Statistical Analysis Plan J2T-DM-KGAA (3)

A Long-Term Study to Assess the Safety and Efficacy of Lebrikizumab in Patients with Moderate-to-Severe Atopic Dermatitis

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1. Statistical Analysis Plan: J2T-DM-KGAA (DRM06-AD07): A Long-Term Study to Assess the Safety and Efficacy of Lebrikizumab in Patients with Moderate-to-Severe Atopic Dermatitis

Lebrikizumab (LY3650150)

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Protocol J2T-DM-KGAA
Phase 3

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3. Revision History

Statistical Analysis Plan (SAP) J2T-DM-KGAA (KGAA) Version 1 was approved on 28 October 2020, prior to any unblinding.

SAP Version 2 was approved on 12 May 2022, after study team unblinding of the treatment assignment of KGAB/AD04, KGAC/AD05, KGAD/AD06 but prior to the unblinding treatment in KGAA/AD07. Revisions in SAP Version 2 include:

Table KGAA.3.1. Protocol-Defined Objectives and Endpoints

Section	Description of Change	Rationale
Section 4	Added responder definition for Sleep-loss	Per feedback from the Food and Drug Administration via advice letter that mere change might not translate to a clinically meaningful improvement and a responder definition for sleep loss is required.
Section 4	• Added endpoints related to Skin Pain NRS as other secondary endpoints • Added TCS/TCI free days from baseline as other secondary endpoint	Skin Pain NRS is only collected for patients enrolled from Study KGAK. TCS/TCI daily diary is only collected for patients enrolled from Study KGAD.
Section 5.1.2	Changed from Week 52 to Week 100	Study KGAA is extended to 100 Weeks study per Study KGAA Protocol Amendment 1.
Section 6.1.1	Added mITT and modified safety population	See footnote in Table KGAA.6.1.
Section 6.1.1	CCI [redacted]	[redacted]
Section 6.1.2	• Clarified the definition of baseline used for efficacy and immunogenicity endpoints • Added the definition of baseline used for clinical laboratory evaluations, vital signs, and other physical findings	Clarification
Section 6.1.3	• Removed exposure analyses for individual analysis group • Added one more analysis group for patients enrolled from KGAB/AC maintenance period lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W arms • Added AE summary for two analysis groups • For Skin Pain NRS, Pruritus NRS, and Sleep Loss collected via eDiary; the weekly mean algorithm is updated to prorated weekly mean.	Food and Drug Administration only has program-wise exposure requirements. So, the overall exposure summary is sufficient. Exploring the potential difference between lebrikizumab 250 mg Q2W and lebrikizumab 250 mg Q4W. Make Study KGAA consistent with other lebrikizumab studies.

Section	Description of Change	Rationale
Section 6.2	• This section has been amended to implement the definition of primary and supportive estimands following ICH E9(R1) addendum. • Added the missing data imputation methods relative to each estimand.	Following ICH E9(R1) addendum. Clarification.
Section 6.4	• Amended section to align with the definition of estimands. • Clarified each missing data methods. • Specified the random seeds for the MCMC-MI method. • Clarified the implementation scope of the MCMC-MI method.	Clarification. Prespecify random seed.
Section 6.8.1	• Added several more variables that will be summarized in demographics and baseline characteristics analysis. • Added Table KGAA.6.5. to clarify the definition of baseline for each specified variable.	Provide more comprehensive demographical and baseline information. Clarification.
Section 6.8.2	Clarified the definition of medical history.	Clarification.
Section 6.9	Corrected the definition of treatment compliance.	Make Study KGAA consistent with other lebrikizumab studies.
Section 6.10	• Clarified the definition of prior and concomitant therapy. • Clarified the definition of atopic dermatitis treatment of interest. • Added definition of flare.	Clarification. Add flare definition to allow for related analysis.
Section 6.11	• Added endpoints related to Skin Pain NRS in Table KGAA.6.7 • Changed the weekly mean algorithm to prorated weekly mean for Pruritus NRS, Sleep-loss due to pruritus. • Added endpoint, 2-point improvement in sleep-loss prorated weekly mean score.	Added to allow Skin Pain NRS analyses. Make Study KGAA consistent with other lebrikizumab studies.
Section 6.11	Added Table KGAA.6.7 Description of Efficacy/Health Outcome Analyses	Clarification.
Section 6.14	• Clarified the definition/scoop of AE in Study KGAA. • Mention that "A listing of AEs of patients from Site CCI and Site CCI will be provided."	Clarification.
Section 6.14.1	• Clarified that drug interruption time period due to the use of long-term systemic rescue therapies will not be removed from study drug exposure calculations. • Updated the algorithm of the duration of exposure by using max of last visit date and last dose date as end date.	Make consistent to PSAP.

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Section	Description of Change	Rationale
Section 6.14.2	No KGAA-specific immunogenicity analyses will be processed. Immunogenicity analyses will be processed in an integrated database.	Study KGAA is an extension study, so KGAA-specific immunogenicity analyses will not be processed. Study KGAA immunogenicity data will be used in an integrated database immunogenicity analysis.
Section 6.16.1	Added this new section to clarify the impact of COVID-19.	Add a new section for COVID-19.
Section 6.17	CCI [redacted]	[redacted]
Section 6.18	• Clarified that during Submission DBL, data from Study KGAK patients will keep blinded. • Clarified that DSMB #5, Submission Data Cutoff Date Test Transfer, and other Test Transfers between DSMB #5 and Study KGAK/AD18 Week 16 DBL will be unblinded for supporting regulatory submission.	Clarification.
Appendix 1	• Revised the visits according to KGAA study schedule of activity. • Added POEM and Skin Pain NRS. • Changed weekly mean algorithm to prorated weekly mean. • Changed from Assessment date to Visit date for postbaseline visits. • Added algorithm for Week 0 weekly mean.	Correction. Added POEM and Skin Pain NRS to allow weekly mean calculation. Make consistent with other lebrikizumab studies.
Appendix 2	Added this new appendix to define rescue medications.	Added per PSAP.
Appendix 3	Added this new appendix to provide more technical details about MCMC-MI.	Clarification.

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; DBL = database lock; DSMB = Data Safety Monitoring Board; ICH = Internation Council on Harmonisation; MCMC-MI = Markov Chain Monte Carlo – multiple imputation; mITT = modified intent-to-treat; NRS = Numerical Rating Scale; POEM = Patient-Oriented Eczema Measure; PSAP = Program Safety Analysis Plan; Q2W = once every 2 weeks; Q4W = once every 4 weeks; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

SAP Version 3 was approved prior to the final database lock for KGAA/AD07. Revisions in SAP Version 3 include:

Section	Description of Change	Rationale
Section 6.1.3	Added that IGA, EASI and Pruritus Numeric Rating Scale (NRS) endpoints will also be summarized at each visit in the overall population.	To document the post hoc analysis performed in the CSR approved on 22 Jan 2025.
Section 6.14	Added that listings of all the patients with AEs from the safety follow-up period will be provided.	To document the post hoc analysis performed in the CSR approved on 22 Jan 2025.

Section	Description of Change	Rationale
Section 6.14.2	Added detailed description of immunogenicity analyses.	To document the immunogenicity analyses performed after the CSR that was approved on 22 Jan 2025.

4. Study Objectives

Table KGAA.4.1 shows the protocol-defined objectives and endpoints of the study. In addition, the analysis of some non-protocol-defined endpoints is described in Section 6.11 to provide supportive evidence of efficacy.

For patients with a parent study, the parent study baseline is used as the baseline for efficacy and immunogenicity endpoints. Patients enrolled directly into Study KGAA per Protocol KGAA Addendum 1.1 do not have a parent study, so the data collected at Addendum Baseline Visit 1 will be used as a baseline for all efficacy and immunogenicity assessments.

