

Statistical Analysis Plan Version 2: J2T-MC-KGBW

A Multicenter, Randomized, Double-Blind, Placebo-controlled, Phase 3 Trial to Investigate the Efficacy and Safety of Lebrikizumab When Used With/Without Topical Corticosteroid Treatment in Participants With Moderate-To-Severe Atopic Dermatitis

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Title Page

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-controlled, Phase 3 Trial to Investigate the Efficacy and Safety of Lebrikizumab When Used with/without Topical Corticosteroid Treatment in Participants with Moderate-To-Severe Atopic Dermatitis

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Compound Number: Lebrikizumab (LY3650150)

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Acronym: ADvance-Asia

Sponsor Name: Eli Lilly and Company

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Version history

This Statistical Analysis Plan (SAP) Version 1 for Study J2T-MC-KGBW (KGBW) is based on Protocol J2T-MC-KGBW (KGBW), dated 23 October 2023, was approved prior to any unblinding on 06 November 2024.

SAP Version 2 was prepared to reflect the study strategy changes in Protocol KGBW Amendment (a), approved date on 3 Apr 2025.

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	06 November 2024	Not Applicable	Original version
2	See date on Page 1	Section 1.1: Revised the primary objective for combo cohort to: “To compare lebrikizumab 250 mg Q2W to placebo in reducing signs and symptoms of AD at Week 16 in participants with moderate-to-severe AD when used in combination with TCS treatment.” Added the major secondary objective for mono cohort: “To compare the efficacy and health outcome measures of lebrikizumab 250 mg Q2W to placebo during the 16-week Induction Period (Week 0 to 16) in participants with moderate-to-severe AD when used as monotherapy” Added major secondary endpoints for mono cohort to be consistent with combo cohort. Under the major secondary endpoints, modified percentage change from baseline of DLQI at week 16 to change from baseline of DLQI at week 16.	Study was modified to bridging study in Protocol Amendment (a) Modified to align with global pivotal study and Protocol Amendment (a)

		Under other secondary endpoints: added: ≥ 4-point improvement from baseline in the subset of participants with ≥ 4-point at baseline score ○ DLQI Deleted number of skin pain-free days in other secondary endpoint. Section 1.2: For combo cohort, changed sample size of 300 to 150.	
		Section 2: Changed hypothesis testing section to include the Bayesian decision criteria; multiplicity adjustment to “not applicable”	Study was modified to bridging study in Protocol Amendment (a) Modified hypothesis testing section and sensitivity analysis for Bayesian method according to CDE’s feedback.
		Section 4.1: Specified that maintenance analysis will be conducted on combined combo and mono cohort with selective efficacy analysis conducted on combo and mono cohort separately; Country-specific analysis will be performed for registration purpose; p-value will be output for descriptive purpose. Section 4.1.1: Clarified that CMH test was conducted for descriptive purposes. Deleted wording related to output p-value and odds ratio for safety outcomes. Added clarification that log-rank test will be performed only when deemed appropriate. Deleted wording related to inferential statistics on continuous lab assessments.	
		Section 4.1.6.1.2: Apply Bayesian decision framework to tipping point analysis instead of CMH test.	

		Section 4.3.2: Modified the main analytical approach to Bayesian modeling for combo cohort.	
		Section 4.3.3: Modified sensitivity analysis for combo cohort. Added sensitivity analysis using Bayesian analysis with supportive estimand. Added sensitivity analysis using different prior choice.	
		Section 4.3.4: Added additional supplementary analysis of co-primary analysis: perform common risk difference analysis under primary estimand framework.	
		Section 4.6: Deleted wording regarding output odds ratio and p values for safety analysis.	
		Section 5: Modified sample size consideration of the adjusted sample size and corresponding Bayesian decision criteria.	
		Section 6.2: Primary endpoint analysis was modified to include Bayesian models.	
		Section 6.14: Added detailed model information for Bayesian hierarchical model used in combo co-primary endpoint analysis.	
		Section 1.1 Under other secondary objectives section, modified “lebrikizumab 250 mg Q2W” to “lebrikizumab”	Clarification

		For maintenance primary estimand, changed the rationale of estimand to: “Therefore, being a responder requires an estimated positive response without systemic rescue medications, no discontinuation of treatment due to lack of efficacy, and no transfer to the escape arm due to lack of efficacy.”	
		Section 3: Deleted sentence of “the following population will be defined for combo and mono cohort separately.” In Table 3.1. specified analysis MSP population will be conducted on “maintenance blinded period” instead of “maintenance period.”	Clarification
		Section 4.1.6.1: Added “DLQI-related continuous endpoints” in table KGBW 4.1.	To specify the imputation method for key secondary endpoint.
		Section 4.1.6.2: Deleted sentences regarding hybrid supportive maintenance estimand.	Editorial consistency
		Section 4.6.4.4.4: In Table KGBW 4.12, added summary of TEAE of keratitis cluster by maximum severity.	To add analysis to summarize keratitis.
		Section 4.8: Modified unblinding data scope for 16-week database lock to include the unblinding of maintenance period treatment. Specified the data processing method for interim maintenance efficacy analysis. Clarified that the unblinding team will be prespecified in	Submission requirement

		the blinding and unblinding of key study team personnel log.	
		Section 4.9: Deleted previous content in this section. Added clarification of “Deleted other secondary endpoint: number of skin pain-free days (skin pain NRS=0)”	All previous changes have been included in Protocol Amendment (a) Modified other secondary endpoint to align with pivotal studies
		Section 6.1: Adjusted the “Imputation Approach if Missing” columns in Table 6.1 due to mismatch while table formatting; changed the last header of Table 6.1 to “Missing rule”	Format change
		Section 6.5: Modified treatment compliance table of maintenance period to reflect the expected injections of maintenance primary population in maintenance blinded period	To clarify the analysis population and period
		Section 6.6.1: Clarified that the indication as “rescue therapy” is not required for rescue therapy identification	To keep consistent with pivotal study
		Section 6.8: Deleted Appendix 8: impact of COVID-19	Not required
		Section 6.11 Updated the rules of deriving TCS potency	Modified the rules to deal with ATC categorization discrepancy

Abbreviations: AD = atopic dermatitis; CDE; CMH = Cochran-Mantel-Haenszel; DLQI = Dermatology Life Quality Index; TCS = topical corticosteroid; TEAE = treatment-emergent adverse event, NRS = numeric rating scale, Q2W = every 2 weeks.

