Statistical Analysis Plan Version 3 J2T-DM-KGAE

An open-label, single-arm study to assess the safety and efficacy of lebrikizumab in adolescent patients with moderate-to-severe atopic dermatitis

NCT04250350

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1. Statistical Analysis Plan: J2T-DM-KGAE (DRM06-AD17): An Open-Label, Single-Arm Study to Assess the Safety and Efficacy of Lebrikizumab in Adolescent Patients with Moderate-to-Severe Atopic Dermatitis

Lebrikizumab (LY3650150)

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[Protocol J2T-DM-KGAE]
[Phase 3]

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3. List of Abbreviations

Term	Definition
ADA	anti-drug antibodies
AD	atopic dermatitis
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
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EASI	Eczema Area and Severity Index
EASI-50	Eczema Area and Severity Index improvement of ≥50%
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

HLT	high-level term
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
ISR	injection site reactions
Lilly	Eli Lilly and Company
LOCF	last observation carried forward
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NAb	Neutralizing anti-drug antibodies
NMSC	non-melanoma skin cancer
OI	opportunistic infection
PD	pharmacodynamic
PhUSE	Pharmaceutical Users Software Exchange
PK	pharmacokinetic
PROMIS	Patient-Reported Outcomes Information System
PT	Preferred Term
Q2W	every 2 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBL	total bilirubin
TE-ADA	treatment-emergent ADA
TEAE	treatment-emergent adverse event
WHO	World Health Organization

4. Revision History

Statistical Analysis Plan Version 1 was approved prior to database lock on September 14, 2020.

Statistical Analysis Plan Version 2 was approved prior to database lock on January 18, 2022.

Statistical Analysis Plan Version 3 was approved prior to database lock.

Changes in Version 2 and Version 3 are documented in the following 2 tables. Minor corrections/additions may not be included.

Revisions in SAP Version 2:

Section	Action
Section 7.3.3	Added Section 7.3.3. Markov chain Monte Carlo - Multiple Imputation (MCMC-MI)
Section 7.13.2	Removed sentence related to AE starting time, since the AE starting time was not collected
Section 7.10	Updated the BSA total calculation in Table KGAE.7.3
Section 7.13.6.3	Added new analyses in Table KGAE.7.10
Section 7.13.6.4	Added new analysis in Table KGAE.7.11
Section 7.13.6.5	Added new analyses in Table KGAE.7.12
Section 7.13.6.8	Added Section 7.13.6.8. Atopic Dermatitis Exacerbation
Section 7.13.6.9	Added Section 7.13.6.9. Suicide/Self-Injury
Throughout the document	Minor editorial changes and/or clarifications were made

Abbreviations: AE = adverse event; BSA = body surface area.

Revisions in SAP Version 3:

Section	Description of Change	Rationale
Section 7.1.1	Added "enrolled" to the definition of the safety population in the body text and in Table KGAE.7.1	Clarification
Section 7.3.1	Added health outcome endpoints to the "as-observed" analyses	Clarification
Section 7.3.2	Updated LOCF strategy	Clarification on strategy for values collected subsequent to treatment discontinuation.
Section 7.3.3	1. Updated MCMC-MI strategy 2. Removed PROMIS measures from Table KGAE.7.2, and updated DLQI/CDLQI analyses	1. Clarification on strategy for imputing baseline. Address strategy for values collected subsequent to treatment discontinuation. Correction to details of SAS code implementation. 2. Correction
Section 7.7.1	Updated subcategories for AD treatments used in the past	Clarification
Section 7.9	Updated description of rescue medications	Clarification

Section	Description of Change	Rationale
Section 7.10	1. Added detail for construction of confidence intervals 2. Updated DLQI(0,1), CDLQI(0,1), and DLQI 4-point improvement variable definitions in Table KGAE.7.3 3. Removed CDLQI 4-point improvement endpoint from Table KGAE.7.3	1. Clarification 2. Clarification 3. There is no established minimum clinically important difference for CDLQI
Section 7.11	Added detail for construction of confidence intervals	Clarification
Section 7.13.1	Added sentence about systemic therapy use with respect to exposure calculation	Clarification
Appendix 1	Added definition of rescue medications	To provide detailed instructions on how to determine rescue medications for this study

Abbreviations: AD = atopic dermatitis; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo-multiple imputation.

