names, teasing, bullying, asking questions** or **avoiding you**?	If 1 question in a domain is missing, that domain is missing.
		CDLQI treatment domain	Response of question 10: 10. How much of a problem has the treatment for your skin been?	Single item, missing if missing.
Post-Inflammatory Dyschromia Scale (PDS)	The PDS is an investigator assessment of cutaneous post-inflammatory hyperpigmentation and/or hypopigmentation which is completed at the visit per the SoA	Post-inflammatory cutaneous change in pigmentation.	0: Areas of normal skin tone 1: Areas of post-inflammatory hyperpigmentation, (mild/barely perceptible hyperpigmentation), 2: Areas of post-inflammatory hyperpigmentation, (moderate/clearly	Single item, missing if missing.

			perceptible hyperpigmentation) 3: Areas of post-inflammatory hyperpigmentation, (severe/prominent hyperpigmentation). -1: Areas of post-inflammatory hypopigmentation, (mild/barely perceptible hypopigmentation), -2: Areas of post-inflammatory hypopigmentation, (moderate/clearly perceptible hypopigmentation) -:3 Areas of post-inflammatory hypopigmentation, (severe/prominent hypopigmentation)	
Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD)	PO-SCORAD is a patient-reported scale used to evaluate the condition of a patient's eczema over the last 3 days in both adults and adolescent participants. There are 3 components to the assessment: • The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall PO-SCORAD calculation). • The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as	PO-SCORAD Score --Change from baseline in PO-SCORAD score --Percent change from baseline in PO-SCORAD score PO-SCORAD75 PO-SCORAD90	PO-SCORAD = A/5 + 7B/2 + C, where A is extent of disease, range 0-100 B is disease severity, range 0-18 C is subjective symptoms, range 0-20 Change from baseline: observed PO-SCORAD score – baseline PO-SCORAD score % change from baseline: $100 \times \frac{Observed\ score - Baseline}{Baseline}$ % Improvement in PO-SCORAD from baseline ≥75%: % change from baseline ≤-75 % Improvement in PO-SCORAD from baseline ≥90%: % change from baseline ≤-90	Missing if components A and B are missing or if component C is missing. Partial assessments performed by patients cannot be saved. Missing if baseline or observed value is missing. Missing if baseline or observed value is missing. Missing if baseline or

	"B" in the overall PO-SCORAD calculation). • Subjective assessment of itch and of sleeplessness is recorded for each symptom by the patient or relative on a VAS, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20 (assigned as "C" in the overall PO-SCORAD calculation.			observed value is missing.
Patient-Oriented Eczema Measure (POEM)	The POEM is a 7-item, validated, questionnaire used by the patient to assess disease symptoms over the last week. The patient is asked to respond to 7 questions on skin dryness, itching, flaking, cracking, sleep loss, bleeding and weeping. All 7 answers carry equal weight with a total possible score from 0 to 28 (answers scored as: No days=0; 1– 2 days = 1; 3-4 days = 2; 5–6 days = 3; everyday = 4). A high score is indicative of a poor quality of life. POEM responses will be captured using an electronic diary and transferred into the clinical database.	POEM score	POEM total score: sum of questions 1 to 7, Range 0 to 28.	If a single question is left unanswered, then that question is scored as 0. If more than one question is unanswered, then the tool is not scored. If more than one response is selected, then the response with the highest score is used.
		Change from baseline in POEM score	Change from baseline: observed POEM score – baseline POEM score	Missing if baseline or observed value is missing.
		4-point improvement	Change from baseline ≤-4	Missing if baseline is missing or observed value is missing.
Pruritis Numeric Rating Scale (NRS)	The Pruritus Numeric Rating Scale (NRS) is a participant-reported, single-item, daily, 11-point scale.	Percent change from baseline Pruritis NRS Score 4-point improvement in Pruritis NRS Score	The Pruritus NRS is used by participants to rate their worst itch severity over the past 24 hours with 0 indicating "No itch" and 10 indicating "Worst itch imaginable." Assessments will be recorded daily by the participant. The minimal clinically important change is 3 points.	Baseline weekly mean score is missing if the patient has 3 or fewer responses within the week before baseline. Post-baseline weekly mean score is missing if the patient has no responses within the week.

		3-point improvement in Pruritus NRS Score	Participants will record the pruritus assessments daily using an electronic diary at home. As indicated in the SoA (Section 1.3), initial electronic diary entries for Pruritus NRS should be completed a minimum of 4 of 7 days before baseline.	
Skin Pain Numeric Rating Scale (NRS)	The Skin Pain NRS is a participant-reported, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable."	Percent change from baseline in Skin Pain NRS Score 4-point improvement in Skin Pain NRS Score	Overall severity of a participant's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours. Assessment will be recorded daily by the participant.	Baseline weekly mean score is missing if the patient has 3 or fewer responses within the week before baseline. Post-baseline weekly mean score is missing if the patient has no responses within the week.
Sleep-Loss Scale	The Sleep-Loss Scale is a participant-reported, single-item, daily scale that measures the extent of sleep loss due to interference of itch over the last night.	Percent change from baseline in Sleep Loss Score 2-point improvement in Sleep Loss Score	The Sleep-Loss Scale is rated based on a 5-point Likert scale (0 [not at all] to 4 [unable to sleep at all]). Assessment will be recorded daily by the participant. The minimal clinically important change is 3 points.	Baseline weekly mean score is missing if the patient has 3 or fewer responses within the week before baseline. Post-baseline weekly mean score is missing if the patient has no responses within the week.
Atopic Dermatitis Control Tool	The Atopic Dermatitis Control Tool is a patient-reported, simple, brief tool for adults and adolescents that evaluates 6 symptoms and effects associated with AD over the past week	Percent change from baseline in ADCT Total Score	Each of the 6 Atopic Dermatitis Control Tool items has a score range from 0 (no problem) to 4 (worst), rating the severity of each concept; the total score ranges from 0 to 24, which is the summation of the responses to all the items. A score of ≥7 points was derived as the threshold to identify participants "not in control."	If 1 question in a domain is missing, that domain is missing.