1. Introduction

1.1. Objectives, Endpoints, and Estimands

Objectives		Endpoints
Combo Cohort	Mono Cohort	
Primary		
To compare lebrikizumab 250 mg Q2W to placebo in reducing signs and symptoms of AD at Week 16 in participants with moderate-to-severe AD when used in combination with TCS treatment.	To compare lebrikizumab 250 mg Q2W to placebo in reducing signs and symptoms of AD at Week 16 in participants with moderate-to-severe AD when used as monotherapy.	Proportion of participants achieving at Week 16: - EASI-75 - IGA score of 0 or 1 and a reduction of ≥ 2 points from baseline to Week 16
Major Secondary		
To compare lebrikizumab 250 mg Q2W to placebo in reducing signs and symptoms of AD at Week 16 in participants with moderate-to-severe AD when used in combination with TCS treatment.	To compare lebrikizumab 250 mg Q2W to placebo in reducing signs and symptoms of AD at Week 16 in participants with moderate-to-severe AD when used as monotherapy.	Proportion of participants achieving at Week 16: - EASI-90 ≥ 4-point improvement from baseline in Itch NRS in the subset of participants with ≥ 4-point Itch NRS at baseline. Percentage change from baseline at Week 16: - EASI score - Itch NRS Change from baseline at Week 16: - DLQI
Other Secondary		
To evaluate the efficacy and health outcome measures of lebrikizumab during the 16-week induction period (Week 0 to Week 16) and 36-week maintenance period (Week 16 to Week 52) in participants with moderate-to-severe AD when used in combination with TCS treatment.	To evaluate the efficacy and health outcome measures of lebrikizumab during the 16-week induction period (Week 0 to Week 16) and 36-week maintenance period (Week 16 to Week 52) in participants with moderate-to-severe AD when used as monotherapy.	Proportion of participants achieving by visit: - EASI-50, EASI-75 and EASI-90 - IGA score of 0 or 1 and a reduction of ≥ 2 points from baseline - maintaining EASI-75 during the 36-week maintenance period among those originally randomized to lebrikizumab 250 mg Q2W and who achieved EASI-75 at Week 16.

Objectives		Endpoints
Combo Cohort	Mono Cohort	
		- maintaining an IGA score of 0 or 1 with a ≥ 2-point improvement from baseline during the 36-week maintenance period among those originally randomized to lebrikizumab 250 mg Q2W who achieved IGA score of 0 or 1 with a ≥ 2-point improvement from baseline at Week 16 - DLQI score of 0 or 1 - CDLQI score of 0 or 1, and ≥ 4-point improvement from baseline in the subset of participants with ≥ 4-point at baseline score - Itch NRS - Skin Pain NRS - DLQI - CDLQI Percentage Change from baseline by visit: - EASI score - Itch NRS - SCORAD Change from baseline by visit: - Itch NRS - Skin Pain NRS - Percent BSA - Sleep-Loss Scale score - CDLQI - DLQI - POEM - WPAI-AD - HADS - EQ-5D-5L index - Change from baseline in ACQ-5 score to Week 16 in participants who have self-reported comorbid asthma.

Objectives		Endpoints
Combo Cohort	Mono Cohort	
To evaluate the efficacy of lebrikizumab 250 mg Q2W during the 16-week induction period (Week 0 to Week 16) in participants with moderate-to-severe AD when used in combination with TCS treatment.		Among participants treated with lebrikizumab in combination with TCS treatment: - proportion of TCS/TCI-free days over the 16-week induction period. - total amount of TCS used over the 16-week induction period Time (days) to TCS/TCI-free use over the 16-week induction period.
To describe the safety of lebrikizumab in participants with moderate-to-severe AD when used in combination with TCS treatment.	To describe the safety of lebrikizumab in participants with moderate-to-severe AD when used as monotherapy.	Summary of safety data, including number and incidence of: - SAEs - TEAEs - discontinuations due to AEs
To measure lebrikizumab exposure in participants with moderate-to-severe AD when used in combination with TCS treatment.	To measure lebrikizumab exposure in participants with moderate-to-severe AD when used as monotherapy.	Average serum lebrikizumab concentration at steady state.
Exploratory		
To assess the growth of adolescent participants treated with lebrikizumab when used in combination with TCS treatment.	To assess the growth of adolescent participants treated with lebrikizumab when used as monotherapy,	Mean changes in growth parameters (height, weight, and BMI) over the course of treatment.
To evaluate the efficacy of lebrikizumab 250 mg Q4W and Q8W during the 52-week treatment period in participants with moderate-to-severe AD when used in combination with TCS treatment.		Among participants treated with lebrikizumab in combination with TCS treatment: - proportion of TCS/TCI-free days over the 36-week maintenance period - total amount of TCS used over the 36-week maintenance period, and - time (days) to TCS/TCI-free use over the 52-week treatment period.
To assess the frequency of immunogenicity of lebrikizumab in participants with moderate-to-severe AD when used in combination with TCS treatment.	To assess the frequency of immunogenicity of lebrikizumab in participants with moderate-to-severe AD when used as monotherapy.	Incidence of TE ADA

Abbreviations: ACQ-5 = Asthma Control Questionnaire-5; AD = atopic dermatitis; AE = adverse event; BMI = body mass index; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area Severity Index; HADS = Hospital Anxiety Depression Scale; IGA = Investigator's Global Assessment; NRS = numeric rating scale; POEM = Patient-Oriented Eczema Measure; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SAE = serious adverse event; SCORAD = SCORing Atopic Dermatitis; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid; TE ADA = treatment-emergent antidrug antibody; TEAE = treatment-emergent adverse event; WPAI-AD = Work Productivity and Activity Impairment - Atopic Dermatitis.

Primary estimand

Primary estimand for combo cohort

The primary clinical question of interest is:

What is the difference between treatment conditions, that is, lebrikizumab + topical corticosteroid (TCS) versus placebo + TCS, in the target participant population in achieving successful responses or means at Week 16, without the use of rescue medication and if all participants continued with treatment except those who discontinued due to lack of efficacy?

The primary estimand is described by the following attributes:

Population: defined through appropriate inclusion and exclusion criteria to reflect the targeted participant population for approval.

Endpoint: applied to all primary and key secondary endpoints.

How to account for intercurrent events (ICEs):

- Participants who require any use of rescue medication or who have discontinued treatment due to lack of efficacy prior to Week 16 will be considered as treatment failures, that is, as non-responders, after the ICEs. Therefore, a composite strategy will be used for these types of ICEs.
- For participants who discontinue treatment due to any other reason prior to Week 16, the hypothetical strategy will be used to estimate what the treatment effect would have been if participants had continued with treatment. Therefore, the hypothetical strategy will be used for these types of ICEs.

Population-level summary: the difference in response proportions or means between the treatment conditions at Week 16.

Rationale for estimand: the primary estimand assumes that if a participant requires any rescue medication, the participant is not receiving sufficient benefit from the treatment. It also assumes that if a participant discontinues treatment early due to lack of efficacy, the burden of treatment outweighs its benefits. Therefore, being a responder requires a positive response without rescue medications and no discontinuation of treatment due to lack of efficacy.

Primary estimand for the mono cohort

The primary clinical question of interest is:

What is the difference between treatment conditions, that is, lebrikizumab versus placebo, in the target participant population in achieving successful responses at Week 16, without the use of rescue medication, and if all participants continued with treatment, except those who discontinued due to lack of efficacy?

The primary estimand is described by the following attributes:

Population: defined through appropriate inclusion and exclusion criteria to reflect the targeted participant population for approval.

Endpoint: applies to all primary and key secondary endpoints.