Table KGAA.4.1. Protocol-Defined Objectives and Endpoints

Study Objective: To assess the long-term safety and efficacy of lebrikizumab in patients 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.
Major Secondary Endpoints: Over the duration of the study: • Proportion of patients with a response of IGA 0 or 1 • Proportion of patients achieving response of EASI-75[a] from baseline.
Other Secondary Endpoints: The following efficacy assessments will be summarized at each visit they are collected: • Change and percent change from baseline in EASI score at each visit • Proportion of patients with EASI-50 and EASI-90 scores at each visit • Percentage of patients with a Pruritus NRS of ≥ 4 points at baseline who achieve a ≥4 points reduction from baseline in the Pruritus NRS score at prespecified time points (for studies in which these data were collected) • Percentage change from baseline in Pruritus NRS score at prespecified time points (for studies in which these data were collected) • Percentage of patients with a Sleep-loss score ≥2 points at baseline who achieve a ≥2 points reduction from baseline in the Sleep-loss score at prespecified time points (for studies in which these data were collected) • Change from baseline in sleep-loss at prespecified time points (for studies in which these data were collected) • Percentage of patients with a Skin-pain NRS ≥ 4 points at baseline who achieve a ≥ 4 points reduction from baseline in the Skin-pain NRS at prespecified time points (for studies in which these data were collected) • Change from baseline in Skin-pain NRS at prespecified time points (for studies in which these data were collected) • Change from baseline in POEM scores at prespecified time points through the end of study (for studies in which these data were collected) • Change from baseline in BSA at prespecified time points through the end of study • Proportion of patients requiring AD concomitant treatment by visit • Proportion of TCS/TCI free days from baseline by visit (for studies in which these data were collected).

Abbreviations: AD = atopic dermatitis; BSA = body surface area; EASI = Eczema Area and Severity Index; IGA = Investigator Global Assessment; NRS = Numerical Rating Scale; POEM = Patient-Oriented Eczema Measure; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

[a] Achieving EASI-75 requires a ≥75% reduction in EASI scores from baseline to a later visit.

[b] Pruritus NRS, Sleep-loss Score, TCS/TCI use, and Skin Pain NRS are only collected up to Week 52, not through the end of study (Week 100).

5. Study Design

5.1. Summary of Study Design

Study KGAA, also known as DRM06-AD07, is a long-term extension study in adult and adolescent (from 12 to up to 18 years, weighing at least 40 kg) patients with moderate-to-severe atopic dermatitis (AD). Approximately 1000 patients may enroll from those who have completed participation in a Phase 3 AD lebrikizumab study (parent study), that is, J2T-DM-KGAB (KGAB; DRM06-AD04), J2T-DM-KGAC (KGAC; DRM06-AD05), J2T-DM-KGAD (KGAD; DRM06-AD06), J2T-DM-KGAE (KGAE; DRM06-AD17), or J2T-MC-KGAK (KGAK; DRM06-AD18). The study design is described in the following subsections. An additional approximately 100 patients are planned to enroll directly into Study KGAA; the study design for these patients is described in detail in Protocol KGAA Addendum 1.1.

Study KGAA is composed of a 100-week treatment period. Patients who complete and patients who early terminate will undergo a follow-up visit approximately 12 weeks after the last study drug injection (Week 98) for safety follow-up. Patients enrolled directly in the study, per Protocol Addendum 1.1, will have a screening period preceding the treatment period.

5.1.1. KGAA Baseline Day 1 and Week 2

Procedures for the Baseline Day 1 visit for Study KGAA are conducted as part of the study exit visit for the parent trial. Patients are evaluated for study eligibility at Study KGAA Baseline Day 1. Patients will be considered enrolled once all Baseline Day 1 procedures have been completed and the investigator has determined that the patient meets the eligibility criteria. Two treatment regimens will be assessed: 250 mg lebrikizumab, administered every 2 weeks (Q2W) and 250 mg lebrikizumab, administered every 4 weeks (Q4W). The regimen assigned to each patient will be based on the treatment received in the patient's respective parent trial as described in Section 5.3.

At the Baseline and Week 2 clinic visits, all patients will be administered pre-filled syringe(s) with a pre-assembled needle safety device. Matching placebo syringes will be used to maintain the blind, where appropriate.

The number and type of investigational products administered at Baseline and Week 2 are as follows:

- Lebrikizumab 250 mg, administered Q2W
    - For patients who were on a placebo arm through the end of the parent study or enrolled directly per Protocol Addendum 1.1: loading doses of 500 mg lebrikizumab (2 lebrikizumab syringes) will be administered at Baseline and Week 2.
    - For patients who were not on a placebo arm through the end of the parent study: at Baseline and Week 2, 1 lebrikizumab 250 mg syringe and 1 placebo syringe will be administered. For patients who are open-label investigational product (IP) in Study KGAA/AD07, no placebo syringe will be administered.

- Lebrikizumab 250 mg, administered Q4W
    - At Baseline, 1 lebrikizumab 250 mg syringe and 1 placebo syringe will be administered. At Week 2, 2 placebo syringes will be administered.

5.1.2. Week 4 to Week 100

Patients will return to the clinic at Weeks 4, 16, and every 12 weeks thereafter, through Week 100 for safety and efficacy assessments. Patients not achieving an Eczema Area and Severity Index (EASI)-50 (a ≥50% reduction in EASI scores from baseline of the parent study) by Week 16, maintaining an EASI-50 response, or not achieving clinical benefit based on principal investigator (PI) discretion should be terminated from Study KGAA.

For Week 4 through Week 98, all patients will receive 1 syringe, Q2W. Placebo syringes will be used to maintain the blind. For patients assigned to lebrikizumab 250 mg Q2W, 1 lebrikizumab syringe will be administered Q2W from Week 4 through Week 98. For patients assigned to lebrikizumab 250 mg Q4W, 1 lebrikizumab syringe will be administered Q4W from Week 4 through Week 96; every 2 weeks after the lebrikizumab administration, a placebo syringe will be administered through Week 98 until site personnel and patients unblinded. The clinic visit at Week 100 is the end of the treatment period.

5.1.3. Safety Follow-Up Visit

All patients will undergo a follow-up visit approximately 12 weeks after the last study drug injection.

5.2. Determination of Sample Size

Sample size for the Study KGAA (DRM06-AD07) protocol is based on the number of patients who completed studies KGAB (DRM06-AD04), KGAC (DRM06-AD05), KGAD (DRM06-AD06), KGAE (DRM06-AD17), or KGAK (DRM06-AD18) who choose to participate in Study KGAA and who meet all eligibility criteria. It is estimated that approximately 900 patients may enroll from the parent studies. An additional approximately 100 patients are entering the study directly, based on the Study KGAA Protocol Addendum 1.1. Given regulatory requirements with regards to a minimum number of exposures for appropriate evaluation of benefit-risk for lebrikizumab, the goal of the addendum is to increase the long-term 1-year exposure safety database by providing lebrikizumab 250 mg Q2W as a treatment to additional patients. The addendum sample size is not based on any statistical power calculations.

The total sample size is expected to be approximately 1000 patients.

5.3. Method of Assignment to Treatment

The regimen assigned to each patient will be based on the treatment received in the patient's respective parent trial.

For the monotherapy trials, Study KGAB (DRM06-AD04) and Study KGAC (DRM06-AD05):

- Patients who were re-randomized in the Maintenance Phase to either 250 mg lebrikizumab Q2W or 250 mg lebrikizumab Q4W will continue to receive the same active treatment regimen.

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- Patients who were receiving a placebo in the Maintenance Phase will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2, followed by 250 mg lebrikizumab Q2W.
- Patients who were moved to the Escape Arm will continue to receive open-label 250 mg lebrikizumab Q2W.
- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding, except for patients from an escape arm, who will receive open-label 250 mg lebrikizumab Q2W. Placebo injections will be utilized in order to maintain the blind and ensure all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

For the topical corticosteroid (TCS) Combination trial, Study KGAD (DRM06-AD06):

- Patients receiving 250 mg lebrikizumab Q2W who achieve an Investigator Global Assessment (IGA) 0,1 or an EASI -75 response (≥EASI-75) at Week 16 will be randomly allocated to receive 250 mg lebrikizumab Q2W or 250 mg lebrikizumab Q4W, in a 2:1 fashion, Q2W:Q4W, respectively.
- Patients receiving 250 mg lebrikizumab Q2W who do not achieve an IGA 0,1 or an EASI-75 response (less than EASI-75) at Week 16 or who were assigned to 250 mg lebrikizumab Q2W and used systemic rescue medication will receive 250 mg lebrikizumab Q2W.
- Patients who were receiving placebo or who were assigned to placebo and used systemic rescue medication will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W.
- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding. Placebo injections will be utilized in order to maintain the blind and ensure all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

For the Adolescent Safety trial, Study KGAE (DRM06-AD17):

- All patients will continue to receive open label 250 mg lebrikizumab Q2W.