5. Study Objectives

Table KGAE.5.1 shows the protocol-defined objectives and endpoints of the study. In addition, the summaries of some non-protocol-defined endpoints are described in Section 7.10 to provide supportive evidence of efficacy.

Table KGAE.5.1. Protocol-Defined Objectives and Endpoints

Study Objective: To evaluate the safety and efficacy of lebrikizumab in adolescent patients (≥12 to <18 years weighing ≥40 kg) with moderate-to-severe AD.
Primary Endpoint: Describe the proportion of patients discontinued from study treatment due to adverse events through the last treatment visit.
Secondary Endpoints: Over the duration of the study: • Percentage of patients with an IGA score of 0 or 1 and a reduction ≥2-points from baseline • Percentage of patients achieving response of Eczema Area and Severity Index improvement of ≥75% (EASI-75) (≥75% reduction from baseline in EASI score) • Percentage change from baseline in EASI score and percentage of patients achieving Eczema Area and Severity Index improvement of ≥50% (EASI-50) and Eczema Area and Severity Index improvement of ≥90% (EASI-90) (≥50 and ≥90% reduction from baseline in EASI score, respectively) • Change from baseline in body surface area (BSA) • Change from baseline in Patient-Reported Outcomes Information System (PROMIS)® Anxiety and Depression measures • Change from baseline and improvement in Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (CDLQI) • Pharmacokinetics (PK)

Abbreviations: IGA = Investigator's Global Assessment; AD = atopic dermatitis.

6. Study Design

6.1. Summary of Study Design

Study J2T-DM-KGAE (KGAE) (also known as DRM06-AD17) is an open-label, single-arm study to assess the safety and efficacy of lebrikizumab in adolescent patients with moderate-to-severe AD. A sample size of approximately 200 adolescent patients (≥12 to <18 years, weighing ≥40 kg) is planned.

The study is composed of a 52-week treatment period, with the last study drug injection at Week 50. Patients completing this 52-week study will be offered active lebrikizumab treatment in a separate long-term extension study, J2T-DM-KGAA (DRM06-AD07). Patients who early terminate or choose not to enter the long-term extension study will undergo a safety follow-up visit approximately 12 weeks after the last study drug injection.

6.1.1. Screening

Screening Period: Patients will be evaluated for study eligibility before the baseline visit (Day 1).

6.1.2. Baseline and Week 2

Patients who meet eligibility criteria are assigned to receive 250-mg lebrikizumab Q2W. At the baseline and Week 2 clinic visits, all patients will be administered a loading dose of 500-mg lebrikizumab as two 2-mL, 250-mg (125-mg/mL) prefilled syringes with a preassembled needle safety device.

6.1.3. Week 4 to Week 52

Patients will return to the clinic at Weeks 4, 6, 8, and every 4 weeks thereafter through Week 52 for safety and efficacy assessments. For Weeks 4 through 50, all patients will be administered one 250 mg lebrikizumab syringe, Q2W. Study drug injections will be administered in the clinic through Week 8 and patients or their caregivers will be instructed on self-administration of the study drug for injections following the Week 8 visit. The clinic visit at Week 52 is the end of the treatment period. Patients completing this 52-week study will be offered active lebrikizumab treatment in a separate long-term extension study (DRM06-AD07/J2T-DM-KGAA).

6.1.4. Safety Follow-up Visit

Patients who early terminate or choose not to enter the long-term extension study will undergo a safety follow-up visit approximately 12 weeks after the last study drug injection.