How to account for ICEs:

- Participants who require any use of rescue medication or who have discontinued treatment due to lack of efficacy prior to Week 16 will be considered as treatment failures, that is, as non-responders, after the ICEs. Therefore, a composite strategy will be used for these types of ICEs.
- For participants who discontinue treatment for any other reason prior to Week 16, the hypothetical strategy will be used to estimate what the treatment effect would have been if participants had continued with treatment. Therefore, the hypothetical strategy will be used for these types of ICEs.

Population-level summary: the difference in response proportions at Week 16 between treatment conditions.

Rationale for estimand: The primary estimand for the mono cohort is chosen based on the same rationale for the primary estimand for the combo cohort.

Supportive estimand(s) for the combo and mono cohort***Supportive estimand for categorical endpoints (composite)***

The supportive clinical question of interest is:

What is the difference between treatment conditions, that is, lebrikizumab + TCS versus placebo + TCS, in the target participant population in achieving a successful response at Week 16, without the use of rescue medication or treatment discontinuation?

The supportive estimand is described by the following attributes:

Population: defined through appropriate inclusion and exclusion criteria to reflect the targeted participant population for approval.

Endpoint: applies to all categorical endpoints.

How to account for ICEs:

- Participants who require any use of rescue medication or who have discontinued treatment prior to Week 16 will be considered as treatment failures, that is, as non-responders, after the ICEs. Therefore, a composite strategy will be used for these types of ICEs.

Population-level summary: the difference in response proportions between treatment conditions.

Rationale for estimand: the composite supportive estimand assumes that if a participant requires any rescue medication or discontinues early for any reason, the participant is not receiving sufficient benefit from the treatment. Therefore, being a responder requires a positive response without rescue medications and no discontinuation of treatment.

Supportive estimand for continuous endpoints (hypothetical)

The supportive estimand for continuous endpoints is a hypothetical estimand representing the supportive clinical question of interest:

What is the difference between treatment conditions in the target participant population in means at Week 16 if rescue medication was not available and all participants adhered to the treatment?

The supportive estimand is described by the following attributes:

Population: defined through appropriate inclusion and exclusion criteria to reflect the targeted participant population for approval.

Endpoint: applies to continuous endpoints.

How to account for ICEs:

- For subjects who require any use of rescue medication or who have discontinued treatment prior to Week 16, the hypothetical strategy will be used to estimate what the treatment effect would have been if rescue medication was not available, and all subjects adhered to the treatment. Therefore, the hypothetical strategy is used for these types of ICEs.

Population-level summary: the difference in means between treatment conditions.

Rationale for estimand: the hypothetical estimand evaluates treatment effect under the ideal condition that rescue medication is not available and all participants will adhere to the randomly assigned intervention.

Details on how missing data (including those as a result of ICEs) will be handled, can be found in Section 4.1.6. Detailed analyses relative to estimands, including analysis type, method and imputation, population, time point, and treatment comparisons for efficacy and health outcome analyses, can be found in [Appendix 2](#) (see Section 6.2).

Table KGBW.1.1 summarizes the analytical strategies that will be conducted on the ICEs for the three estimands.

Table KGBW.1.1 Description of Primary and Supportive Estimands for Induction Period

Estimand	Analysis Strategy for Intercurrent Events			Missing Data Imputation Method
	Rescue Medication	Treatment Discontinuation		
		Due to lack of efficacy	Due to any other reasons	
Primary Estimand (Hybrid)	Composite: Set to baseline	Composite: Set to baseline	Hypothetical: Set to missing	MCMC-MI
Supportive Estimand for Categorical Endpoints (Composite)	Composite: Set to nonresponder	Composite: Set to nonresponder	Composite: Set to nonresponder	NRI
Supportive Estimand for Continuous Endpoints (Hypothetical)	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	MMRM/LOCF

Abbreviations: LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo multiple imputation; MMRM = mixed-effects model for repeated measures; NRI = nonresponder imputation.

Primary and supportive estimands for the maintenance period for the combo and mono cohorts

There will be 3 estimands of interest in analyzing endpoints for the maintenance period. In terms of estimating the treatment effects for the maintenance period, 3 types of ICEs will be considered: initiation of rescue medication, permanent treatment discontinuation, and transfer to the escape arm.

Maintenance primary estimand (hybrid estimand)

The maintenance primary estimand is a hybrid estimand representing the clinical question of interest:

What are the response proportions or means for each treatment condition (that is, Lebrikizumab 250 mg taken once every 4 weeks [Q4W] and 8 weeks [Q8W]), in the target participant population, in successful responses or means at Week 52 achieved without the use of systemic rescue medication, without transferring to the escape arm, if topical rescue medication were not available and if all participants continued with treatment except those who discontinued due to lack of efficacy?

The maintenance primary estimand is described by the following attributes:

Population: Maintenance Primary Population (MPP) as described in Section 3.

Endpoint: apply to key categorical and continuous endpoints (that is, the Investigator's Global Assessment [IGA], Eczema Area and Severity Index [EASI], and Itch Numeric Rating Scale [NRS] related endpoints) for the Maintenance Period in both the combo cohort and mono cohort.

How to account for ICEs

- Participants who require any use of systemic rescue medication, discontinue treatment due to lack of efficacy after Week 16, or transfer to the escape arm will be considered as treatment failures, that is, as nonresponders, after the ICEs. Therefore, a composite strategy is used for these types of ICEs.
- For participants who require any use of topical rescue medication, the hypothetical strategy will be used to estimate what the response proportions or means for each treatment condition would have been if participants continued with treatment. Therefore, the hypothetical strategy will be used for these types of ICEs.
- For participants who discontinue treatment for reasons other than lack of efficacy after Week 16, the hypothetical strategy will be used to estimate what the response proportions or means for each treatment condition would have been if participants continued with treatment. Therefore, the hypothetical strategy is used for these types of ICEs.

Population-level summary: the difference in response proportions or means for each treatment condition.

Rationale for estimand: the primary estimand for the maintenance period assumes that if a participant requires any systemic rescue medication or has transferred to the escape arm, the participant is not receiving sufficient benefit from the treatment. It also assumes that if a participant discontinues treatment early due to lack of efficacy, the burden of treatment outweighs its benefits. Therefore, being a responder requires an estimated positive response without systemic rescue medications, no discontinuation of treatment due to lack of efficacy, and no transfer to the escape arm due to lack of efficacy.

Maintenance supportive estimand for categorical endpoints (composite)

The maintenance supportive estimand for categorical endpoints only is a composite estimand representing the clinical question of interest:

What are the response proportions for each treatment condition (that is, Lebrikizumab 250 mg every 4 weeks [Q4W] and 8 weeks [Q8W]), in the target participant population, in successful responses at Week 52 achieved without use of topical or systemic rescue medication, treatment discontinuation, or transfer to the escape arm?

The maintenance supportive estimand is described by the following attributes:

Population: MPP as described in Section 3.

Endpoint: applies to all categorical endpoints for the Maintenance Period in the combo cohort and the mono cohort.

How to account for ICEs:

- Participants who require any use of topical or systemic rescue medication, discontinue treatment after Week 16, or transfer to the escape arm will be considered as treatment failures, that is, as nonresponders, after the ICEs. Therefore, a composite strategy will be used for these types of ICEs.