			The threshold for meaningful within-person change was estimated to be 5 points.	
Participant Reported Satisfaction Question	The question on participant satisfaction asks "How satisfied are you with this treatment's ability to treat your skin condition?"	PRSQ Score	The response options range from 1 (not satisfied) to 5 (completely satisfied).	Single item, missing if missing.
WPAI-AD	The Work Productivity and Activity Impairment Questionnaire–Atopic Dermatitis is a participant-reported, 6-item questionnaire that records impairment due to AD over the past 7 days in adolescents and adults	Percent change from baseline in WPAI AD Absenteeism Score Percent change from baseline in WPAI AD Presenteeism Score Percent change from baseline in WPAI AD Work Productivity Loss Score Percent change from baseline in WPAI AD Activity Impairment Score	The Work Productivity and Activity Impairment Questionnaire– Atopic Dermatitis consists of 6 items grouped into 4 domains: absenteeism (work time missed), presenteeism (impairment at work or reduced on the job effectiveness), work productivity loss (overall work impairment or absenteeism plus presenteeism), and activity impairment. Absenteeism, presentism, and work productivity will only be reported by those who are currently employed (working for pay) at the time of the scale completion. The recall period for the scale is over the past 7 days. Scores are calculated as impairment percentages (Reilly et al. 1993), with higher scores indicating greater impairment and less productivity	If 1 question in a domain is missing, that domain is missing.

Abbreviations: AD = atopic dermatitis; HRQoL = health-related quality of life; NA = not applicable; QoL = quality of life.

[a] Secondary endpoints.

5.12 Health Outcomes/Quality-of-Life Analyses

The description and derivation of the health outcomes/QoL analyses are described in Table KGBP.5.4. For categorical parameters, the number and percentage of patients in each category will be presented, as well as a 90% Wilson-Score confidence interval for the percentage. For continuous parameters, descriptive statistics will include n (number of patients), mean, standard deviation, Q1, median, Q3, minimum, and maximum. These summaries will be provided for the data as-observed and after implementation of LOCF and MCMC-MI imputation as described in Sections 5.4.2 and 5.4.3. Patient-Reported Outcomes Information System and DLQI/CDLQI will be reported by clinic visit.

5.13 Safety Analyses

The planned analyses of safety data will be performed with an intent to maintain consistency with compound-level standard safety analyses. These standards are based on internal standards which were informed by CDISC standards, regulatory guidance (eg, FDA Clinical Review Template), and cross-industry standardization efforts (eg, PhUSE white papers from the Standard Analyses and Code Sharing Working Group provided in the PhUSE Computational Science Deliverables Catalog [WWW]).

The laboratory (including hormone), vital sign (including growth), and immunogenicity safety summaries will be based on the safety population. The extent of exposure and AE tables will be based on the safety population.

These analysis populations are fully defined in Table KGBP.5.1.

Not all displays described in this section will necessarily be included in the CSRs. Any display described and not provided in the CSR would be available upon request. Not all displays will necessarily be created as a “static” display. Some may be incorporated into interactive display tools instead of or in addition to a static display. Any display created interactively will be included in the CSR if deemed relevant to the discussion.

5.13.1. Extent of Exposure

A by-patient listing of exposure duration with the number of active injections and total dose will be provided for the Safety Population.

The duration of exposure will be calculated as:

Duration of exposure (days)=

Date of last visit (scheduled or unscheduled) in the Treatment Period –

Date of first dose+1

The number and percentage of patients in each of the following categories will be included in the summaries:

>0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥112 days, ≥120 days, >=168 days. Note that patients may be included in more than 1 category.

The summaries will also include the following information:

- total exposure in patient years, calculated as:

$$Total\ exposure\ in\ patient\ years = \frac{Sum\ of\ duration\ of\ exposures\ for\ all\ patients\ in\ treatment\ group}{365.25}$$

- mean and median total dose; total dose (in mg) is calculated by the number of active injections taken multiplied by 250.
- Total number of injections received will be derived from the *Exposure as Collected* eCRF page and on the *Exposure as Collected: Missed Injections at Home* eCRF page.

5.13.2. Adverse Events

A TEAE is defined as an event that first occurred or worsened in severity after baseline (i.e., AEs with an onset date on or after the date of the first injection of study drug). The MedDRA lowest level- term will be used in the treatment-emergent computation. The maximum severity for each lowest -level term during the baseline period will be used as baseline. The treatment period will be included as post-baseline for the summaries. For events with a missing severity during the baseline period, the events will be treated as 'mild' in severity for determining treatment-emergence. Events with a missing severity during the postbaseline period will be treated as 'severe', and treatment-emergence will be determined by comparing to baseline severity. For events occurring on the day of first taking study medication, the events will be assumed to be posttreatment.