6.2. Determination of Sample Size

CCI [redacted]

6.3. Method of Assignment to Treatment

This is a single-arm study. All enrolled patients are assigned to 250-mg lebrikizumab Q2W.

7. A Priori Statistical Methods

7.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly. 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® 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.

7.1.1. Analysis Populations

All non-PK analyses will be performed using the safety population. All enrolled patients who receive at least 1 confirmed dose of lebrikizumab 250 mg will be included in the safety population.

All PK analyses will be performed using the PK population. All patients who are enrolled and have a predose sample and at least 1 postdose analyzable sample will be included in the PK population.

All entered patients, consisting of all patients who signed informed consent, and the safety population, will be used to summarize patient disposition. These populations will also be used for listings.

The number of patients included in each population will be summarized.

Table KGAE.7.1 describes the analysis populations.

Table KGAE.7.1. Analysis Populations

Population	Description
All Entered Patients	All patients who signed informed consent. Patient flow will be summarized.
Safety Population	All enrolled patients who received at least 1 confirmed dose of lebrikizumab 250 mg. All non-PK analyses will be performed using the safety population.
PK Population	All patients who are enrolled and have a predose sample and at least 1 postdose analyzable sample. All PK analyses will be performed using this population.

Abbreviations: PK = pharmacokinetic(s).

7.1.2. General Considerations for Analyses

Data will be summarized using descriptive statistics. No inferential testing will be performed. Categorical variables will be tabulated with frequencies and percentages. Continuous variables will be tabulated with mean, median, standard deviation, and range (minimum and maximum).

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 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 postbaseline observation or to each scheduled postbaseline visit for laboratory and vital signs results: baseline will be the last scheduled nonmissing assessment recorded during the baseline period.

7.2. Adjustments for Covariates

No statistical tests will be performed.

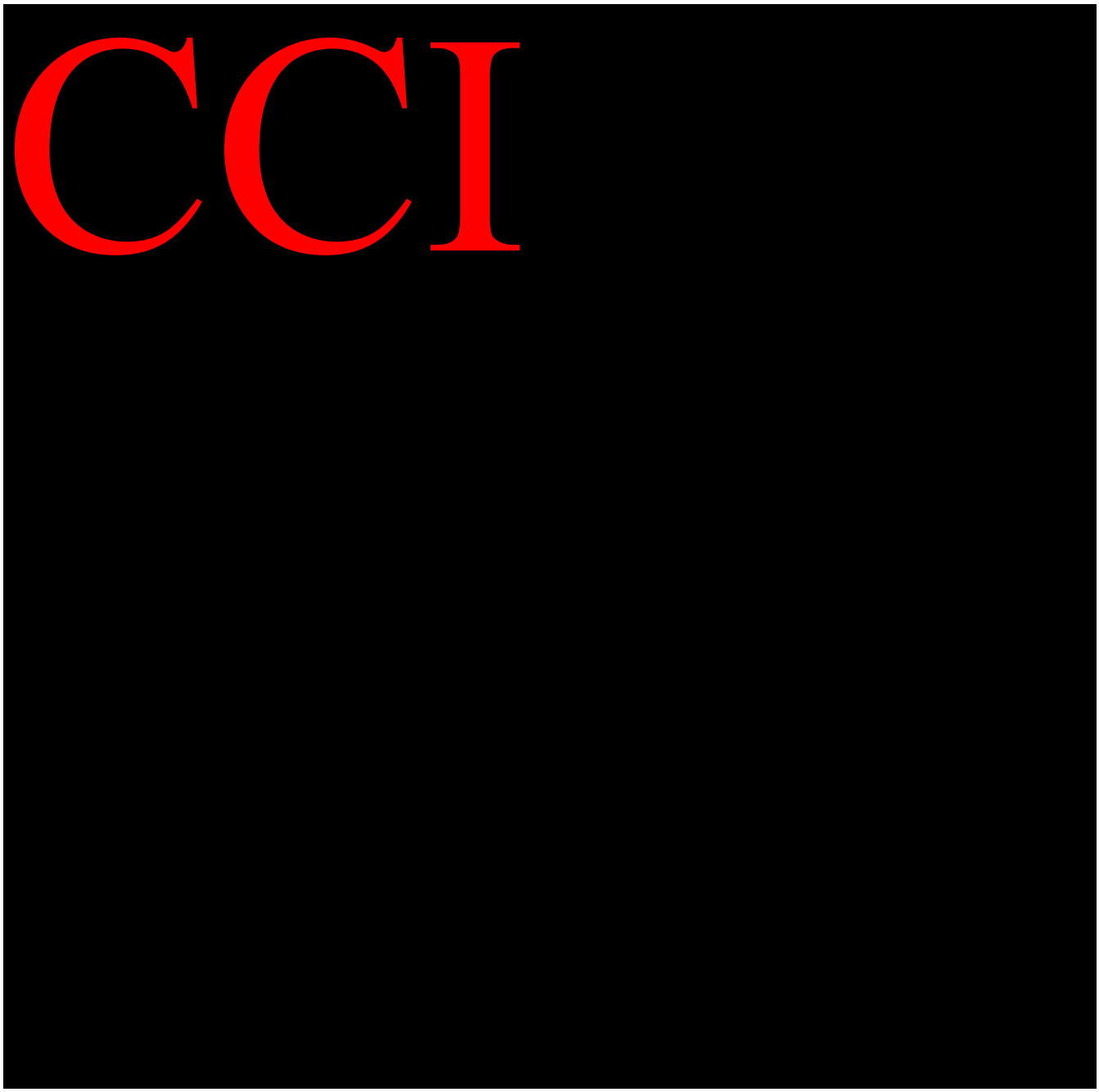
7.3. Handling of Dropouts or Missing Data