Population-level summary: response proportions for each treatment condition.

Rationale for estimand: This composite supportive estimand assumes that if a participant requires any rescue medication, the participant is not receiving sufficient benefit from the treatment. It also assumes that if a participant discontinues treatment after Week 16 or has been transferred to the escape arm, the burden of treatment outweighs its benefits. Therefore, being a responder requires a positive response without rescue medications, no discontinuation of treatment, and no transfer to the escape arm.

Maintenance supportive estimand for continuous endpoints (hypothetical)

The maintenance supportive estimand for continuous endpoints only is a hypothetical estimand representing the clinical question of interest:

What are the means for each treatment condition (that is, Lebrikizumab 250 mg Q4W and 8 weeks [Q8W]), in the target participant population, in means at Week 52, if rescue medication was not available and all participants adhered to the treatment and did not transfer to the escape arm?

The maintenance supportive estimand is described by the following attributes:

Population: MPP as described in Section 3.

Endpoint: apply to all continuous endpoints for the maintenance period.

How to account for ICEs:

- For participants who require any use of rescue medication, discontinue treatment after Week 16, or transfer to the escape arm, a hypothetical strategy will be used to estimate what the means for each treatment condition would have been if rescue medication was not available and all participants adhered to the treatment and did not transfer to the escape arm. Therefore, the hypothetical strategy is used for these types of ICEs.

Population-level summary: the means for each treatment condition.

Rationale for estimand: this hypothetical estimand evaluates the treatment effect under the ideal condition that rescue medication is not available and all participants would adhere to the randomly assigned intervention without transferring to the escape arm.

Details on how missing data, including data missing as a result of ICEs, will be handled can be found in Section 4.1.6.2. Detailed analyses relative to estimands including analysis type, method and imputation, population, time point, and treatment comparisons for the efficacy and health outcome analyses can be found in Appendix 2 (Section 6.2).

[Table KGBW.1.2](#) summarizes the analytical strategies that will be conducted on the ICEs for the 4 maintenance estimands. ICEs and missing data will be summarized by treatment group for the induction period in the intent-to-treat (ITT) population, and for the maintenance blinded period in the MPP, respectively.

Table KGBW.1.2. Description of Primary and Supportive Estimands for Maintenance Period

Maintenance Estimand	Analysis Strategy for Intercurrent Events				Transfer to escape arm	Missing data imputation method
	Rescue Medication		Treatment Discontinuation			
	Topical rescue medication	Systemic rescue medication	Due to lack of efficacy	Due to any other reasons		
Maintenance Primary Estimand (Hybrid)	Hypothetical: Set to missing	Composite: Set to baseline	Composite: Set to baseline	Hypothetical: Set to missing	Composite: Set to baseline	Primary analysis: MCMC-MI
Maintenance Supportive Estimand for Categorical Endpoints (Composite)	Composite: Set to nonresponder	Composite: Set to nonresponder	Composite: Set to nonresponder	Composite: Set to nonresponder	Composite: Set to nonresponder	NRI
Maintenance Supportive Estimand for Continuous Endpoints (Hypothetical)	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	LOCF

Abbreviations: LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo multiple imputation; NRI = nonresponder imputation.

1.2. Study Design

Study KGBW is a randomized, double-blind, placebo-controlled, parallel-group study, which is 52 weeks in treatment duration. The study is designed to evaluate the efficacy and safety of lebrikizumab compared with placebo when used with or without TCS treatment using a 16-week induction period and a 36-week maintenance period of lebrikizumab for participants with moderate-to-severe atopic dermatitis (AD).

Study Population

Participants are eligible for Study KGBW if they:

- are ≥ 18 years or an adolescent (≥ 12 to < 18 years of age and weighing ≥ 40 kg) with moderate-to-severe AD for at least 1 year, defined according to the AAD Consensus Criteria (Eichenfield et al. 2014); or have chronic eczema and meet the AAD criteria
- have an EASI score ≥ 16
- have an IGA score ≥ 3 , and

- have $\geq 10\%$ body surface area (BSA) of AD involvement.

Investigators should review vaccination status in adolescent participants (≥ 12 to < 18 years) and determine the benefits and risks involved in their participation. Prior to initiating therapy, investigators should review participants' immunization records according to current local immunization guidelines. No change in the start or resumption of vaccine is required, and pediatric participants will follow the local immunization guidelines, with the exception of live vaccines. If a participant has received a live vaccine within 12 weeks of the baseline visit or intends to receive a live vaccine during the study, the participant is not eligible for the study. For complete inclusion/exclusion criteria, please refer to Protocol KGBW Sections 5.1 and 5.2.

Screening

Approximately 280 participants, including approximately 58 adolescent participants (≥ 12 to < 18 years and weighing ≥ 40 kg), will be enrolled. Participants will be assigned to either the combo cohort (lebrikizumab/placebo + TCS) ($n=150$) or mono cohort (lebrikizumab/placebo) ($n=130$) based on investigator's decision. Enrollment will be stopped in either cohort once the participant number reaches the planned number in that cohort.

Induction Period

During the 16-week Induction Period, participants will be randomized in a 2:1 ratio to treatment within cohort:

- Combo cohort:
 - Lebrikizumab 250 mg (loading dose of 500 mg given at baseline and Week 2) by subcutaneous (SC) injection every 2 weeks (Q2W) in combination with TCS treatment ($n=100$)
 - Placebo in combination with TCS treatment ($n=50$)
- Mono cohort:
 - Lebrikizumab 250 mg (loading dose of 500 mg given at baseline and Week 2) by SC injection Q2W ($n=87$)
 - Placebo ($n=43$)

For combo cohort, participants will be stratified at randomization according to age (adolescent participants ≥ 12 to < 18 years versus ≥ 18 years) and disease severity (IGA 3 versus IGA 4). For mono cohort, participants will be stratified by age (adolescent participants ≥ 12 to < 18 years vs. ≥ 18 years), disease severity (IGA 3 versus IGA 4), and country (China versus Korea). TCS should be washed out 7 days prior to baseline for all participants in the mono cohort. Daily use of mid-potency TCS (low-potency TCS and/or topical calcineurin inhibitor (TCI) for sensitive areas) will be initiated at least 7 days prior to baseline for all participants in the combo cohort (not allowed to be tapered or stopped during the Screening Period). In the combo cohort, mid-potency TCS, low-potency TCS, and TCIs may be tapered or stopped after baseline, as needed, based on treatment response.

Maintenance Period (either in the combo or mono cohort)

After completion of the Week 16 visit:

- Participants receiving lebrikizumab 250 mg Q2W:
 - who achieve an IGA score of 0 or 1 and/or a $\geq 75\%$ reduction in EASI score ($\geq \text{EASI-75}$) response at Week 16 will be randomly allocated to receive lebrikizumab 250 mg Q4W or every 8 weeks (Q8W), in a 1:1 fashion within the cohort, and
 - who achieve neither an IGA score of 0 or 1 nor a 75% reduction in EASI score ($< \text{EASI-75}$) response at Week 16 will enter the escape arm.
- Participants receiving placebo:
 - who achieve an IGA score of 0 or 1 and/or an EASI-75 response ($\geq \text{EASI-75}$) at Week 16 will continue to receive placebo, and
 - who achieve neither an IGA score of 0 or 1 nor an EASI-75 response ($< \text{EASI-75}$) at Week 16 will enter the escape arm and will receive a loading dose of lebrikizumab 500 mg at Week 16 and Week 18.