The planned summaries for AEs are provided in Table KGBP.5.5 and are described more fully in compound-level safety standards and in the AE-related PhUSE white paper [Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Document (PhUSE 2017)].

Summary tables will be presented for the safety population. Summary tables will include the number and percentage of patients reporting an event. For events that are gender-specific (as defined by MedDRA), the number of participants at risk will include only patients from the given gender.

Table KGBP.5.5. Summary Tables/Listings Related to Adverse Events

Summaries	Population
Overview of AEs	Safety
Summary of TEAEs by PTs	Safety
Summary of TEAEs by PTs within SOC	Safety
Summary of TEAE PTs by maximum severity	Safety
Summary of SAEs by PT within SOC	Safety
Summary of AEs leading to treatment discontinuation by PT with SOC	Safety

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Summary of TEAEs possibly related to study drug by PTs within SOC	Safety
Summary of treatment-emergent adverse events – facial dermatitis follow-up form	Safety
Listing of SAEs (including Death)	Safety
Listing of primary AEs leading to study treatment discontinuation	Safety
Listing of TEAEs	Safety

Abbreviations: AE = adverse event; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

5.13.2.1. Common Adverse Events

The percentages of patients with TEAEs will be summarized using MedDRA PT for the common TEAEs (occurred in ≥1% before rounding in any column in the table).

5.13.2.2. Deaths, Other Serious Adverse Events and Other Notable Adverse Events

The number and percentage of patients reported with an SAE during the treatment period will be summarized using MedDRA PT. A listing of SAEs will be provided.

The number and percentage of patients who permanently discontinued from study treatment due to an AE (including AEs that led to death) during the treatment period will be summarized using MedDRA PT. Events will be ordered by decreasing frequency.

5.13.3. Clinical Laboratory Evaluation

As described more fully in compound-level safety standards and in the laboratory-related PhUSE white papers (PhUSE 2013; PhUSE 2015), the clinical laboratory evaluations will be summarized as described in Table KGBP.5.6. Hormone analytes are summarized/plotted similarly.

Table KGBP.5.6. Summary Tables/Listing of Clinical Laboratory Evaluations

Summaries	Population
Box plots of observed values by visit Box plots for change from baseline values by visit	Safety
Change from baseline to last observations	Safety
Treatment-emergent abnormal high lab values (ie, patients shifting from a normal/low maximum baseline value to a high maximum postbaseline value) or abnormal low lab values (ie, patients shifting from normal/high minimum baseline value to a low minimum postbaseline value)	Safety
Shift tables showing the number of patients who shift from each category of maximum (minimum) baseline observation to each category of maximum (minimum) postbaseline observation. Here categories may be low, normal, or high with cut-offs defined in the compound-level safety standards.	Safety
Listing of abnormal findings for laboratory analyte measurements, including qualitative measures	Safety

5.13.4. Vital Signs and Other Physical Findings

As described more fully in compound-level safety standards and in the laboratory-related PhUSE white papers (PhUSE 2013; PhUSE 2015), vital signs will be summarized similarly to the clinical laboratory evaluation (Table KGBP.5.7). For vital signs, treatment-emergent low and high are based on a combination of a specified value and a change or percentage change as defined in the compound-level safety standards.

Table KGBP.5.7. Summary Tables/Figures Related to Vital Signs

Summaries	Population
Box plots for observed values by visit	Safety
Box plots for change from baseline values by visit	Safety
Tables with the number and percentage of subjects who shift from normal/high to low (ie, treatment-emergent low) and the number and percentage of subjects who shift from normal/low to high (ie, treatment-emergent high); the limits are defined in the compound-level safety standards	Safety

5.13.5. Immunogenicity

At the visits and times specified in the SoA, venous blood samples will be collected for the purpose of determining antibody production against lebrikizumab. To aid interpretation of these results, a blood sample for PK analysis will be collected at the same time points. All samples for immunogenicity should be taken pre-dose when applicable and possible. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample collection will be recorded. Immunogenicity samples will be stored at a facility designated by the sponsor and may be assessed at a later date using a validated assay designed to detect anti-drug antibodies (ADAs) in the presence of lebrikizumab at a laboratory designated by the sponsor. Samples may also be used for the development and control of an immunogenicity assay.

5.13.6. Special Safety Topics including Adverse Events of Special Interest

This section includes areas of interest whether due to observed safety findings, potential findings based on drug class, or safety topics anticipated to be requested by a regulatory agency for any reason. In general, potential AESI relevant to these special safety topics will be identified by 1 or more SMQs, by a Lilly-defined MedDRA PT listing based upon the review of the most current version of MedDRA, or by treatment-emergent relevant laboratory changes, as described below. Additional special safety topics may be added as warranted.

Unless otherwise specified, the AESI will be summarized for the safety population.

Full details of the search terms and rules for deriving AESI in each of the sections below are described in the compound-level safety standards along with information about the types of summaries and listings to be provided. In the event that the listing of terms or analysis changes for a special safety topic, it will be documented in the compound-level safety standards, which will supersede this document; it will not warrant an amendment to the individual study SAP.

5.13.6.1. Hepatic Safety

Hepatic labs include alanine aminotransferase (ALT) aspartate transaminase (AST), total bilirubin (TBL), and serum alkaline phosphatase (ALP).