For the Vaccine trial, Study KGAK (DRM06-AD18):

- Patients receiving 250 mg lebrikizumab Q2W will continue to receive 250 mg lebrikizumab Q2W.
- Patients who were receiving a placebo will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W.
- Treatment regimen assignment will remain blinded during the long-term extension study until unblinding (that is, until Study KGAK/AD18 is unblinded). Placebo injections will be utilized in order to maintain the blind and ensure that all patients receive the same number and frequency of injections regardless of treatment regimen assignment.

For patients entering the study directly, per Study KGAA Protocol Addendum 1.1, all patients will receive a loading dose of 500 mg lebrikizumab at the time of enrollment (Baseline) and at Week 2 followed by open label 250 mg lebrikizumab Q2W.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly). The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used.

Analyses and summaries from assessment of endpoints described in the protocol are planned to be included in a clinical study report (CSR). Analyses and summaries for key safety data are also planned to be included in the CSR. Results from additional efficacy analysis and other safety analyses 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 analysis, unless specified otherwise.

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6.1.1. Analysis Populations

Table KGAA.6.1. Analysis Populations

Population	Description
All Entered Patients	All patients who signed informed consent. The All Entered Patients population will be used for tables and/or listings of disposition that include screen failures and inclusion and exclusion criteria.
ITT Population	All patients assigned to treatment, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned.
mITT Population	ITT population excluding all patients from Site CCI and Site CCI. This population will be used to summarize patient disposition, demographics, and efficacy analyses, plus to list patient data.
Safety Population	All patients who receive at least 1 confirmed dose of lebrikizumab will be included in the Safety Population.
Modified Safety Population	Safety population excluding all patients from Site CCI and Site CCI. Demographics, extent of exposure, treatment compliance, prior/concomitant medication use, adverse event, and immunogenicity safety analyses will be performed using the Modified Safety Population.
CCI	[redacted]

Abbreviations: CCI; ITT = intent-to-treat; mITT = modified intent-to-treat.

[a] Site CCI only participated in Studies KGAC/AD05, KGAD/AD06, KGAK/AD18, and Site CCI only participated in Study KGAK/AD18. So, analyses with only data from Studies KGAB/AD04, KGAE/AD17, and Protocol KGAA Addendum 1.1 will not be impacted.

[b] The rationale for excluding patients from Site CCI is in a directed site audit triggered by statistically implausible data in Study KGAD/AD06 at this study site, and the same site was also included in this Study KGAA/AD07. It was determined that some or all of the study patients at this site did not meet the eligibility criterion of having moderate-to-severe atopic dermatitis, and associated data was unreliable.

[c] The rationale for excluding patients from Site CCI is a clinical site audit of lebrikizumab atopic dermatitis Studies KGAK/AD18 and KGAA/AD07 at this site which resulted in critical findings. It was determined by the audit that there was a lack of source documentation needed to substantiate eligibility for all patients enrolled at this site. Additionally, a quality issue was opened where data relating to patient's moderate-to-severe atopic dermatitis is either unreliable, inconsistent, and/or missing source documentation.

An analysis of safety in patients under 18 years of age (that is, adolescents) will be conducted as appropriate.

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

6.1.2. Baseline Definition

The baseline used for efficacy and immunogenicity endpoints is as follows:

- The parent study baseline is used for patients with a parent study.
- The data collected at the addendum Baseline Visit 1 is used for patients who enrolled directly into Study KGAA per Protocol Addendum 1.1. If a measurement is missing at

addendum Baseline Visit 1, then the last available measurement before the first injection will be used as the patient's baseline.

The baseline used for clinical laboratory evaluations, vital signs, and other physical findings is as follows:

- For patients with a parent study, the Study KGAA baseline will be used. If Study KGAA baseline is missing, then the last available measurement from the parent study will be used.
- For patients enrolled directly per Study KGAA Protocol Addendum 1.1, the Study KGAA baseline will be used. Clinical laboratory evaluations will be processed at the Screening visit per KGAA/AD07 Addendum 1.1, and these results will be used as a laboratory evaluation analysis baseline. If the Study KGAA baseline is missing, then the last available measurement before the first injection will be used.

6.1.3. General Considerations for Analyses

Descriptive statistics will be used to summarize the efficacy and safety results. For categorical parameters, the number and percentage of patients in each category will be presented. For continuous parameters, descriptive statistics will include n (number of patients), mean, standard deviation, median, minimum and maximum.

Some summaries, such as disposition, demographics, exposure, and safety data will be performed for all data combined.

Disposition, demographics, and efficacy data will be summarized separately for the following analysis groups unless specified otherwise:

- patients coming from parent Study KGAD (DRM06-AD06) who were lebrikizumab Q2W responders in KGAD and then were randomized in Study KGAA, by treatment group in KGAA
- patients coming from parent Studies KGAD (DRM06-AD06) and KGAK (DRM06-AD18) combined
- patients coming from parent Studies KGAB (DRM06-AD04) and KGAC (DRM06-AD05) combined
- patients coming from parent Studies KGAB (DRM06-AD04) and KGAC (DRM06-AD05), received lebrikizumab 250 mg Q2W during the parent study induction period and received lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W during the maintenance period and are not in the escape arm.
- patients coming from parent Study KGAE (DRM06-AD17)
- patients directly enrolled per Protocol KGAA Addendum 1.1.

IGA, EASI and Pruritus Numeric Rating Scale (NRS) endpoints will also be summarized at each visit in the overall population (that is, the Study KGAA main cohort).

Other data also may be summarized using these 6 study groupings. Notably, the adverse event (AE) data will be summarized separately, for

- patients coming from parent Study KGAD (DRM06-AD06) who were lebrikizumab Q2W responders in Study KGAD and then were randomized in Study KGAA.

- patients coming from parent Studies KGAB (DRM06-AD04) and KGAC (DRM06-AD05) who received lebrikizumab 250 mg Q2W during the parent study induction period and received lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W during the maintenance period and are not in the escape arm.

Pruritus NRS, Sleep-loss due to Pruritus, Patient-Oriented Eczema Measure (POEM), and Skin-pain NRS are collected via eDiary. For patients directly enrolled per Study KGAA Protocol Addendum 1.1, 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 other patients enrolled from a parent study, the last available weekly mean from the parent study before Study KGAA first injection will be used as Study KGAA Week 0 weekly mean. The eDiary data for Pruritus NRS, Sleep-loss due to Pruritus, POEM, and Skin-pain NRS are mapped to study visit per Appendix 1.

All safety data from this study (including Protocol KGAA Addendum 1.1) will be used as part of the integrated summaries. For the purposes of the CSR for Study KGAA (DRM06-AD07) alone, a listing and summary of serious adverse events (SAEs) and AEs leading to permanent discontinuation of the study drug will be created. For safety data from patients who enrolled from a parent study, parent study AEs that end before the first dose date of Study KGAA will not be reported to avoid double counting. For Protocol KGAA Addendum 1.1, all AEs will be reported for patients who enrolled directly into Study KGAA.

6.2. Primary and Secondary Estimands

6.2.1. Estimand of Primary Objective (Safety)

The **estimand of primary objective** is the proportion of modified Safety Population patients discontinued from study treatment due to adverse events through the last treatment visit.

6.2.2. Estimands of Secondary Objectives (Efficacy)

The secondary clinical question of interest is: what is the proportion of patients who meet the clinical requirements for response AND without discontinuation due to lack of efficacy?

The **primary estimand of the secondary objective** is described by the following attributes:

A. Population: modified intent-to-treat (mITT) population as defined in Section 6.1.1;
B. Variable: apply to all secondary endpoints.
C. How to account for intercurrent events (ICEs):
    a. Subjects who discontinued treatment due to lack of efficacy during Study KGAA will be considered as treatment failures, that is, nonresponders, after the ICEs. Therefore, a composite strategy will be used for these types of ICEs.
    b. For subjects who discontinued treatment due to any other reasons, the hypothetical strategy will be used to estimate what the treatment effect would have been if subjects continued with treatment. Therefore, the hypothetical strategy will be used for these ICEs.
D. Population-level summary: response proportions or means.