Treatment regimen assignment will remain blinded during the Maintenance Period. Placebo injections will be utilized in order to maintain the blind and ensure that all participants receive the same number and frequency of injections regardless of treatment regimen assignment.

Low to mid-potency TCS can be used when needed per the investigator's opinion.

Escape arm (either in the combo or mono cohort)

In the escape arm, participants will receive 250 mg lebrikizumab Q2W. Low to mid-potency TCS can be used when needed per the investigator's opinion.

Escape arm from Week 16:

- Participants who achieve neither an IGA score of 0 or 1 nor an EASI-75 response ($< \text{EASI-75}$) at Week 16 will enter the escape arm.
- Participants who receive rescue treatment in the Induction Period will also be eligible to enter the escape arm at Week 16.
- Participants who required systemic rescue medication in the Induction Period must temporarily discontinue study intervention and must wait for the rescue medication washout (≥ 5 half-lives of the medication) prior to entering the escape arm.
- Only participants who receive placebo in the Induction Period will receive a loading dose of lebrikizumab 500 mg at Week 16 and Week 18 followed by lebrikizumab 250 mg Q2W. Participants not achieving at least 50% improvement from baseline in Eczema Area and Severity Index score (EASI-50) response at 2 consecutive visits in the escape arm after Week 32 of treatment will be discontinued from the study.

Escape arm after Week 20:

- Participants who do not maintain an EASI-50 response at Week 24, 32, 40 or 48 in the Maintenance Period will be assigned to the escape arm and receive lebrikizumab 250 mg Q2W as open-label treatment through Week 50.
- Participants not achieving an EASI-50 response at 2 consecutive visits in the escape arm after 8 weeks of treatment will be discontinued from the study.

All study intervention injections during the study will be administered by site staff at the clinic.

Safety follow-up visit

Participants who terminate early from the study or complete the 52-week treatment period will undergo a safety follow-up visit approximately 12 weeks after the last study intervention injection as outlined in the Schedule of Activities (SoA) in Protocol KGBW.

Efficacy, Health Outcomes, and Safety Assessments

Efficacy and health outcomes will be measured through:

- IGA
- EASI
- SCORing Atopic Dermatitis (SCORAD)
- BSA involvement
- Itch NRS
- sleep-loss scoring system
- skin pain NRS
- TCS use
- quality of life and impact of disease (these will be assessed using the Patient-Oriented Eczema Measure [POEM], Dermatology Life Quality Index/Children's Dermatology Life Quality Index [DLQI/CDLQI], Work Productivity and Activity Impairment – Atopic Dermatitis [WPAI-AD], and Hospital Anxiety Depression Scale [HADS])
- 5-level version of EQ-5D (EQ-5D-5L), and
- Asthma Control Questionnaire-5 (ACQ-5) (to be completed by participants reporting comorbid asthma at study entry).

Safety will be assessed in all participants by:

- adverse event (AE) monitoring
- serum chemistry
- hematology
- urinalysis laboratory testing
- physical examination, and
- pulse and blood pressure (vital signs).

Serum samples will be collected for pharmacokinetic (PK) analysis and immunogenicity.

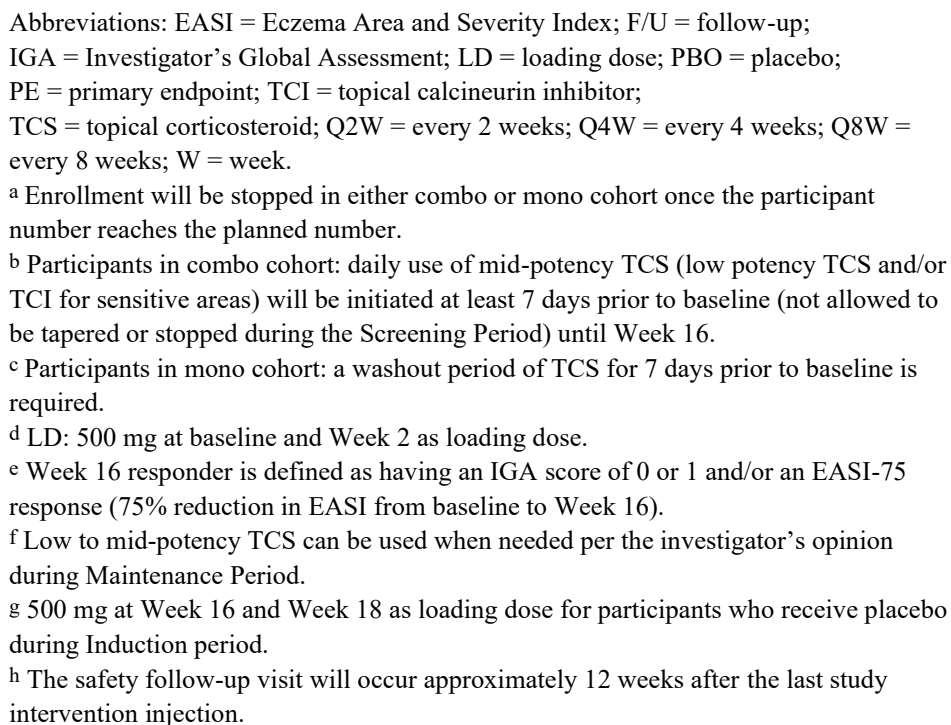


Figure KGBW.1.1. Illustration of study design for Clinical Protocol J2T-MC-KGBW.

2. Statistical Hypotheses

Bayesian decision criterion will be used to assess the treatment effect by determining whether the

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for both co-primary endpoints (EASI-75 and IGA0/1 with 2-point reduction at Week 16) in Combo cohort.

2.1. Multiplicity Adjustment

Not applicable.