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.

7.3.1. 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. Therefore, this estimand is conditional and targets the effect of treatment conditional on completion of treatment through the time point of interest. Because the estimand is defined for a subpopulation conditional on an intercurrent event, it is not causal. Summaries based on observed data at each postbaseline visit will be provided. All efficacy and health outcome endpoints will be summarized using an “as observed” analysis.



7.4. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. The countries will be categorized into geographic regions (US, EU, rest of world) which will be used for subgroup analyses, described in Section 7.14.

7.5. Multiple Comparisons/Multiplicity

No statistical tests will be performed.

7.6. Patient Disposition

The following patient disposition summaries will be provided (details of the analysis populations can be found in Section 7.1.1):

- The total number and percentage of patients entering each statistical analysis population is defined in Section 7.1.1 (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 were treated and completed treatment, and the number and percentage of patients who discontinued the treatment at any time, by primary reason for discontinuation of treatment (analysis population: safety population).

  - The primary endpoint of Study KGAE is the proportion of patients discontinued from study treatment due to AEs through the last treatment visit.

- 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: safety population).

All patients who were treated (i.e., in the safety population) and 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 region, country, and center/site will be summarized with the number of patients who entered the study, number of treated patients, number of patients discontinued from study treatment, and number of patients discontinued from the study.

7.7. Patient Characteristics

7.7.1. Demographics and Baseline Characteristics

Patient demographic variables and baseline characteristics will be summarized for the safety population. 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)
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Other, or Not Reported)
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, or Unknown)
- region (US, EU, or rest of world)
- country
- weight (kg)
- weight category (<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 safety 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
    - 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, and
    - topical calcineurin inhibitors
    - systemic treatments: systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, janus kinase inhibitors, azathioprine, methotrexate, phototherapy, photochemotherapy, dupilumab, tralokinumab, and other biologics (e.g., B-cell depleting biologics)
    - other non-biologic medication/treatment
- IGA score: 3 versus 4
- EASI score
- BSA
- PROMIS® anxiety score
- PROMIS depression score, and
- DLQI/CDLQI.