The **first supportive estimand of the secondary objective** is described by the following attributes:

A. Population: mITT population as defined in Section 6.1.1;
B. Variable: apply to all secondary endpoints.
C. How to account for ICEs: as observed strategy will be used, that is, only data from completers at the visit are relevant.
D. Population-level summary: response proportions or means.

The **second supportive estimand of the secondary objective** is described by the following attributes:

A. Population: modified ITT population as defined in Section 6.1.1;
B. Variable: apply to all secondary endpoints.
C. How to account for ICEs: for subjects who discontinue treatment, the hypothetical strategy will be used to estimate what the treatment effect would have been if all subjects adhered to the treatment. Therefore, the hypothetical strategy is used for these types of ICEs.
D. Population-level summary: response proportions or means.

Analytical details on how missing data, including data missing as a result of intercurrent events, will be handled can be found in Section 6.4. Endpoints will be analyzed as described in Section 6.11 and Section 6.14. No statistical test will be performed.

Table KGAA.6.2. summarizes different analyses that will be conducted on the secondary endpoints.

Table KGAA.6.2. Analysis of Secondary Endpoints

Estimand	Treatment Discontinuation		Missing Data Imputation Method
	Due to lack of efficacy	Due to any other reasons	
Primary	Composite: Set to baseline	Hypothetical: Set to missing	MCMC-MI
Supportive	As observed	As observed	As observed analysis
Supportive	Hypothetical: Set to missing	Hypothetical: Set to missing	LOCF

Abbreviations: LOCF = last observation carried forward; MCMC-MI = Markov Chain Monte Carlo – Multiple imputation.

6.3. Adjustments for Covariates

No statistical tests will be performed.

6.4. Handling of Dropouts or Missing Data

Depending on the estimand being addressed, different methods will be used to handle missing data. A description of the estimands can be found in Section 6.2.

For the primary objective, no supportive estimand or sensitivity analysis will be performed.

For the primary estimand of the secondary objective, missing data, including data missing as a result of ICEs, will be imputed based on Markov Chain Monte Carlo – Multiple imputations (MCMC-MI) as described in Section 6.4.3. An as observed analysis (see Section 6.4.1) and last observation carried forward (LOCF) (see Section 6.4.2) will be used in the supportive estimands of secondary objective.

Table KGAA.6.3 describes the planned imputation methods for efficacy and health outcome endpoints for the treatment period.

Table KGAA.6.3. Imputation Techniques for Various Variables During Treatment Period

Type of Endpoints	Efficacy and Health Outcome Endpoints	Estimand of Secondary Endpoints (Analysis Strategy for Intercurrent Events)	Missing Data Imputation Method
Categorical	IGA, EASI, Pruritus NRS, Skin Pain NRS, and Sleep-loss related categorical endpoints at pre-specified timepoints[a]	Primary Estimand	MCMC-MI/As Observed[b]
		Supportive Estimand	As Observed, LOCF
	Remaining categorical endpoints	Supportive Estimand	As Observed, LOCF
Continuous	EASI percent change, Pruritus NRS percent change, Skin Pain NRS percent change, and Sleep-loss change from Baseline[a]	Primary Estimand	MCMC-MI/As Observed[b]
		Supportive Estimand	As Observed, LOCF
	Remaining continuous endpoints were collected at multiple postbaseline timepoints including (but not limited to) BSA, and POEM	Supportive Estimand	As Observed, LOCF

Abbreviations: BSA = body surface area; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo multiple imputation; NRS = Numeric Rating Scale; POEM = Patient-Oriented Eczema Measure.

[a] Pruritus NRS, Skin Pain NRS, Sleep-loss is assessed only up to week 52. Skin Pain NRS is only collected for patients enrolled from KGAK. Pruritus NRS and Sleep-loss are not collected for patients enrolled from KGAE.

[b] MCMC-MI will be implemented for the following two analysis groups only: 1. Patients coming from parent study KGAD (DRM06-AD06) who were lebrikizumab Q2W responders in KGAD and then were randomized in KGAA, by treatment group in KGAA; 2. Patients coming from parent studies KGAB (DRM06-AD04) and KGAC (DRM06-AD05), received lebrikizumab 250 mg Q2W during parent study induction period and received lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W during the maintenance period and not in escape arm. For other analysis groups, As Observed will be missing data imputation method.

6.4.1. As Observed Analysis

The "as observed" strategy is used in the so-called "observed cases" or "completers" analysis ubiquitous in the literature, though is not one of the recommended strategies in the ICH E9(R1). For this analysis, only data from completers at the visit are relevant. This estimand is conditional and targets the effect of treatment conditional on completion of treatment through the timepoint of interest. As the estimand is defined for a subpopulation conditional on an ICE, it is not considered causal. A summary based on observed data at each postbaseline visit will be provided. All efficacy data will be summarized using an "as observed" analysis.

6.4.2. Last Observation Carried Forward

In this missing data approach, the values after treatment discontinuation will be made missing. All missing values will be imputed using LOCF. For patients who enrolled directly into Study KGAA per Protocol KGAA Addendum 1.1, a baseline value will be used for imputation if there is no postbaseline observation. For other patients who enrolled from a parent study, the available observations during the parent study will also be used for imputation purposes.

6.4.3. Markov chain Monte Carlo-Multiple Imputation

This method of imputing missing data will be used to implement the primary estimand of the secondary objective. This method will only be implemented for the following two analysis groups:

1. Patients coming from parent Study KGAD (DRM06-AD06) who were lebrikizumab Q2W responders in KGAD and then were randomized in KGAA, by treatment group in KGAA.
2. Patients coming from parent Studies KGAB (DRM06-AD04) and KGAC (DRM06-AD05), received lebrikizumab 250 mg Q2W during the parent study induction period and received lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W during the maintenance period and are not in the escape arm.

For patients who discontinue from the study treatment due to lack of efficacy, set the patient's baseline value subsequent to this time through Week 100. The MCMC-MI will be used to handle the remaining missing data. Imputation will be conducted within each treatment group and for different parent studies (including Protocol KGAA Addendum 1.1) independently so the pattern of missing observations in 1 imputation 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 KGAA.6.4. The SAS PROC MI with MCMC option will be used to conduct the MCMC-MI. Each complete data set will be analyzed with the specified analysis. The results from these analyses will be combined into a single inference 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. As 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 a 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.

The approach to handling missing data for Pruritus NRS, Skin Pain NRS, and Sleep-loss are the same. We use Pruritus NRS as an example. For derivation of the following Pruritus NRS responses, no rounding will be performed. The imputed Pruritus NRS value will be compared directly to the observed mean baseline Pruritus-NRS value to determine whether a response was achieved:

Percentage of patients with a Pruritus NRS of ≥4-points at Baseline who achieve a ≥4-point reduction from Baseline.

Imputation of continuous data will parallel that of binary variables. The imputed values will be used for the secondary endpoints such as:

- Percentage change in Pruritus NRS score from Baseline to Week 52 (for studies in which these data were collected).
- Percentage change in EASI score from Baseline at each visit.

Table KGAA.6.4. Seed Values for MCMC-Multiple Imputation

Analysis	Seed values
IGA and its related derived endpoints.	724145708
EASI and its related derived endpoints.	175356158
Pruritus NRS and its related derived endpoints.	1339532552
Sleep-lose due to pruritus and its related derived endpoints.	234325234
Skin Pain NRS and its related derived endpoints.	454236342

Abbreviations: EASI = Eczema Area and Severity Index score; IGA = Investigator's Global Assessment for AD; MCMC = Markov Chain Monte Carlo; NRS = Numeric Rating Scale.

6.5. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. The countries will be categorized into geographic regions which will be used for subgroup analyses, as described in Section 6.15.

6.6. Multiple Comparisons/Multiplicity

No statistical tests will be performed.

6.7. Patient Disposition

The following patient disposition summaries will be provided (details of the analysis populations can be found in Section 6.1.1):

- Total number and percentage of patients entering each statistical analysis population are defined in Section 6.1.1 (Analysis Population: All Entered Patients).
- The number and percentage of patients who entered the study, were assigned to treatment, and screen failed will be provided overall and by screen fail reason (Analysis population: All Entered Patients).