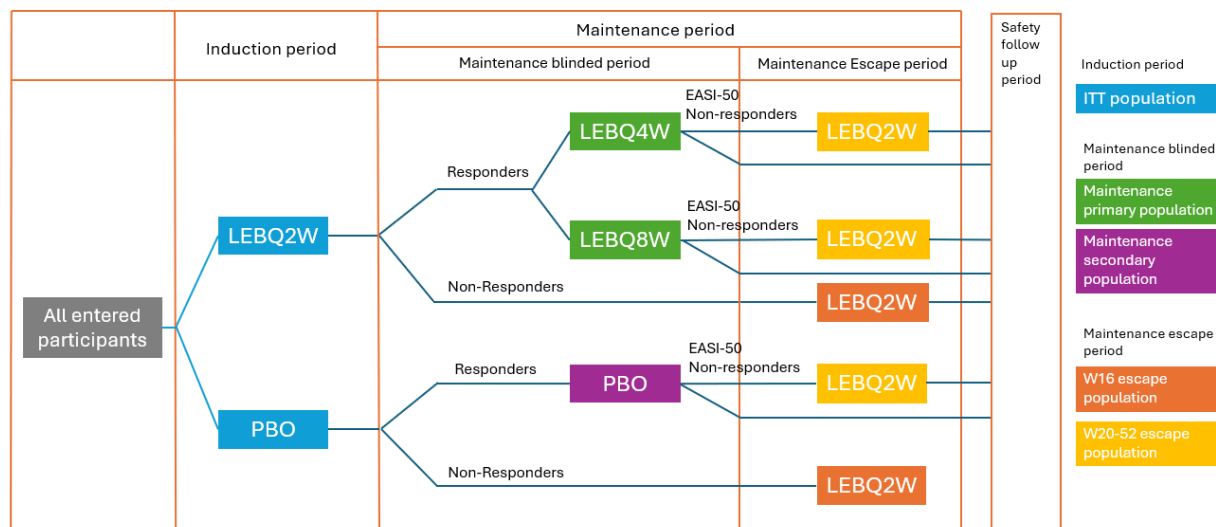
3. Analysis Sets

The populations are defined for as follows. The treatment groups and comparisons in each period and analysis population are defined in [Table KGBW.3.1](#).

Participant Analysis Set	Description
Entered	All participants who signed informed consent/assent. Participant flow will be summarized.
Intent-to-Treat (ITT)	All randomized participants, even if the participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Participants will be analyzed according to the treatment group to which they were assigned. Unless otherwise specified, efficacy and health outcome analyses for the Induction Period will be conducted on this population.
Safety Population	All randomized participants who received at least 1 dose of study intervention during the Induction Period. Safety analyses for the Induction Period will be conducted on this population.
Maintenance Period Primary Population (MPP)	All participants who were randomized to lebrikizumab 250 mg Q2W at baseline visit and rerandomized to lebrikizumab 250 mg Q4W or lebrikizumab 250 mg Q8W (that is, participants who achieved an IGA of 0 or 1 and/or EASI-75 and were re-randomized at Week 16) and received at least 1 dose of study intervention during the Maintenance Period. Participants will be analyzed according to the treatment to which they were assigned. Only information prior to escape will be presented. Efficacy, health outcome, and safety analyses for the Maintenance Period will be conducted primarily on the Maintenance Period Primary Population.
Maintenance Period Secondary Population (MSP)	Participants who were randomized to placebo at baseline visit (Visit 2, Week 0) and continued placebo (that is, participants who achieved an IGA score of 0 or 1 and/or EASI-75 at Week 16) and received at least 1 dose of study intervention during the Maintenance Period. Only information prior to entering the escape arm will be presented. Selective efficacy analyses for the Maintenance Period will be conducted on the MSP.
Maintenance W16 Escape Population	Participants who moved to the escape arm at Week 16 (either due to not meeting IGA and EASI criteria, or used rescue therapy during the Induction Period), and received at least 1 dose of study intervention during the Maintenance Period. Selective efficacy analyses for the Maintenance Period will be conducted on the Maintenance W16 Escape Population.
Maintenance W20-52 Escape Population	Maintenance Period Primary and Secondary Population who escaped to lebrikizumab 250 mg Q2W due to EASI-50 nonresponse at Weeks 24, 32, 40, and 48. Selective efficacy analyses for the Maintenance Period will be conducted on the Maintenance Period Escape Population to assess whether these participants regain EASI-50 response or achieve a higher level of response (for example, EASI-75) following escape arm treatment.

Participant Analysis Set	Description
All Lebrikizumab Safety Population	All randomized participants who received at least 1 dose of lebrikizumab treatment during Combined Induction and Maintenance Periods. Safety analyses for the Combined Induction and Maintenance Periods will be conducted on the All Lebrikizumab Safety Population. Selective safety analyses for the Combined Induction and Maintenance Periods plus the Follow-Up Period will be conducted on the All Lebrikizumab Safety Population.
Pharmacokinetic Analysis	All participants who received at least 1 dose of lebrikizumab and have at least 1 evaluable PK sample.

Abbreviations: EASI-50 = $\geq 50\%$ reduction from baseline in Eczema Area and Severity Index; EASI-75 = $\geq 75\%$ reduction from baseline in Eczema Area and Severity Index; IGA = Investigator's Global Assessment; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; W = Week.



Abbreviations: EASI = Eczema Area and Severity Index; ITT = intent-to-treat; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.

Figure KGBW.3.1 Analysis populations flow for Study KGBW.

Table KGBW.3.1. Treatment Groups and Comparisons for Each Study Period and Analysis Population

Study Period	Analysis Population	Treatment Groups	Abbreviation	Inferential Comparisons When Applicable
Induction Period	ITT Safety	Placebo Lebrikizumab 250 mg Q2W Total	PBO LEB250Q2W Total	LEB250Q2W vs. PBO
Maintenance Blinded Period	MPP	Lebrikizumab 250 mg Q2W_Res/ Lebrikizumab 250 mg Q4W Lebrikizumab 250 mg Q2W_Res/ Lebrikizumab 250 mg Q8W Total	LEB_Res/ LEB250Q4W LEB_Res/ LEB250Q8W Total	No Between-Group or Overall Comparisons
Maintenance Blinded Period	MSP	Placebo_Res/Placebo	PBO_Res/PBO	No Between-Group or Overall Comparisons
Maintenance Escape Period	Maintenance W16 Escape Population	Placebo_NonResp/ Lebrikizumab 250 mg Q2W Lebrikizumab 250 mg_NonResp/Lebrikizumab 250 mg Q2W	PBO_NonResp/ LEB250Q2W LEB_NonResp/ LEB250Q2W Total	No Between-Group or Overall Comparisons
Maintenance Escape Period	Maintenance W20-52 Escape Population	Placebo/Placebo/Lebrikizumab 250 mg Q2W Lebrikizumab 250 mg Q2W/Lebrikizumab 250 mg Q4W/Lebrikizumab 250 mg Q2W Lebrikizumab 250 mg Q2W /Lebrikizumab 250 mg Q8W/Lebrikizumab 250 mg Q2W Total	PBO_Res/PBO_NonResp/LEB250Q2W LEB250Q2W/LEB250Q4W/ LEB250Q2W LEB250Q2W/LEB250Q8W/ LEB250Q2W Total	No Between-Group or Overall Comparisons
Combined Induction and Maintenance Periods	All Lebrikizumab Safety Population	Any Lebrikizumab	N/A	No Between-Group or Overall Comparisons

Study Period	Analysis Population	Treatment Groups	Abbreviation	Inferential Comparisons When Applicable
Combined Induction and Maintenance Periods + FU	All Lebrikizumab Safety Population	Any Lebrikizumab	N/A	No Between-Group or Overall Comparisons

Abbreviations: FU = follow-up; ITT = intent-to-treat; LEB = lebrikizumab; MPP = Maintenance Period Primary Population; MSP = Maintenance Period Secondary Population; NonResp = nonresponder; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Res = responder; W = week.