7.7.2. Medical History

Medical histories are defined as the conditions/events recorded on the *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 safety population using the MedDRA PT nested within SOC.

The number and percentage of patients with specific medical history events of interest prespecified on the *History Assessment* eCRF (hand dermatitis, facial dermatitis, conjunctivitis, herpes zoster, and others) will be summarized for the safety population.

7.8. Treatment Compliance

Treatment compliance with investigational product will be summarized for patients who receive at least 1 confirmed dose of lebrikizumab (i.e., the safety population). 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 *Study Drug Administration* eCRF page and on the prompt "Please select the number of syringes successfully injected' in the *Dosing Diary*.

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.

7.9. Prior and Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical drug classes using the latest version of the WHO drug dictionary. Medication start and stop dates will be compared to the date of first dose of treatment to be classified as prior or concomitant.

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 and continue into the treatment period.

Prior medication and concomitant medication will be summarized by drug class and PT for the safety population.

Rescue medications used during the study treatment period will be presented for the safety population based on the information collected on the *Atopic Dermatitis Treatments* eCRF page. This will include: (1) topical therapy, (2) systemic therapy (e.g., systemic corticosteroids, phototherapy, cyclosporin, etc.). More information on the definition of rescue medications can be found in Appendix 1.

7.10. Efficacy Analyses

Table KGAE.7.3 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 95% confidence interval for the percentage. The 95% confidence interval

will be constructed using the asymptotic method, without continuity correction (that is, the normal approximation to the binomial distribution). For continuous parameters, descriptive statistics will include n (number of patients), mean, standard deviation, median, minimum, and maximum. These summaries will be provided for the data as-observed, and after implementation of LOCF and MCMC-MI imputation methods.

The IGA, EASI, and BSA will be reported by clinic visit.

Table KGAE.7.3. 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] • IGA (0)	• Observed score of 0 or 1 and change from baseline ≤-2 • Observed score of 0	Missing if baseline or observed value is missing 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 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 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: $EASI = 0.1*EASI_{head\ and\ neck} + 0.3*EASI_{trunk} + 0.2*EASI_{upper\ limbs} + 0.4*EASI_{lower\ limbs}$	NA: partial assessments cannot be saved.
		• 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-50[a]	% improvement in EASI score from baseline ≥50%: % change from baseline ≤-50	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 = $BSA_{head\ and\ neck}$ + BSA_{trunk} + $BSA_{upper\ limbs}$ + $BSA_{lower\ limbs}$	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: Very much = 3 A lot = 2 A little = 1 Not at all = 0	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) in patients who had baseline DLQI score >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 al. 2005).	Missing if DLQI total score is missing
		4-point improvement in patients who had baseline DLQI score ≥4[a]	Change from baseline ≤-4	Missing if baseline is missing or observed value is missing.

	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).	DLQI total score change from baseline[a]	Calculated as: observed DLQI (total score) - baseline DLQI (total score)	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? 6. How much has your skin make it difficult for you to do any sport?	If 1 question in a domain is missing, that domain is missing.
		DLQI work and school domain	Sum of responses of questions 7A and 7B:	If the answer to question 7A is missing, this domain is

			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?	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) in patients who had baseline CDLQI score >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
		CDLQI total score change from baseline[a]	Calculated as: observed CDLQI (total score) - baseline CDLQI (total score)	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 skin been? 2. Over the last week, how embarrassed or **self conscious**, **upset** or **sad** have you been because of your skin?	If 1 question in a domain is missing, that domain is missing.
		CDLQI sleep domain	Response of question 9 9. Over the last week, how much has	Single item, missing if missing