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- The number and percentage of patients who were assigned to treatment completed treatment, the number and percentage of patients who discontinued the treatment at any time, by the assigned treatment group, and the primary reason for discontinuation of treatment (Analysis population: mITT).
    - The primary endpoint of Study KGAA 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 assigned to treatment completed the study (including the safety follow-up period), and the number and percentage of patients who discontinued the study at any time, by the assigned treatment group and the primary reason for discontinuation. Of the patients who discontinued the study at any time, the number and percentage of patients who completed the safety follow-up period (Analysis population: mITT).

All patients who were assigned treatment (that is, in the ITT 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 mITT patients for each treatment group, number of patients discontinued from study treatment, and number of patients discontinued from the study. This information will be summarized overall, for adults and adolescents.

6.8. Patient Characteristics

6.8.1. Demographics and Baseline Characteristics

Patient demographic variables and baseline characteristics will be summarized by treatment group for the mITT population and the modified safety population. The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages.

The following demographic information will be included:

- age
- age group (adolescents [from 12 up to 18], adults 18 and over)
- age group (adolescents [from 12 up to 18], adults 18 up to 65, from 65 up to 75, 75 and over)
- sex (male, female)
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Other, Not Reported)
- ethnicity for the United States (US) patients (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)
- region (US, European Union [EU], Rest of World)
- country
- weight (kg)
- weight category (under 60 kg, from 60 up to 100 kg, at least100 kg)
- height (cm)
- body mass index (BMI) (kg/m^2)

- BMI category: underweight (less than 18.5 kg/m^2), normal (from 18.5 up to 25 kg/m^2), overweight (at least 25 and up to 30 kg/m^2), obese (at least 30 and up to 40 kg/m^2), and extreme obese (at least 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 the date of onset of AD and the date of birth collected on the case report form (CRF).
- Duration since AD onset (years): for patients who enrolled from parent studies, it is calculated as the difference between the date of informed consent in the parent study and the date of onset of AD collected on the CRF from the parent study. For patients who enrolled directly per Protocol KGAA Addendum 1.1, it is calculated as the difference between the date of informed consent in Study KGAA and the date of onset of AD collected on the Study KGAA CRF.
- Duration since AD onset category (0 to up to 2 years, 2 to up to 5 years, 5 to up to10 years, 10 to up to 20 years, at least 20 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 (for patients with a parent study, AD history drug use was assessed at parent study screening. Plus, use of these drugs during the parent studies was recorded)
    - none
    - TCS
    - TCI
    - immunosuppressive/immunomodulating drugs: systemic corticosteroids; cyclosporine; mycophenolate-mofetil; IFN-γ; janus kinase inhibitors; azathioprine; methotrexate
    - phototherapy
    - photochemotherapy (PUVA)
    - other Biologics (for example, cell depleting biologics), and
    - other non-Biologic medication/treatment
- IGA for AD score: 3 versus 4
- EASI score
- Body Surface Area (BSA)
- Pruritus NRS
- Pruritus NRS: less than 4, at least 4
- Sleep-loss due to pruritus
- Sleep-loss due to pruritus: less than 2, at least 2
- POEM
- Skin Pain NRS, and

- Skin Pain NRS: less than 4, at least 4.

The baseline definition of all demographics and baseline characteristics is summarized in Table KGAA.6.5.

Table KGAA.6.5. Patient Characteristics Baseline

Variable	Baseline Summary	
	Parent Studies[a]	KGAA
Basic demographic information		
Age, Age groups	X	
Sex	X	
Race	X	
Ethnicity for US patients	X	
Region	X	
Country	X	
Weight, Weight category		X
Height		X
BMI, BMI category		X
Baseline disease/clinical characteristics		
Age at onset (years)	X	
Duration since AD onset (years), Duration since AD onset category	X	
Anatomical area affected by AD	X	
AD treatment used in the past	X	
Immunosuppressive/immunomodulating drugs	X	
IGA for AD score	X	
EASI score	X	
BSA	X	
Pruritus NRS, Pruritus NRS category	X	
Sleep-loss due to pruritus, Sleep-loss due to pruritus category	X	
POEM	X	
Skin Pain NRS, Skin Pain NRS category	X	

Abbreviations: AD = atopic dermatitis; BMI = body mass index; BSA = Body Surface Area; EASI = Eczema Area and Severity Index; IGA = Investigator Global Assessment; NRS = Numeric Rating Scale; POEM = Patient Oriented Eczema Measure.

[a] For patients enrolled in Study KGAA directly per Protocol Addendum 1.1, baseline will be the Study KGAA baseline.

6.8.2. Medical History

Medical histories are defined as the conditions and events recorded on the *Medical History* electronic CRF (eCRF) and the *Adverse Event* eCRF from the parent study (including ongoing conditions and events that occur before the date of the first injection in Study KGAA and continue during Study KGAA) for patients with a parent study. For patients enrolling directly per the Protocol KGAA Addendum 1.1, medical histories include the conditions and events on the

KGAA *Medical History* eCRF and the conditions/events on the KGAA *Adverse Event* eCRF that occur before the date of the first injection in Study KGAA. If a medical history event worsens in severity or has a recurrence on or after the date of the first injection in Study KGAA, it will be recorded as an AE on the KGAA *Adverse Event* eCRF with the date of worsening or recurrence as the start date and will be considered as an AE.

The number and percentage of patients with medical histories will be summarized by treatment group for the overall mITT population and by age group 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 *History Assessment* eCRF (hand dermatitis, facial dermatitis, conjunctivitis, herpes zoster, and others), from the parent study for patients with a parent study and from Study KGAA for patients enrolling directly per Protocol KGAA Addendum 1.1, will be summarized by treatment group for the mITT population overall and by age group within the mITT Population.

6.9. Treatment Compliance

Treatment compliance with the investigational product will be summarized for patients who receive at least one confirmed dose of lebrikizumab for the Modified Safety Population in the Study KGAA 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 total number of injections expected can be derived from the interactive web response system study drug dispense dataset.
- The total number of injections administered will be based on the *Study Drug Administration* eCRF page and on the prompt "Did you or a caregiver successfully inject the study drug?" in the *Dosing Diary* and *Dosing Diary - Paper*.

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

6.10. 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 in Study KGAA 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 in Study KGAA. *Concomitant medications* are those medications that start before, on, or after the first day of Study KGAA treatment and continue into the treatment period.

Prior medication and concomitant medication will be summarized by the treatment group for the mITT Population.

Specific AD treatment used during the Study KGAA treatment period will be presented by the treatment group for the mITT Population. This will include: topical AD treatment (including TCS, TCI, and crisaborole) and systemic AD treatment (including systemic corticosteroids, immunosuppressants, biologics, and phototherapy). The TCS will be presented by potency. A definition of rescue medications is provided in Appendix 2. For patients coming from parent Study KGAD, daily TCS/TCI use will continue to be collected via patient diary until Week 52 and will be summarized.

Flare

Disease flares will be assessed based on rescue therapy usage. Flare is defined as the initiation or intensification of rescue therapy. A summary of the percentage of patients rescued by visit will be provided.

6.11. Efficacy Analyses

Table KGAA.6.6 includes the description and derivation of the efficacy/health outcomes, measures, and endpoints.

Table KGAA.6.7 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for efficacy/health outcomes analyses.

For categorical parameters, the number and percentage of patients in each category will be presented. For continuous parameters, descriptive statistics will include n (number of patients), mean, standard deviation, median, minimum and maximum.

The Investigator's Global Assessment, EASI, and BSA will be reported by clinic visit. Pruritus NRS, Sleep-loss, POEM, and Skin-pain NRS will be summarized by the time points described in Appendix 1.

For patients with a parent study, the parent study baseline is used as the baseline for efficacy endpoints. Patients enrolled directly into Protocol KGAA Addendum 1.1 do not have a parent study, so the data collected at addendum Baseline Visit 1 will be used as a baseline for all efficacy assessments. More details are available in Section 6.1.2.