Table KGBP.5.8. Summary Tables/Figure Related to Hepatic Safety

Summaries	Population
ALT and AST: The number and percentage of subjects with a measurement greater than or equal to 3 times (3X), 5 times (5X), and 10 times (10X) the performing lab ULN during the treatment period for all subjects with a postbaseline value and for subsets based on various levels of baseline value TBL and ALP: The number and percentage of subjects with a measurement greater than or equal to 2 times (2X) the performing lab ULN during the treatment period will be summarized for all subjects with a postbaseline value and for subsets based on various levels of baseline value	Safety
Plot of maximum postbaseline ALT vs. maximum postbaseline total bilirubin	Safety

Abbreviations: ALP = serum alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate transaminase; TBL = total bilirubin; ULN = upper limit of normal.

5.13.6.2. Eosinophilia and Eosinophil-Related Disorders

In addition to the standard laboratory summaries (Section 5.13.3), eosinophilia and eosinophil-related AEs will be summarized. Details regarding- eosinophil-related PTs are in the compound-level safety standards.

Table KGBP.5.9. Summary Tables Related to Eosinophilia and Eosinophil-Related Adverse Events

Summaries	Population
Shift table summarizing the number and percentage of participants within each maximum baseline category versus each maximum postbaseline category	Safety

Summary of eosinophil-related TEAE by PT	Safety

Abbreviations: AE = adverse event; PT = Preferred Term; TEAE = treatment-emergent adverse event.

5.13.6.3. Infections, including herpes infections and relevant parasitic infections

Infections will be defined using the PTs from the MedDRA Infections and Infestations SOC. The MedDRA terms used to identify infections considered to be opportunistic infections (OI) in patients with immune-mediated inflammatory conditions treated with immunomodulatory drugs are based on Winthrop et al. (2015) and are listed in the compound-level safety standards. The list contains narrow (more specific) and broad (less specific) PTs with respect to these prospectively defined OIs. Definitions of herpes infections, parasitic infections, and skin infections are listed in the compound-level safety standards.

Table KGBP.5.10. Summary Tables/Listing Related to Infection Related Adverse Events

Summaries	Population
Summary of treatment-emergent infections by maximum severity	Safety
Summary of serious infections by PT	Safety
Summary of infection AEs resulting in permanent study drug discontinuation	Safety
Treatment-emergent adverse events - opportunistic and potential opportunistic infections	Safety
Treatment-emergent adverse events - herpes and parasitic infections	Safety
Treatment-emergent adverse events - skin infections	Safety
Treatment-emergent adverse events - infections characterization and follow-up form	Safety
Listing of patients with potential OIs, serious infections, herpes, and parasitic infections	Safety

Abbreviations: AE = adverse event; OI = opportunistic infections; PT = Preferred Term.

5.13.6.4. Conjunctivitis

Conjunctivitis events are events of special interest and will be identified using PTs nested within the categories of conjunctivitis and keratitis as described in the compound-level safety standards:

Table KGBP.5.11. Summary Table/Listing Related to Conjunctivitis

Summaries	Population
Summary of TEAE of conjunctivitis within categories	Safety
Treatment-emergent adverse events - conjunctivitis and eye inflammation characterization follow-up form	Safety
Listing of patients with conjunctivitis	Safety

Abbreviation: TEAE = treatment-emergent adverse event.

5.13.6.5. Hypersensitivity

Potential hypersensitivity reactions will be determined using the following SMQs: anaphylactic reaction, hypersensitivity, and angioedema. Potential hypersensitivity will be categorized as immediate (ie, occurring the same day as drug administration) and non-immediate (ie, occurring after the day of study drug administration but prior to subsequent drug administration). The planned summaries are provided in Table KGBP.5.12.

Table KGBP.5.12. Summary Tables/Listing Related to Hypersensitivity

Summaries	Population
Treatment-emergent adverse events - potential immediate hypersensitivity reactions (events occurring on day of study drug administration)	Safety
Treatment-emergent adverse events - potential nonimmediate hypersensitivity reactions (events occurring after day of study drug administration)	Safety

5.1.1.1. 5.13.6.6. Injection Site Reactions (ISRs)

Injection site reactions are AEs localized to the immediate site of the administration of a drug. The evaluation of study drug related ISRs will be through the unsolicited reporting of ISR TEAEs. Injection site reactions will be defined using the MedDRA high-level term (HLT) of ISR, excluding certain PTs (eg, those PTs related to injections into a joint) and administration site reactions as described in the compound-level safety standards.

Table KGBP.5.13. Summary Tables Related to Injection Site Reactions

Summary	Population
Summary of TEAE of ISR overall, and by PT	Safety

Abbreviations: HLT = high-level term; ISR = injection site reaction; PT = Preferred Term; TEAE = treatment-emergent adverse event.

5.13.6.7. Malignancies

Malignancies will be defined using PTs from the Malignant tumors SMQ and summarized separately for the 2 categories: Non-melanoma skin cancer (NMSC) and malignancies excluding NMSC.

Table KGBP.5.14. Summary Tables Related to Malignancies

Summary	Population
Summary of TEAE of malignancies within categories of NMSC and malignancy excluding NMSC	Safety

Abbreviations: NMSC = non-melanoma skin cancer; TEAE = treatment-emergent adverse event.

5.13.6.8. Atopic Dermatitis Exacerbation

Atopic dermatitis exacerbation will be defined using PTs specified in the Compound Level Safety Standards and summarized for the Safety Population.

Table KGBP.5.15. Summary Tables Related to Atopic Dermatitis Exacerbation

Analysis	Population
Summary of TEAE of atopic dermatitis exacerbation	Safety

Abbreviations: TEAE = treatment-emergent adverse event.