4. Statistical Analyses

4.1. General Considerations

All analyses will be conducted in combo cohort and mono cohort individually for induction period. Country-specific analysis will be performed in mono cohort to support registration in China.

Analysis for maintenance period will be conducted on combined combo and mono cohort, whereas selective efficacy analysis for maintenance period will be performed on combo and mono cohort separately.

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.

All statistical processing will be performed using SAS® unless otherwise stated. Unless otherwise stated, all confidence intervals (CIs) will be given at a 2-sided 95% level. For descriptive purposes, p-values will be provided.

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.

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.

4.1.1. General Consideration for Induction Period

Induction Period starts after the first injection of study treatment at Baseline Visit (Week 0, Visit 2) and ends prior to the first injection of study treatment at Week 16 or the early termination visit (ETV) (between Day 1 and Week 16). For participants who were randomized but discontinued the study before the first injection, the Induction Period starts on the date of randomization. For participants who were randomized but received the first injection after the date of randomization, the Induction Period starts on the date of first injection.

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 Baseline Visit (Day 1). If the participant does not take any injection, the last available value on or prior to randomization date will be used. Change from baseline will be calculated as the visit value of interest minus the baseline value.

For Itch NRS, Skin Pain NRS and Sleep-Loss due to Itch collected via electronic Clinical Outcome Assessment (eCOA), the baseline period is the 7-day window prior to the first injection. A participant must have responses on at least 4 of 7 days to calculate a baseline weekly mean. If a participant has 3 or fewer responses, the baseline mean value will be considered missing. eCOA data for Itch NRS, Skin Pain and Sleep-loss due to Itch are mapped to study visit per [Appendix 10](#) (Section 6.10).

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 Screening Visit (Visit 1) to the date/time of the first injection in Induction Period.

- Treatment-emergent adverse events (TEAEs): baseline will be all results (including medical histories which are ongoing at the date of informed consent) 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.

Demographics and baseline characteristics will be summarized for ITT and adolescent population as described in [Appendix 3](#) (Section 6.3). Medical history and prior medications will be summarized for ITT population as described in [Appendix 4](#) (Section 6.4) and [Appendix 6](#) (Section 6.6).

The randomization to treatment groups is stratified by age (adolescent participants 12 to <18 years versus adults ≥ 18 years), baseline disease severity (IGA 3 versus IGA 4) and country (China versus Korea, for mono cohort only). Unless otherwise specified, the statistical analysis models for Induction Period will adjust for country (mono cohort analysis only), age and baseline disease severity.

For assessment of the co-primary endpoints from combo cohort, the following will be provided:

- Crude proportions for each treatment group along with the 95% 2-sided asymptotic (that is, not continuity corrected) CIs.
- Mean posterior risk difference using Bayesian hierarchical modeling (McGlothlin and Viele 2018) with a mixture prior, as indicated in [Appendix 13](#) (Section 6.13), along with 90% credible intervals.
- Posterior probability that the risk difference is greater than zero.

For all assessments of the primary endpoints and other binary efficacy and health outcomes endpoints, the following will be provided:

- Crude proportions for each treatment group along with the 95% 2-sided asymptotic (that is, not continuity corrected) CIs will be provided.

- The estimated common risk difference along with 95% CIs. The common risk difference is the difference in proportions adjusted for the stratification factors as mentioned above. SAS® PROC FREQ will be used for the estimates and CIs, where the CIs are calculated by using Mantel-Haenszel-Sato method (Sato 1989).
- Cochran-Mantel-Haenszel (CMH) test will be used to compare the treatment groups while adjusting for the stratification factors. The CMH p-value will be reported, and the CMH adjusted odds ratio along with the 95% 2-sided asymptotic (that is, not continuity corrected) CI, both for descriptive purpose.

Treatment comparisons of key continuous efficacy variables and health outcome variables at each postbaseline time point will be made using analysis of covariance (ANCOVA) with the following in the model: treatment group, baseline value, and stratification factors mentioned above. Type III tests for least squares (LS) means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value, and 95% CI, unless otherwise specified, will also be reported.

Treatment comparisons of other continuous efficacy variables and health outcome variables with multiple postbaseline measurements will be made using mixed-model for repeated measures (MMRM). When MMRM is used, the model includes treatment, baseline value, visit, the interaction of the baseline value-by-visit, the interaction of treatment-by-visit, and the stratification factors mentioned in Section 4.1.6 as fixed factors. The covariance structure to model the within-participant errors will be unstructured. If this analysis fails to converge, the heterogeneous autoregressive [ARH(1)], followed by the heterogeneous compound symmetry (CSH), followed by the heterogeneous Toeplitz (TOEPH), followed by the autoregressive [AR(1)], followed by the compound symmetry (CS) will be used. The restricted maximum likelihood (REML) will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the LS means will be used for the statistical comparison; the 95% CI will also be reported.

For variables that are not collected at each postbaseline visit, data may exist at visits where the variable was not scheduled to be collected. In these situations, data from the early discontinuation visit that do not correspond to the planned collection schedule will be excluded from the MMRM analysis. Also, for by-visit summaries/displays such as boxplots, the weeks when data were not scheduled to be collected may not be displayed. However, unscheduled assessments within any defined study period will still be used in the shift analyses, and for imputing values for the change from baseline to last observation carried forward (LOCF) endpoint analyses.

The Kaplan-Meier (KM) product limit method maybe used to estimate the survival for time-to-event analyses. The log-rank test stratified by the stratification factors will be reported when deemed appropriate. A KM plot of the time-to-event by treatment group may be provided.

Treatment compliance will be performed on the safety population for induction period, as described in [Appendix 5](#) (Section 6.5).

4.1.2.General Considerations for Analyses During Maintenance Period

Maintenance Period starts at the first injection of study intervention at Week 16 and ends at Week 52 or the ETV (between Weeks 16 and 52) unless specified otherwise.

For the efficacy and health outcome analyses, baseline is defined as the last available value before the first injection in the Induction Period and, in most cases, will be the value recorded at Baseline Visit (Visit 2, Week 0).

Unless otherwise specified, efficacy and health outcome variables at Week 16 prior to entering the Maintenance Period will be presented for the visit-wise reports for the Maintenance Period.

Unless specified otherwise, for the safety analyses during the Maintenance Period, baseline is defined as the last available value before the first injection in the Maintenance Period. In most cases, this will be the measure recorded at Week 16. For TEAEs, baseline is the events ongoing just prior to the first injection of the study drug injection at Week 16.

For participants in the MPP who meet escape criteria (EASI-50 nonresponse) and escape to lebrikizumab 250 mg Q2W at Weeks 24, 32, 40 and 48, only data in the Maintenance Blinded Period (up to the time of escape) will be included in both efficacy and safety analyses.

4.1.2.1. Maintenance Primary and Secondary Populations

The number and percentage of participants achieving or maintaining categorical efficacy and health outcome responses will be summarized by treatment group for all scheduled visits, including Week 52.