			your **sleep** been affected by your skin problem?	
		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 Last week, was it **school time?** → **If school time:** Over the last week, how much did your skin affect your **school work?** **OR** was it **holiday time?** → **If holiday time:** How much over the last week, has your skin problem interfered with your enjoyment of the **holiday?**	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.
Patient-Reported Outcomes Measurement Information System (PROMIS®)	PROMIS is a set of person-centered measures that evaluate and monitor physical, mental, and social health in adults and children. There are PROMIS instruments for assessing anxiety and for assessing depression. Patients will complete pediatric versions of these for the duration of the study.	PROMIS anxiety total score[a] PROMIS depression total score[a]	A PROMIS anxiety has 8 questions on Emotion Distress-Anxiety (or Pediatric Anxiety) (Short Form 8a). Each score ranges from 1-5. Total raw scores are converted to T-scores, with higher scores representing greater anxiety. A PROMIS depression has 8 questions on Emotion Distress-Depression (or Pediatric Depressive Symptom) (Short Form 8a). Each score ranges 1-5. Total raw scores are converted to T-scores with higher scores representing greater depression. Calculation is made by HealthMeasures Scoring Service, powered by Assessment Center[SM].	Total score can be derived even with partial response, as the instrument uses item-response theory method.
		Change from baseline in PROMIS anxiety total score Change from baseline in PROMIS depression total score	Change from baseline: observed score - baseline PROMIS anxiety total score Change from baseline: observed score - baseline PROMIS depression total score	Missing if baseline or observed value is missing

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

[a] Secondary endpoints.

7.11. Health Outcomes/Quality-of-Life Analyses

The description and derivation of the DLQI/CDLQI and the PROMIS® anxiety and depression are described in Table KGAE.7.3. For categorical parameters, the number and percentage of patients in each category will be presented, as well as a 95% confidence interval for the percentage. The 95% confidence interval will be constructed using the same method described for the efficacy endpoints. For continuous parameters, descriptive statistics will include n (number of patients), mean, standard deviation, median, minimum, and maximum. These summaries will be provided for the data as-observed, and after implementation of LOCF and MCMC-MI imputation methods. Patient-Reported Outcomes Information System and DLQI/CDLQI will be reported by clinic visit.

7.12. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Details of PK/PD analyses can be found in a separate PK/PD analysis plan. Pharmacokinetics is one of the study's secondary endpoints.

7.13. 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 (e.g., FDA Clinical Review Template), and cross-industry standardization efforts (e.g., 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 KGAE.7.1.

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.

7.13.1. Extent of Exposure

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

The duration of exposure will be calculated as:

$$\begin{aligned} &Duration\ of\ exposure\ (days) \\ &\quad = Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ in\ the\ Treatment\ Period \\ &\quad - Date\ of\ first\ dose + 1 \end{aligned}$$

Drug interruption time period due to the use of systemic rescue therapies will not be removed from study drug exposure calculations.

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, ≥150 days, ≥183 days, ≥210 days, and ≥273 days, ≥365 days; note that patients may be included in more than 1 category.
- >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 to <90 days, ≥90 to <120 days, ≥120 to <150 days, ≥150 to <183 days, ≥183 to <210 days, ≥210 to <273 days, ≥273 to <365 days, and ≥365 days)

Additional exposure ranges may be considered if necessary.

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 *Study Drug Administration* eCRF and use the response to the question, "Please select the number of syringes successfully injected," in the Dosing Diary.

7.13.2. 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 postbaseline 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 KGAE.7.4 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, as described in Table KGAE.7.4, 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 KGAE.7.4. Summary Tables/Listings Related to Adverse Events

Summaries	Population (Section 7.1.1)
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
Summary of TEAEs possibly related to study drug by PTs within SOC	Safety
Listing of SAEs (including Death)	Safety
Listing of primary AEs leading to study treatment discontinuation	Safety
Listing of TEAEs (for Japan submission only)	Safety

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

7.13.2.1. 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).

7.13.2.2. 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.

7.13.3. 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 KGAE.7.5. Hormone analytes are summarized/plotted similarly.