5.13.6.9. Suicide/Self-Injury

The PTs from the suicide/self-injury SMQ [20000037] will be summarized.

Table KGBP.5.16. Summary Tables Related to Suicidal Ideation and Behavior

Analysis	Population
Summary of TEAE of suicide/self-injury	Safety

Abbreviations: TEAE = treatment-emergent adverse event.

5.14 Subgroup Analyses

Subgroup analyses will be conducted for the primary endpoint, EASI-75 at Week 16, using descriptive statistics.

The following subgroups will be analyzed:

- Baseline Severity
- Sex
- Age (≥12 to <18, ≥18)
- Race +/- ethnicity
- Fitzpatrick phototype

Some additional subgroup analyses may be added. The analysis of additional subgroups will not require an amendment to the SAP.

5.15 Protocol Deviations

Protocol deviations will be identified throughout the study. Important protocol deviations are defined as those deviations from the protocol likely to have a significant impact on the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

Potential examples of important protocol deviations include patients who violated the inclusion/exclusion criteria, used an interfering concomitant medication, and significant non-compliance with study medication (<75% of expected injections). Refer to a separate document called "KGBP Trial Issues Management Plan" for the important protocol deviations with categorizations.

The number and percentage of patients having important protocol deviations will be summarized within category and subcategory of deviation for Weeks 0-16 of the Treatment Period using the ITT population and for Weeks 16-24 of the Treatment Period using Treatment Period II Population.

A by-patient listing of important protocol deviations will be provided for the ITT population.

5.16 Interim Analyses and Data Monitoring

Interim Analysis:

One interim analysis (primary lock) will be conducted after all enrolled participants have been evaluated at Week 16 or discontinued prior to Week 16. This interim database lock will include all efficacy and safety data collected by the cutoff date. Due to the open-label and descriptive nature of this study, there is no unblinding nor alpha adjustment.

Additional analyses and snapshots of study data may be performed to fulfill the need for regulatory interactions or publication purposes.

Final DBL: A final DBL will occur after all patients have either completed the study through the 12-week safety follow-up period of the study or discontinued the current study.

5.17 Annual Report Analyses

Based on regulatory requirements for the DSUR, reports will be produced (if not already available from the study CSR) for the reporting period covered by the DSUR.

5.18 Clinical Trial Registry Analyses

Additional analyses will be performed (if not already available from the study CSR) for the purpose of fulfilling the CTR requirements.

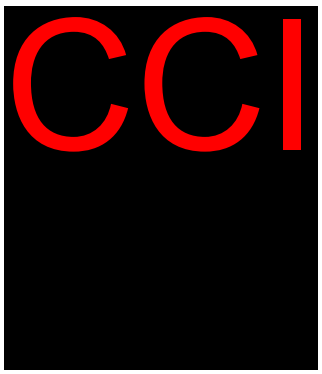
Analyses provided for the CTR requirements include the following:

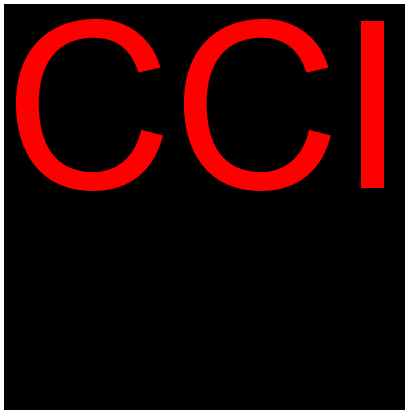
Summary of AEs, provided as a dataset, will be converted to an XML file. Both SAEs and 'other' AEs are summarized by MedDRA PT.

- An AE is considered 'serious' whether or not it is a TEAE.
- An AE is considered in the 'other' category if it is both a TEAE and is not serious. For each SAE and 'other' AE, for each term the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term, and
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'other' AEs that occur in <5% of patients/subjects may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures (eg, the CSR, manuscripts, and so forth).

5.19 Biomarker Analysis

Serum samples will be collected to discern responder variability within the study and to track response variability to lebrikizumab. Biomarkers will include but not limited to:





Samples will be collected according to the schedule described in the SoA and as detailed in laboratory manual provided separately to sites.

6 Unblinding Plan

Not applicable.

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7 References

Adelekun A, Onyekaba G, Lipoff JB. Skin color in dermatology textbooks: An updated evaluation and analysis. J Am Acad Dermatol. 2021;84(1):194-196. https://doi.org/10.1016/j.jaad.2020.04.084

Auriemma M, Vianale G, Amerio P, Reale M. Cytokines and T cells in atopic dermatitis. Eur Cytokine Netw. 2013;24(1):37-44. https://doi.org/10.1684/ecn.2013.0333

Basra MK, Salek MS, Camilleri L, et al. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230(1):27 33. https://doi.org/10.1159/000365390

Bieber T. Atopic dermatitis. N Engl J Med. 2008;358(14):1483-1494. https://doi.org/.1056/NEJMra074081

Bieber T, Novak N. Pathogenesis of atopic dermatitis: new developments. Curr Allergy Asthma Rep. 2009;9(4):291-294. https://doi.org/10.1007/s11882-009-0041-2

Bieber T. Atopic dermatitis 2.0: from the clinical phenotype to the molecular taxonomy and stratified medicine. Allergy. 2012;67(12):1475-1482. https://doi.org/10.1111/all.12049