Table KGAA.6.6. Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints

Measure	Description	Variable	Derivation / Comment	Definition of Missing
IGA	The IGA is a static assessment and rates the severity of the 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 to 4 0 represents "clear" 4 represents "severe"	Single item, missing if missing.
		• IGA (0,1)[a] • IGA (0)	• Observed score of 0 or 1 • Observed score of 0	Single item, missing if missing.
EASI	The EASI scoring system uses a defined process 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 to 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 to 72, and the final EASI score will be obtained by weight-averaging these 4 scores. Hence, the final EASI score will range from 0 to 72 for each time point.	EASI score	Derive EASI region score for each of the 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. The total EASI score is as follows: $EASI = 0.1*EASI_{head\ and\ neck} + 0.3*EASI_{trunk} + 0.2*EASI_{upper\ limbs} + 0.4*EASI_{lower\ limbs}$	N/A – partial assessments cannot be saved.
		• Change from baseline in EASI score • Percent change from baseline EASI score	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.

Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints

Measure	Description	Variable	Derivation / Comment	Definition of Missing
EASI	The EASI scoring system uses a defined process 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 to 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 to 72, and the final EASI score will be obtained by weight-averaging these 4 scores. Hence, the final EASI score will range from 0 to 72 for each time point.	EASI-50	% 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	% Improvement in EASI score from baseline ≥90%: % Change from baseline ≤-90	Missing if baseline or observed value is missing.

Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints

Measure	Description	Variable	Derivation / Comment	Definition of Missing
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 the total body surface. BSA will be determined by the Investigator or designee using the patient palm = 1% rule	BSA score	BSA Total = $BSA_{head\ and\ neck} + BSA_{trunk} + BSA_{upper\ extremities} + BSA_{lower\ extremities}$	N/A – partial assessments cannot be saved.
		Change from baseline in BSA score	Change from baseline: observed BSA score – baseline BSA score	Missing if baseline or observed value is missing.
Skin Pain NRS [d]	Skin Pain NRS is a patient-administered, validated, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." Overall severity of a patient's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours. Assessments will be recorded daily by the patient using an electronic diary.	Skin Pain NRS prorated weekly mean score	The prorated weekly mean is based on the previous 7 days. If the patient has at least one daily score, the weekly mean is the prorated average of daily scores within the given week. Single item; range 0-10. eDiary data are mapped to timepoint per Appendix 1.	Weekly mean score missing if the patient has no Skin Pain NRS responses within the week.
		• Change from baseline in Skin Pain NRS prorated weekly mean score • Percent change from baseline in Skin Pain NRS prorated weekly mean score	• Change from baseline: observed Skin Pain prorated weekly mean score – baseline Skin Pain weekly mean score • % Change from baseline: $100 \times \frac{Observed\ score - Baseline}{Baseline}$	Missing if baseline or observed value is missing.

Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints

Measure	Description	Variable	Derivation / Comment	Definition of Missing
Skin Pain NRS [d]	Skin Pain NRS is a patient-administered, validated, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." Overall severity of a patient's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours. Assessments will be recorded daily by the patient using an electronic diary.	4-point improvement in Skin Pain NRS weekly mean score	Change from baseline in Skin Pain NRS prorated weekly mean score ≤-4	Missing if baseline is missing or observed value is missing.
Pruritus NRS[b]	The Pruritus NRS is an 11-point scale used by patients 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 patient using an electronic diary.	Pruritus NRS prorated weekly mean score	The prorated weekly mean is based on the previous 7 days. If the patient has at least one daily score, the weekly mean is the prorated average of daily scores within the given week. Single item; range 0-10. eDiary data are mapped to timepoint per Appendix 1.	Weekly mean score missing if the patient has no Pruritus-NRS responses within the week.
		• Change from baseline in Pruritus NRS prorated weekly mean score • Percent change from baseline in Pruritus NRS prorated weekly mean score	• Change from baseline: observed Pruritus prorated weekly mean score – baseline Pruritus weekly mean score • % Change from baseline: $100 \times \frac{Observed\ score - Baseline}{Baseline}$	Missing if baseline or observed value is missing.

Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints

Measure	Description	Variable	Derivation / Comment	Definition of Missing
Pruritus NRS[b]	The Pruritus NRS is an 11-point scale used by patients 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 patient using an electronic diary.	4-point improvement in Pruritus NRS prorated weekly mean score	Change from baseline in Pruritus NRS weekly mean score ≤-4	Missing if baseline is missing or observed value is missing.
Sleep-loss due to pruritus[b]	Sleep-loss due to pruritus will be assessed by the patient. Patients rate their sleep based on a 5-point Likert scale (0 [not at all] to 4 [unable to sleep at all]). Assessments will be recorded daily by the patient using an electronic diary.	Sleep-loss prorated weekly mean score	The prorated weekly mean is based on the previous 7 days. If the patient has at least one daily score, the weekly mean is the prorated average of daily scores within the given week. Single item; range 0 - 4. eDiary data are mapped to timepoint per Appendix 1.	Weekly mean score missing if the patient has no Sleep-loss score responses within the week.
		• Change from baseline in Sleep-loss prorated weekly mean score • Percent change from baseline in Sleep-loss prorated weekly mean score	• Change from baseline: observed sleep loss prorated weekly mean score – baseline sleep loss score • % Change from baseline: $100 \times \frac{Observed\ score - Baseline}{Baseline}$	Missing if baseline or observed value is missing.
		2-point improvement in Sleep-loss prorated weekly mean score	Change from baseline in Sleep-loss weekly mean score ≤-2	Missing if baseline is missing or observed value is missing.

Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints

Measure	Description	Variable	Derivation / Comment	Definition of Missing
POEM[b]	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.

Abbreviations: AD = atopic dermatitis; BAS = Body Surface Area; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; N/A = not applicable; NRS = Numeric Rating Scale; POEM = Patient Oriented Eczema Measure; TCI = Topical Calcineurin Inhibitors; TCS = Topical corticosteroids.

[a] Secondary endpoints.

[b] Daily pruritus, sleep-loss, and weekly/in-office POEM were only collected for patients participating in Studies KGAB, KGAC, KGAD, and KGAK.

[c] TCS/TCI data, only collected for patients participating in Study KGAD.

[d] Daily Skin-pain NRS only collected for patients participating in Study KGAK.

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Table KGAA.6.7. Description of Efficacy/Health Outcome Analyses

Measure	Variable	Analysis Method	Population (Section 6.1.1)	Time Point	Analysis Type
IGA	Proportion of patients achieving IGA (0,1)	Descriptive analysis with MCMC-MI[a]	mITT	All scheduled visits in the Treatment Period at which scales are collected	Secondary analysis
	Proportion of patients achieving IGA (0)	Descriptive analysis with As Observed	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
		Descriptive analysis with LOCF	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
EASI	Change from baseline in EASI score	Descriptive analysis with MCMC-MI[a]	mITT	All scheduled visits in the Treatment Period at which scales are collected	Secondary analysis
	Percent change from baseline in EASI score	Descriptive analysis with As Observed	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
		Descriptive analysis with LOCF	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
	Proportion of patients achieving EASI-75	Descriptive analysis with MCMC-MI[a]	mITT	All scheduled visits in the Treatment Period at which scales are collected	Secondary analysis
	Proportion of patients achieving EASI-90	Descriptive analysis with As Observed	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
	Proportion of patients achieving EASI-50	Descriptive analysis with LOCF	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis

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Description of Efficacy/Health Outcome Analyses

Measure	Variable	Analysis Method	Population (Section 6.1.1)	Time Point	Analysis Type
BSA Affected by AD	Change from baseline in BSA score	Descriptive analysis with As Observed	mITT	All scheduled visits in the Treatment Period at which scales are collected	Secondary analysis
		Descriptive analysis with LOCF	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
Pruritus NRS	Change from baseline in Pruritus NRS	Descriptive analysis with MCMC-MI[a]	mITT	All scheduled visits in the Treatment Period at which scales are collected	Secondary analysis
	Percent Change from baseline in Pruritus NRS	Descriptive analysis with As Observed	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
		Descriptive analysis with LOCF	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
	Proportion of patients achieving at least a 4-point improvement in pruritus NRS in patients who had baseline pruritus NRS ≥4	Descriptive analysis with MCMC-MI[a]	mITT patients with baseline pruritus NRS ≥4	All scheduled visits in the Treatment Period at which scales are collected	Secondary analysis
		Descriptive analysis with As Observed	mITT patients with baseline pruritus NRS ≥4	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
		Descriptive analysis with LOCF	mITT patients with baseline pruritus NRS ≥4	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis

Description of Efficacy/Health Outcome Analyses

Measure	Variable	Analysis Method	Population (Section 6.1.1)	Time Point	Analysis Type
Sleep-loss Score	Percent Change from baseline in Sleep-loss Score Change from baseline in Sleep-loss Score	Descriptive analysis with MCMC-MI[a]	mITT	All scheduled visits in the Treatment Period at which scales are collected	Secondary analysis
		Descriptive analysis with As Observed	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
		Descriptive analysis with LOCF	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
	Proportion of patients achieving at least 2-point improvement sleep-loss in patients who had baseline Sleep-loss ≥ 2	Descriptive analysis with MCMC-MI[a]	mITT patients with baseline Sleep-loss ≥ 2	All scheduled visits in the Treatment Period at which scales are collected	Secondary analysis
		Descriptive analysis with As Observed	mITT patients with baseline Sleep-loss ≥ 2	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
		Descriptive analysis with LOCF	mITT patients with baseline Sleep-loss ≥ 2	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
Skin Pain NRS	Percent Change from baseline in Skin Pain Score Change from baseline in Skin Pain Score	Descriptive analysis with MCMC-MI[a]	mITT	All scheduled visits in the Treatment Period at which scales are collected	Secondary analysis
		Descriptive analysis with As Observed	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
		Descriptive analysis with LOCF	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis

Description of Efficacy/Health Outcome Analyses

Measure	Variable	Analysis Method	Population (Section 6.1.1)	Time Point	Analysis Type
Skin Pain NRS	Proportion of patients achieving at least a 4-point improvement in Skin Pain NRS in patients who had baseline Skin Pain NRS ≥4	Descriptive analysis with MCMC-MI[a]	mITT patients with baseline Skin Pain NRS ≥4	All scheduled visits in the Treatment Period at which scales are collected	Secondary analysis
		Descriptive analysis with As Observed	mITT patients with baseline Skin Pain NRS ≥4	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
		Descriptive analysis with LOCF	mITT patients with baseline Skin Pain NRS ≥4	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis
POEM	Change from baseline in POEM score	Descriptive analysis with As Observed	mITT	All scheduled visits in the Treatment Period at which scales are collected	Secondary analysis
		Descriptive analysis with LOCF	mITT	All scheduled visits in the Treatment Period at which scales are collected	Supplementary analysis

Abbreviations: AD = atopic dermatitis; BSA = body surface area; EASI = Eczema Area and Severity Index; IGA = Investigator Global Assessment; ITT = intent-to-treat; LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo multiple imputation; NRS = Numeric Rating Scale; POEM = Patient Oriented Eczema Measure.

[a] MCMC-MI will be implemented for the following two analysis groups only: 1. Patients coming from parent study KGAD (DRM06-AD06) who were lebrikizumab Q2W responders in KGAD and then were randomized in KGAA, by treatment group in KGAA; 2. Patients coming from parent studies KGAB (DRM06-AD04) and KGAC (DRM06-AD05), received lebrikizumab 250 mg Q2W during the parent study induction period and received lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W during the maintenance period and not in escape arm.

6.12. Health Outcomes/Quality-of-Life Analyses

The POEM is described in Table KGAA.6.6.

6.13. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Details of the pharmacokinetic (PK)/pharmacodynamic (PD) analyses can be found in a separate PK/PD analysis plan.

6.14. Safety Analyses

For the purposes of Study KGAA alone, the following are planned:

- listing of SAEs
- listing of AEs leading to permanent discontinuation of study drug
- summary of SAEs, and
- summary of AEs leading to permanent discontinuation of study drug.

The data will be pooled by treatment, 250 mg lebrikizumab Q2W, 250 mg lebrikizumab Q4W, and 250 mg lebrikizumab overall.

All summaries will be based on the Modified Safety Population. These analysis populations are fully defined in Section 6.1.1. A treatment emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after the date of the first injection in Study KGAA/AD07 and on or prior to the date of the last visit within the treatment period. A listing of AEs of patients from Site CCI and Site CCI will be provided.

Listings of all the patients with AEs from the safety follow-up period will be provided.

For patients enrolled from parent studies, SAEs that occur on or after the date of first visit to Study KGAA will be reported. For patients who enrolled directly into Study KGAA per Protocol Addendum 1.1, SAEs that occur on or after the date of informed consent will be reported.

The safety data from this study, such as AEs, vital signs, and laboratory data will be used as part of integrated safety assessments and ongoing safety review through study end.

6.14.1. Extent of Exposure

Exposure will be reported for patients in the Modified Safety Population. Exposure to lebrikizumab from the patient's parent study and from Study KGAA will be combined for reporting the extent of exposure in an integrated analysis. For Study KGAA, only exposure in Study KGAA will be reported. Exposure will be reported for lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, and lebrikizumab 250 mg overall. Drug interruption time period due to the use of long-term systemic rescue therapies will not be removed from study drug exposure calculations as described in compound level safety standards.

The duration of exposure in Study KGAA will be calculated as:

$$Duration\ of\ exposure\ (days) = \max[Date\ of\ \text{KGAA}\ last\ visit\ (scheduled\ or\ unscheduled)\ in\ the\ Treatment\ Period, Date\ of\ last\ dose] - Date\ of\ \text{KGAA}\ first\ dose + 1$$

While Study KGAA is still ongoing, before its final lock, there are patients who may have home injections after their last clinical visit, so the maximum date of the last dose and last visit will be used.

Total exposure to lebrikizumab 250 mg Q2W, total exposure to lebrikizumab 250 mg Q4W, and total exposure to lebrikizumab 250 mg overall will be summarized, by number and percentage of patients, using the following categories:

- >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 (1 year), ≥548 days, ≥730 days (2 years). 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, ≥365 days to <548 days, ≥548 days to <730 days, ≥730 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 mg.
- Total number of injections received will be derived from the *Study Drug Administration* eCRF and the information from the Dosing Diary.

6.14.2. Immunogenicity

The analyses of immunogenicity will be processed with parent studies' data together in an integrated database. More details are specified in Program Safety Analysis Plan (PSAP). No Study KGAA-specific immunogenicity analyses will be conducted.

6.14.2.1. Analysis Sets

Patients may transition from one of the parent studies or enroll directly into Study KGAA without being first enrolled in other studies. Immunogenicity analyses will be focused on patients who received at least one injection of lebrikizumab and have been monitored for at least 26 weeks since the day of the first exposure. This comprises of patients from Studies KGAB/AD04, KGAC/AD05, KGAD/AD06, KGAA/AD07 (direct entry patients), KGAE/AD17, KGAK/AD18, including those who discontinued before enrolling in Study KGAA.

For patients who are assigned to lebrikizumab either in parent Study or KGAA and receive at least 1 dose of the study drug and are treatment-emergent (TE) antidrug antibody (ADA) evaluable, the incidence rates of TE ADA status and maximum titer distributions are tabulated. This analysis will utilize the Atopic Dermatitis All Lebrikizumab Exposure Integrated Immunogenicity Analysis Set with New Immunogenicity Assay and will include no-drug follow-up period.

Table KGAA.6.8 summarizes the immunogenicity analysis set.

Table KGAA.6.8. Immunogenicity Analysis Set

Analysis Set	Population	Description	Baseline	Post Baseline Period
Atopic Dermatitis All Lebrikizumab Exposure Integrated Immunogenicity Analysis Set with New Immunogenicity Assay (KGAB, KGAC, KGAD, KGAA, KGAE, KGAK)	Modified Safety Population (see Table KGAA.6.1)	Patients who received at least one injection of lebrikizumab and have been monitored for at least 26 weeks. This comprises patients from studies KGAB/AD04, KGAC/AD05, KGAD/AD06, KGAA/AD07 (direct entry patients), KGAE/AD17, KGAK/AD18, including those who discontinued before enrolling in Study KGAA.	See Section 6.1.2	Postbaseline includes all observations after the day of first dose of the analysis period and before the end of KGAA Main study, or to the end of the parent study in case participant discontinued before entering KGAA Main.