Table KGAE.7.5. Summary Tables/Listing of Clinical Laboratory Evaluations

Summaries	Population
Box plots of observed values by visit Box plots for change values by visit	Safety
Change from baseline to last observations	Safety
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	Safety
Treatment-emergent abnormal high lab values (i.e., patients shifting from a normal/low maximum baseline value to a high maximum postbaseline value) or abnormal low lab values (i.e., 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

7.13.4. 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 KGAE.7.6). 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 KGAE.7.6. 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
Scatterplots of baseline-by-maximum values and baseline-by-minimum values	Safety
Tables with the number and percentage of subjects who shift from normal/high to low (i.e., treatment-emergent low) and the number and percentage of subjects who shift from normal/low to high (i.e., treatment-emergent high); the limits are defined in the compound-level safety standards	Safety

7.13.4.1. Adolescent standardized Growth

Weight, height, and BMI data will be merged to the CDC standard growth data (released in 2000) by age and gender in order to compare patients' growth with the standard. Z-score and standardized percentile of weight, height, and BMI at each visit will be calculated and compared to the 2000 CDC growth charts. The summaries of growth data will be performed on the safety population.

The Z-score and percentile calculations are based on algorithms and data provided by the National Center for Health Statistics. The details are provided on the CDC website (CDC resources page [WWW]).

The following summaries and plots will be provided:

Table KGAE.7.7. Summary Table/Figure Related to Adolescent Standardized Growth

Summaries	Population
Summaries for baseline, mean change of actual measure, z-score and standardized percentile of weight, height, and BMI	Safety
Scatterplot of mean weight, height, and BMI standardized percentile versus lebrikizumab exposure time	Safety

Abbreviations: BMI = body mass index.

7.13.5. Immunogenicity

An individual sample is potentially examined multiple times in a hierarchical procedure to produce a sample ADAs assay result and may yield a sample NAb assay result. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). A patient is considered TE-ADA positive when at least 1 postbaseline ADA sample meets the definition of TE-ADA.

Compound-level safety standards will be followed in the analyses of immunogenicity. Listings of immunogenicity assessments will be provided along with the summary of specified TEAEs by TE-ADA status. The summary of TE-ADA and NAb status will be produced for the safety population, where the postbaseline period for reporting is the same as described for AEs in Section 7.13.2.

7.13.6. 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.

7.13.6.1. Hepatic Safety

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

Table KGAE.7.8. 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.

7.13.6.2. Eosinophilia and Eosinophil-Related Disorders

In addition to the standard laboratory summaries (Section 7.13.3), eosinophilia and eosinophil-related AEs will be summarized. Details regarding eosinophil-related PTs are in the compound-level safety standards.

Table KGAE.7.9. 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.

7.13.6.3. 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 KGAE.7.10. 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.

7.13.6.4. 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 KGAE.7.11. 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.

7.13.6.5. Hypersensitivity

Potential hypersensitivity reactions will be determined using the following SMQs: anaphylactic reaction, hypersensitivity, and angioedema. Potential hypersensitivity will be categorized as immediate (i.e., occurring the same day as drug administration) and non-immediate (i.e., occurring after the day of study drug administration but prior to subsequent drug administration). The planned summaries are provided in Table KGAE.7.12.

Table KGAE.7.12. 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
Listing of patients with hypersensitivity	Safety

7.13.6.6. 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 (e.g., those PTs related to injections into a joint) and administration site reactions as described in the compound-level safety standards.

Table KGAE.7.13. 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.

7.13.6.7. 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 KGAE.7.14. 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.

7.13.6.8. 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 KGAE.7.15. Summary Tables Related to Atopic Dermatitis Exacerbation

Analysis	Population
Summary of TEAE of atopic dermatitis exacerbation	Safety

Abbreviations: TEAE = treatment-emergent adverse event.

7.13.6.9. Suicide/Self-Injury

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

Table KGAE.7.16. Summary Tables Related to Suicidal Ideation and Behavior

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

Abbreviations: TEAE = treatment-emergent adverse event.