Bieber T, Straeter B. Off-label prescriptions for atopic dermatitis in Europe. Eur J Aller Clin Immunol. 2015;70(1):6-11. https://doi.org/10.1111/all.12498

Brunner PM, Guttman-Yassky E. Racial differences in atopic dermatitis. Ann Allergy Asthma Immunol. 2019;122(5):449-455. https://doi.org/10.1016/j.anai.2018.11.015

Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol. 2004;140(12):1513-1519. https://doi.org/10.1001/archderm.140.12.1513

Chen V, Akhtar S, Zheng C, et al. Assessment of changes in diversity in dermatology clinical trials between 2010-2015 and 2015-2020: A Systematic Review. JAMA Dermatol. 2022;158(3):288-292. https://doi.org/10.1001/jamadermatol.2021.5596

Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. J Invest Dermatol. 2019;139(3):583-590. doi: 10.1016/j.jid.2018.08.028.

Choy DF, Hsu DK, Seshasayee D, et al. Comparative transcriptomic analyses of atopic dermatitis and psoriasis reveal shared neutrophilic inflammation. J Allergy Clin Immunol. 2012;130(6):1335-1343. https://doi.org/10.1016/j.jaci.2012.06.044

Davis EC, Callender VD. Postinflammatory hyperpigmentation: a review of the epidemiology, clinical features, and treatment options in skin of color. J Clin Aesthet Dermatol. 2010;3(7):2031

Ebede T, Papier A. Disparities in dermatology educational resources. J Am Acad Dermatol. 2006;55(4):687-690. https://doi.org/10.1016/j.jaad.2005.10.068

Eichenfield LF et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338-351. 10.1016/j.jaad.2013.10.010

Esche C, de Benedetto A, Beck LA. Keratinocytes in atopic dermatitis: inflammatory signals. Curr Allergy Asthma Rep. 2004;4(4):276-284. https://doi.org/10.1007/s11882-004-0071-8

Faye O, Meledie N'Djong AP, Diadie S, et al. Validation of the Patient-Oriented SCORing for atopic dermatitis tool for black skin. J Eur Acad Dermatol Venereol. 2020;34(4):795-799. https://doi.org/10.1111/jdv.15999

Gooderham MJ, Hong HC, Eshtiaghi P, Papp KA. Dupilumab: A review of its use in the treatment of atopic dermatitis. Am Acad Dermatol. 2018;78(3):S28-S36. https://doi.org/10.1016/j.jaad.2017.12.022

Guttman-Yassky E, Blauvelt A, Eichenfield LF, et al. Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a Phase 2b randomized clinical trial. JAMA Dermatol. 2020;156(4):411-420. https://doi.org/10.1001/jamadermatol.2020.0079

Hamid Q, Naseer T, Minshall EM, et al. In vivo expression of IL-12 and IL-13 in atopic dermatitis. J Allergy Clin Immunol. 1996;98(1):225-231. https://doi.org/10.1016/s00916749(96)70246-4

Hanifin JM, Thurston M, Omoto M, et al. EASI Evaluator Group. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol. 2001;10(1):11-18. https://doi.org/10.1034/j.1600-0625.2001.100102.x

Harrop J, Chinn S, Verlato G, et al. Eczema, atopy and allergen exposure in adults: a population based study. Clin Exp Allergy. 2007;37(4):526-35. doi: 10.1111/j.1365-2222.2007.02679.x.

He JQ, Chan-Yeung M, Becker AB, et al. Genetic variants of the IL13 and IL4 genes and atopic diseases in at-risk children. Genes Immun. 2003;4(5):385-389. https://doi.org/10.1038/sj.gene.6363985

High, WA, Tomasini CF, Argenziano G, Zalaudek I. Basic principles of dermatology. In Bolognia JL, Jorizzo JL, Schaffer JV., editors. Dermatology (3rd ed.). China: Elsevier;2012:pp.8

Hongbo Y, Thomas CL, Harrison MA, et al. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol. 2005;125(4):659-664. https://doi.org/10.1111/j.0022-202x.2005.23621.x

Hummelshoj T, Bodtger U, Datta P, et al. Association between an interleukin-13 promoter polymorphism and atopy. Eur J Immunogenet. 2003;30(5):355-359. https://doi.org/10.1046/j.1365-2370.2003.00416.x

Ibraheim MK, Gupta R, Dao H, et al. Evaluating skin of color education in dermatology residency programs: data from a national survey. Clin Dermatol. 202125:S0738081X(21)00257 1. https://doi.org/10.1016/j.clindermatol.2021.11.015

Jeong CW, Ahn KS, Rho NK, et al. Differential in vivo cytokine mRNA expression in lesional skin of intrinsic vs. extrinsic atopic dermatitis patients using semiquantitative RT-PCR. Clin Exp Allergy. 2003;33(12):1717-1724. https://doi.org/10.1111/j.1365-2222.2003.01782.x

Jungersted JM, Høgh JK, Hellgren LI, et al. Ethnicity and stratum corneum ceramides. Br J Dermatol. 2010;163(6):1169-1173. https://doi.org/10.1111/j.1365-2133.2010.10080.x

Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups-Variations in epidemiology, genetics, clinical presentation and treatment. Exp Dermatol. 2018;27(4):340-357. https://doi.org/10.1111/exd.13514

Khilji FA, Gonzalez M, Finlay AY. Clinical meaning of change in Dermatology Life Quality Index scores. Br J Dermatol. 2002;147(suppl 62):25-54.