6.14.2.2. Analyses

The number and proportion of patients who are TE ADA+ will be tabulated for the overall lebrikizumab treated patients, where proportions are relative to the number of patients who are TE ADA evaluable. The tabulation will include the number and proportion of patients with ADAs Present at baseline and the number and proportion of TE ADA+ patients exhibiting neutralizing antibodies (NAb). Analysis will be conducted for all patients, and those aged 12 to under 18.

The baseline ADA, along with the baseline titer distribution for individuals with ADA Present at baseline, and the distribution of postbaseline maximum titers for TE ADA+ patients, will be presented.

Table KGAA.6.9 provides the list of planned core immunogenicity analyses.

Table KGAA.6.9. List of Core Immunogenicity Analyses

Analysis	Details	Analysis Set
Incidence of Antidrug Antibodies and Neutralizing Antibodies	Within the patients evaluable for TE ADA, the number and percentage of patients with the following will be summarized: Patients evaluable for TE ADA ADA Present at baseline and NAb Present at baseline, TE ADA+, TE ADA Inconclusive, and TE ADA-, Treatment-induced TE ADA+ and treatment-boosted TE ADA+, TE ADA+ with NAb Present postbaseline, and TE ADA+ without NAb Present postbaseline, but having NAb Inconclusive at the follow up visit.	Atopic Dermatitis All Lebrikizumab Exposure Integrated Immunogenicity Analysis Set with New Immunogenicity Assay (KGAB, KGAC, KGAD, KGAA, KGAE, KGAK)
Characterization of Postbaseline Maximum Titer Distribution.	The distribution of the maximum titer values for the TE ADA+ patients will be summarized.	

Abbreviations: ADA = antidrug antibodies; Nab = neutralizing antibodies; TE = treatment-emergent.

6.15. Subgroup Analyses

6.15.1. Efficacy Subgroup Analyses

Subgroup analyses will be conducted for the secondary endpoints, the proportion of patients achieving an IGA of 0 or 1, and the proportion achieving EASI-75 across the treatment period in the mITT population.

The following subgroups will be analyzed:

- Age group (adolescents [from 12 up to 18], adults 18 and over)
- Sex (male, female)
- Region (US, EU, Rest of World)

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

6.15.2. Safety Subgroup Analyses

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

6.16. 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 wellbeing.

Potential examples of important protocol deviations include patients who violated the inclusion and exclusion criteria, used an interfering concomitant medication, and significant non-compliance with study medication (under 75% of expected injections). Refer to a separate

document called "KGAA 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 by treatment group using the ITT population.

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

6.16.1. Impact of COVID-19

Impact of pandemic (for example, COVID-19 [coronavirus disease 2019]) on analyses will be systemically addressed prior to study unblinding at submission database lock (DBL), once the impact on the study conduct are fully understood. A summary or listing may be provided to summarize missing visits due to COVID-19.

6.17. CCI

6.18. Interim Analyses and Data Monitoring

Data Monitoring Committee/Data Safety Monitoring Board (DMC/DSMB): The lebrikizumab Phase 3 AD programs' 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 one or more of the clinical studies. Details outlining the roles and responsibilities of the DSMB are documented in the "Dermira DRM06 DSMB Program Charter" and the planned analyses are outlined in the DSMB analysis plan prior to the first unblinded assessment.

Access to the unblinded safety data will be limited to the DSMB. The study team will not have access to the unblinded data. Only the DSMB is authorized to evaluate unblinded data. 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.

A small group could be unblinded including but not limited to global patient safety, medical, statistics, data management, regulatory, etc. who do not have direct interaction with the sites to prepare for regulatory interactions, safety updates, and disclosures if needed, while another team remains blinded to carry the day to day study work. The regulatory submission and related preparation will include DSMB #5, Submission interim, 4 Month Safety Update, and test transfers between DSMB #5 and KGAK/AD18 Week 16 DBL. Treatment, dispense, PK, and ADA information of patients enrolled from the KGAK/AD18 study will keep blinded until KGAK/AD18 study unblinded. A separate unblinding plan will provide a detailed rationale and procedure for unblinding to maintain the integrity of the study.

Submission DBL: An unblinded interim analysis will be performed to support regulatory submissions when it is estimated the regulatory requirement for safety exposure for the lebrikizumab program is met. Only the non-KGAK patients will be unblinded. This DBL will include all data collected by the cut-off date except the data from KGAK patients.

Week 100 DBL: Another unblinded interim analysis will be performed at the time (that is, a cut-off date) the last patient completes Week 100, 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 100.

Final DBL: A final DBL will occur after all patients have completed the safety follow-up period of the study or discontinued from the study.

Additional interim analyses may also be performed for regulatory interactions, safety updates, and disclosures.

6.19. Annual Report Analyses

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

6.20. Clinical Trial Registry Analyses

Additional analyses will be performed (if not already available from the study CSR) to fulfill the Clinical Trial Registry (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 treatment group, 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 and treatment group, the following are provided:
    - the number of patients at risk of an event,
    - the number of patients who experienced each event term, and
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures, for example, the CSR, manuscripts, and so forth.

7. Unblinding Plan

Unblinding details are specified in a separate unblinding plan.

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8. References

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Appendix 1. Study Visit Mapping for Pruritus NRS, Sleep-loss, POEM, and Skin-Pain NRS Diary

Pruritus NRS, Skin Pain NRS, and Sleep-loss score are collected as a daily diary, entries will be mapped to study week by the following:

Week	Start Day	End Day
Week 0	Date of First Injection – 7	Date of First Injection – 1
Week 2	Week 2 Visit Date – 7	Week 2 Visit Date – 1
Week 4	Week 4 Visit Date – 7	Week 4 Visit Date – 1
Week 16	Week 16 Visit Date – 7	Week 16 Visit Date – 1
Week 28	Week 28 Visit Date – 7	Week 28 Visit Date – 1
Week 40	Week 40 Visit Date – 7	Week 40 Visit Date – 1
Week 52	Week 52 Visit Date – 7	Week 52 Visit Date – 1

Note: If the date of the first injection is missing, the randomization date will be used.

If multiple assessments on a single day are present, use the first assessment. If at least 1 of the 7 days contains nonmissing daily assessments, the postbaseline weekly score will be calculated using a prorated weekly average. If the range of 7 days are all missing daily assessments, then the weekly score is missing.

The POEM is collected every week via eDiary until Week 52 visit, the visit week mapping will follow the following rule: the last collected POEM data before the visit date would be used, the evaluation window is injection date – 7 to injection date -1 for baseline, and visit date – 7 to visit date – 1 for post-baseline. For example, if a patient gets an injection on the 14th, we would use the scale completed between the 13th and the 7th.

Appendix 2. Definition of Rescue Medications

The following topical treatments and systemic treatments are defined as:

1. **Topical Atopic Dermatitis Treatment (including TCS, 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 systemic corticosteroids, immunosuppressants, biologics, and phototherapy/photochemotherapy)**

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 Preferred terms of Abrocitinib or Ruxolitinib excluding Preferred terms mentioned in Biologics

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 medical to manually review to confirm whether the medication in question is indeed ‘Phototherapy’ or ‘Photochemotherapy’

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Appendix 3. Details of Combining Estimates for Categorial Endpoints with Multiple Imputation

Following the implementation of the Markov Chain Monte Carlo multiple imputation (MCMC-MI) as specified in Section 6.4.3, the 25 data sets with imputations should be set together and sorted by imputation number. The following sections describe the processes for combining descriptive statistics for the individual imputed data sets into one descriptive statistic for reporting. All calculations are performed in SAS software version 9.4.

The response rates, overall and by treatment arm, and their associated standard errors (SEs) are computed for each imputed data set using PROC FREQ. The response rates and SEs from the resulting output are combined across the 25 imputed data sets using PROC MIANALYZE, separately for each arm and the overall group.

Note that the estimate and 95% confidence interval (CI) bounds output by PROC MIANALYZE are percentages (that is, they are in terms of the response rate). To obtain the number of responders, the estimated percentage is multiplied by the number of individuals in the analysis population and rounded to the nearest integer.

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