7.14. Subgroup Analyses

7.14.1. Efficacy Subgroup Analyses

Subgroup analyses will be conducted for the secondary endpoints IGA (0,1) and EASI-75 across the treatment period in the safety population, using descriptive statistics.

The following subgroups will be analyzed:

- region (US, EU, or rest of world), and
- weight category (<60 kg, ≥60 to <100 kg, or ≥100 kg).

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

7.14.2. Safety Subgroup Analyses

Subgroup analysis for safety related endpoints will be performed within the context of the integrated safety analysis.

7.15. 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 "KGAE 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 using the safety population.

A by-patient listing of important protocol deviations will be provided.

7.16. Interim Analyses and Data Monitoring

Interim analyses may be performed for regulatory interactions, safety updates, and disclosures. A final DBL and analysis will be conducted after all patients have either completed the study through the 12-week safety follow-up visit, discontinued early, or entered the long-term extension study, J2T-DM-KGAA (DRM06-AD07).

DMC/DSMB:

The lebrikizumab Phase 3 AD program's DSMB is an independent expert advisory group commissioned and charged with the responsibility of evaluating cumulative safety at regular intervals, as well as on an ad hoc basis, as needed. The DSMB will consist of members external

to Lilly and follow the rules defined in the DSMB charter, focusing on potential and identified risks for this molecule. Data Monitoring Committee membership will include, at a minimum, a physician with expertise in dermatology and a statistician. No member of the DSMB may have contact with study sites. This committee will make recommendations as to a) continue the clinical studies without modification, b) continue the clinical studies with modifications, or c) terminate 1 or more of the clinical studies. Details outlining the roles and responsibilities of the DMC are documented in the "Dermira DRM06 DSMB Program Charter", and the planned analyses are outlined in the DMC analysis plan.

The purpose of the DSMB is to advise Lilly regarding patient safety; however, the DSMB may request key efficacy data to put safety observations into context and to confirm a reasonable benefit/risk profile for ongoing patients in the study.

Week 52 DBL: Another interim analysis will be performed at the time (i.e., a cut-off date) the last patient completes Week 52 or the early termination visit from the study. This DBL will include all data collected by the cut-off date and is the final analysis for the efficacy endpoints up to Week 52.

The study will not be terminated early on the basis of efficacy following these interim analyses.

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, discontinued the current study, or enrolled into the long-term extension study.

Depending on the regulatory submission timeline, the Week 52 DBL and the final DBL may be combined (i.e., 1 final DBL will occur after all patients have either completed the study through the 12-week safety follow-up period of the study, discontinued the study early, or entered the long-term extension study DRM06-AD07).

7.17. 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.

7.18. 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 (e.g., the CSR, manuscripts, and so forth).

8. Unblinding Plan

Not applicable.

9. References

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10. Appendices

Appendix 1. Definition of Rescue Medications

This appendix provides the definition of rescue medications for this study, including topical and systemic treatments defined as follows:

1. **Topical Atopic Dermatitis Treatment (including corticosteroids, TCI and crisaborole)**

Route of topical treatments includes: Topical and Transdermal.

Topical Corticosteroids (TCS): ATC code is D07

High Potency TCS: ATC codes: D07AC or D07AD

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

Topical calcineurin inhibitor (TCI): Preferred Term includes: TACROLIMUS, PIMECROLIMUS

Crisaborole: Preferred Term includes: CRISABOROLE

2. **Systemic Atopic Dermatitis Treatment (including oral corticosteroids, immunosuppressant, biologics and phototherapy/photochemotherapy)**

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

Systemic Corticosteroids: ATC code is H02

Immunosuppressant: Defined as: ATC2 is L04 or Preferred terms of Abrocitinib or Ruxolitinib

Biologics: Defined as following Preferred terms:

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

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

Signature Page for CCI [redacted]

Approval	PPD 12-May-2022 15:03:34 GMT+0000

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