Kiebert G, Sorensen SV, Revicki D, et al. Atopic dermatitis is associated with a decrement in health-related quality of life. Int J Dermatol. 2002;41(3):151-8. doi: 10.1046/j.13654362.2002.01436.x.

Kurtti A, Austin E, Jagdeo J. Representation of skin color in dermatology-related google image searches. J Am Acad Dermatol. 2022;86(3):705-708. https://doi.org/10.1016/j.jaad.2021.03.036

La Grutta S, Richiusa P, Pizzolanti G, et al. CD4(+)IL-13(+) cells in peripheral blood well correlates with the severity of atopic dermatitis in children. Allergy. 2005;60(3):391-395. https://doi.org/10.1111/j.1398-9995.2005.00733.x

Muizzuddin N, Hellemans L, Van Overloop L, et al. Structural and functional differences in barrier properties of African American, Caucasian and East Asian skin. J Dermatol Sci. 2010;59(2):123-8. doi: 10.1016/j.jdermsci.2010.06.003.

Neis MM, Peters B, Dreuw A, et al. Enhanced expression levels of IL-31 correlate with IL-4 and IL-13 in atopic and allergic contact dermatitis. J Allergy Clin Immunol. 2006;118(4):930-937. https://doi.org/10.1016/j.jaci.2006.07.015

Newton L, DeLozier AM, Griffiths PC, et al. Exploring content and psychometric validity of newly developed assessment tools for itch and skin pain in atopic dermatitis. J Patient Rep Outcomes. 2019;3(1):42. https://doi.org/10.1186/s41687-019-0128-z.

Noda S, Suárez-Fariñas M, Ungar B, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. J Allergy Clin Immunol. 2015;136(5):1254-1264. https://doi.org/10.1016/j.jaci.2015.08.015

Novak N, Kruse S, Kraft S, et al. Dichotomic nature of atopic dermatitis reflected by combined analysis of monocyte immunophenotyping and single nucleotide polymorphisms of the interleukin-4/interleukin-13 receptor gene: the dichotomy of extrinsic and intrinsic atopic

dermatitis. J Invest Dermatol. 2002;119(4):870-875. https://doi.org/10.1046/j.15231747.2002.00191

Pariser DM, Simpson EL, Gadkari A, et al. Evaluating patient-perceived control of atopic dermatitis: design, validation, and scoring of the Atopic Dermatitis Control Tool (ADCT). Curr Med Res Opin. 2020;36(3):367-376. https://doi.org/10.1080/03007995.2019.1699516.

Price KN, Hsiao JL, Shi VY. Race and ethnicity gaps in global hidradenitis suppurativa clinical trials. Dermatology. 2021;237(1):97-102. https://doi.org/10.1159/000504911

Purwar R, Werfel T, Wittmann M. IL-13-stimulated human keratinocytes preferentially attract CD4+CCR4+ T cells: possible role in atopic dermatitis. J Invest Dermatol. 2006;126(5):1043 1051. https://doi.org/10.1038/sj.jid.5700085

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5):353 365. https://doi.org/10.2165/00019053-199304050-00006

Sacotte R, Silverberg JI. Epidemiology of adult atopic dermatitis. Clin Dermatol. 2018; 36(5):595–605. https://doi.org/10.1016/j.clindermatol.2018.05.007

Sangha AM. Dermatological Conditions in SKIN OF COLOR-: Managing atopic dermatitis. J Clin Aesthet Dermatol. 2021;14(3 Suppl 1):S20-S22.

Schwartzman G, Lei D, Ahmed A, et al. Longitudinal course and phenotypes of health-related quality of life in adults with atopic dermatitis. Clin Exp Dermatol. 2022;47(2):359-372. https://doi.org/10.1111/ced.14948

Seegräber M, Srour J, Walter A, et al. Dupilumab for treatment of atopic dermatitis. Expert Rev Clin Pharmacol. 2018;11(5):467-474. https://doi.org/10.1080/17512433.2018.1449642

Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol. 2013;132(5):1132-8. https://doi.org/10.1016/j.jaci.2013.08.031

Silverberg JI, Margolis DJ, Boguniewicz M, et al. Distribution of atopic dermatitis lesions in united states adults. J Eur Acad Dermatol Venereol. 2019;33(7):1341-1348. https://doi.org/10.1111/jdv.15574

Silverberg JI, DeLozier A, Sun L, et al. Psychometric properties of the itch numeric rating scale, skin pain numeric rating scale, and atopic dermatitis sleep scale in adult patients with moderateto-severe atopic dermatitis. Health Qual Life Outcomes. 2021;19(1):247. https://doi.org/10.1186/s12955-021-01877-8

Simon D, Wollenberg A, Renz H, Simon HU. Atopic dermatitis: Collegium Internationale Allergologicum (CIA) update 2019. Int Arch Allergy Immunol. 2019;178(3):207-218. https://doi.org/10.1159/000497383

Simpson E, Eckert L, Gadkari A, et al. Validation of the Atopic Dermatitis Control Tool (ADCT©) using a longitudinal survey of biologic-treated patients with atopic dermatitis. BMC Dermatol. 2019;19(1):15. https://doi.org/10.1186/s12895-019-0095-3

Stalder JF, Barbarot S, Wollenberg A, et al. PO-SCORAD Investigators Group. Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. Allergy. 2011;66(8):1114-21. https://doi.org/10.1111/j.1398-9995.2011.02577.x

Suárez-Fariñas M, Dhingra N, Gittler J, et al. Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. J Allergy Clin Immunol. 2013;132(2):361-370. https://doi.org/10.1016/j.jaci.2013.04.046

Tazawa T, Sugiura H, Sugiura Y, Uehara M. Relative importance of IL-4 and IL-13 in lesional skin of atopic dermatitis. Arch Dermatol Res. 2004;295(11):459-464. https://doi.org/10.1007/s00403-004-0455-6

Van Bever HPS, Llanora G. Features of childhood atopic dermatitis. Asian Pac J Allergy Immunol. 2011;29(1):15-24.

Wei W, Anderson P, Gadkari A, et al. Extent and consequences of inadequate disease control among adults with a history of moderate to severe atopic dermatitis. J Dermatol. 2018;45(2):150-157. https://doi.org/10.1111/1346-8138.14116

Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016;387(10023):1109-1122. https://doi.org/10.1016/S0140-6736(15)00149-X

Weidinger S, Beck LA, Bieber T, et al. Atopic dermatitis. Nat Rev Dis Primers. 2018;4(1):1. https://doi.org/10.1038/s41572-018-0001-z

Werfel T, Allam JP, Biedermann T, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. J Allergy Clin Immunol. 2016;138(2):336-349. https://doi.org/10.1016/j.jaci.2016.06.010

Williams H, Stewart A, von Mutius E, et al. Is eczema really on the increase worldwide? J Allergy Clin Immunol. 2008;121(4):947-954.e15. https://doi.org/10.1016/j.jaci.2007.11.004

Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis. 2015;74(12):2107-2116. https://doi.org/10.1136/annrheumdis-2015-207841

Yosipovitch G, Reaney M, Mastey V,et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol. 2019; 181(4):761-769. https://doi.org/10.1111/bjd.17744

Yosipovitch G, Rams A, Baldasaro J, et al. Content Validity And Assessment of the psychometric properties and score interpretation of a Sleep-Loss Scale score in atopic dermatitis. Revolutionizing Atopic Dermatitis – December, 2021

Zhao CY, Wijayanti A, Doria MC, et al. The reliability and validity of outcome measures for atopic dermatitis in patients with pigmented skin: A grey area. Int J Womens Dermatol. 2015;1(3):150-154. https://doi.org/10.1016/j.ijwd.2015.05.002

Zuberbier T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. J Allergy Clin Immunol. 2006;118(1):226-32. https://doi.org/10.1016/j.jaci.2006.02.031

Appendix 1. Definition of Rescue Medications

The AD rescue therapy in this study is defined as: high-potency TCS >10 days, topical JAK inhibitors, and systemic AD therapy. The topical and systemic treatments are defined as follows:

1. **Topical AD Treatment (including TCSs, TCI, crisaborole, and Ruxolitinib)**

   Route of topical treatments includes: Topical and Transdermal.

   TCS: ATC code is D07

   High Potency TCS: ATC codes are D07AC or D07AD

   Low or moderate potency TCS: ATC code is D07, excluding D07AC or D07AD

   TCI: PT includes: TACROLIMUS, PIMECROLIMUS

   Crisaborole: PT includes: CRISABOROLE

   Topical Ruxolitinib: ATC code is D11AH09

2. **Systemic AD Treatment (including systemic corticosteroids, immunosuppressant, biologics, and phototherapy/PUVA)**

   Route of systemic treatments administration includes: Oral, Intra-Arterial, Intramuscular, Intraperitoneal, Intravenous, Subcutaneous, and Transdermal. (This condition applies to the following categories except for phototherapies.)

   Systemic Corticosteroids: ATC code is H02

   Immunosuppressant: Defined as: ATC2 is L04 or PTs of Abrocitinib or Ruxolitinib excluding PTs mentioned in Biologics

   Biologics: Defined as following PTs:

   Infliximab, Infliximabum, Etanercept, Etanerceptum, Adalimumab, Adalimumabum, Certolizumab, Certolizumabum, Certolizumab pegol, Golimumab, Golimumabum, Ozoralizumab, Afelimomab, Afelimomabum, Tumor Necrosis Factor Alpha (TNF-) Inhibitors, Tabalumab, Tregalizumab, Anakinra, Basiliximab, Basiliximabum, Daclizumab, Daclizumabum, Tocilizumab, Tocilizumabum, Mepolizumab, Mepolizumabum, Rilonacept, Rilonaceptum, Ustekinumab, Canakinumab, Briakinumab, Fezakinumab, Sirukumab, Sarilumab, Lebrikizumab, Secukinumab, Olokizumab, Gevokizumab, Brodalumab, Ladarixin, Ixekizumab, Dupilumab, Tildrakizumab, Tildrakizumabum, Reslizumab, Reslizumabum, Guselkumab, Guselkumabum, Olamkicept, Fletikumab, Bimekizumab, Mirikizumab, Risankizumab, Abatacept, Ligelizumab, Vedolizumab, Belimumab, Nemolizumab, Tralokinumab, Omalizumab

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Phototherapy or PUVA:

Programming search of medication name (actual term or PT) contains ‘photo’ then medicals to manually review to confirm whether the medication in question is indeed ‘Phototherapy’ or ‘Photochemotherapy’.

PPD PPD
23 Jun 2023 14:52:57 UTC (Z)
REASON: I approve this document
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PPD PPD
09 Jun 2023 20:08:20 UTC (Z)
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