Each continuous efficacy and health outcome measure score and the change from baseline (or percentage improvement) will be summarized by treatment group at all scheduled visits during the Maintenance Period, including Week 52 using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). No inferential statistics will be provided for these populations.

For the MPP, the KM product limit method will be used to estimate the survival for time-to-event analyses (for example, time to loss of IGA score of 0 or 1, or loss of EASI-50). A KM plot of the time-to-event by treatment group may be provided.

For maintenance period secondary population (MSP), no efficacy analysis will be conducted in this population. Only selected safety analyses may be conducted.

Treatment compliance will be summarized for MPP only, as described in [Appendix 5](#) (Section 6.5).

4.1.2.2. Maintenance Escape Population

For the Maintenance Week 16 Escape Population, the number and percentage of participants achieving or maintaining selected categorical efficacy and health outcome responses will be summarized by treatment group for all scheduled visits, including Week 52. Selected continuous secondary efficacy and health outcome measures score and the change from baseline (or percentage improvement) will be summarized by treatment group at all scheduled visits during

the Maintenance Period, including Week 52 using descriptive statistics (n, mean, SD, median, minimum, and maximum). No inferential statistics will be provided for this population.

For the Maintenance W20-52 Escape Population who were treated with lebrikizumab 250 mg Q2W following loss of response (EASI-50 nonresponse), the number and percentage of participants regaining EASI-50 response or achieving EASI-75 will be summarized every 4 weeks after lebrikizumab 250 mg Q2W treatment. No inferential statistics will be provided for this population.

4.1.3.General Considerations for Safety Analyses for Combined Induction and Maintenance Periods

Adverse events, exposure summary, and categorical laboratory/vital signs changes will be provided for the All Lebrikizumab Safety Population during the Combined Induction and Maintenance Periods. For participants who were first exposed to lebrikizumab during the Induction Period, the baseline for TEAEs will utilize the baseline for the Induction Period described in Section 4.1.1. For participants who were first exposed to lebrikizumab during the Maintenance Period, the baseline for TEAEs will utilize the baseline for the Maintenance Period described in Section 4.1.2.

More details on baseline and postbaseline definitions can be found in the Compound-Level Safety Standards.

4.1.4.General Considerations for Safety Analyses for Combined Induction and Maintenance Periods Plus Follow-Up Period

Selective AE summaries will be provided for the All Lebrikizumab Safety Population during the Combined Induction and Maintenance Periods plus Follow-Up Period. The baseline definition for this population is the same as Section 4.1.3. More details on baseline and postbaseline definitions can be found in the Compound Level Safety Standard.

4.1.5.Adjustments for Covariates

Unless otherwise specified, the statistical analysis models for the Induction Period efficacy and health outcome analysis will include the following stratification factors for baseline randomization: age (adolescent participants 12 to <18 versus adults ≥ 18 years), baseline disease severity (IGA 3 versus IGA 4) and country (China versus Korea, mono cohort analysis only).

In general, when an MMRM is to be used for analyses, baseline value and baseline-by-visit interactions will be included as covariates. When an ANCOVA is to be used for analyses, baseline value will be included as a covariate.

4.1.6.Handling of Dropouts or Missing Data

Depending on the estimand being addressed, different methods will be used to handle missing data. Description of the estimands can be found in Section 1.1.

4.1.6.1. Handling of Dropouts or Missing Data for Induction Period

For efficacy analysis relative to the primary estimand, missing data including those as a result of intercurrent events will be imputed based on Markov Chain Monte Carlo Multiple Imputation

(MCMC-MI). The description of the MCMC-MI method can be found in Section 4.1.6.1.1. Tipping point analysis as described in Section 4.1.6.1.2 will serve as the sensitivity analysis for the primary analysis.

For efficacy analysis relative to the supportive estimand for categorical endpoints, missing data including those resulting from intercurrent events will be imputed as nonresponders. The description of nonresponder imputation (NRI) can be found in Section 4.1.6.1.3.

For efficacy analysis relative to the supportive estimand for continuous endpoints collected multiple times postbaseline, an MMRM will be performed without explicit imputation. The description of MMRM can be found in Section 4.1.6.1.4.

For efficacy analysis relative to the supportive estimand for continuous endpoints collected only once postbaseline, missing data including those as a result of intercurrent events will be imputed using Last Observation Carried Forward (LOCF). The description of LOCF can be found in Section 4.1.6.1.5.

Table KGBW.4.1 describes the planned imputation methods for efficacy and health outcome endpoints.

Table KGBW.4.1. Imputation Techniques for Various Variables during Induction Period

Type of Endpoints	Efficacy and Health Outcome Endpoints	Estimand (Analysis Strategy for Intercurrent Events)	Missing Data Imputation Method (Analysis Method)
Categorical	IGA, EASI, and Itch NRS-related categorical endpoints at prespecified timepoints	Primary Estimand (Hybrid)	MCMC-MI (Bayesian, CMH)
		Supportive Estimand (Composite)	NRI (CMH)
	Remaining categorical endpoints	Supportive Estimand (Composite)	NRI (CMH)
Continuous	EASI, Itch NRS, and DLQI-related continuous endpoints	Primary Estimand (Hybrid)	MCMC-MI (ANCOVA)
		Supportive Estimand (Hypothetical)	No imputation (MMRM)
	Remaining continuous endpoints at multiple postbaseline timepoints	Supportive Estimand (Hypothetical)	No imputation (MMRM)
	Remaining continuous endpoints collected only once postbaseline	Supportive Estimand (Hypothetical)	LOCF (ANCOVA)

Abbreviations: ANCOVA = analysis of covariance; CMH = Cochran-Mantel-Haenszel; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment for AD; LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo multiple imputation; MMRM = mixed-effects model for repeated measures; NRI = nonresponder imputation; NRS = numeric rating scale.

4.1.6.1.1. Markov Chain Monte Carlo Multiple Imputation

The primary method of handling missing efficacy data relative to the primary estimand will be as follows for both binary and continuous endpoints:

For participants who receive rescue medication (that is, for combo cohort, high-potency TCS or systemic AD treatment; for mono cohort, any potency TCS or systemic AD treatment, as defined in [Appendix 11](#) [Section 6.11]), or discontinue treatment due to lack of efficacy, set to the participant's baseline value subsequent to this time through Week 16. The MCMC-MI will be used to handle the remaining missing data. Imputation will be conducted within each treatment group independently so the pattern of missing observations in one treatment group cannot influence missing value imputation in another. The SAS PROC MI with MCMC option will be used to conduct the MCMC-MI. The imputation model will include the relevant baseline and postbaseline.

For each imputation process, 25 datasets with imputations will be calculated. The initial seed values are given in [Table KGBW.4.2](#). 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.

CMH test statistic will be transformed using the Wilson-Hilferty transformation and then standardized (Ratitch et al. 2013) prior to combining them using SAS PROC MIANALYZE. Details of combining estimates and test statistics for categorical endpoints with multiple imputation can be found in [Appendix 12](#) (Section 6.12).

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

For derivation of an EASI-75 and EASI-90 response, no rounding will be performed. The imputed Week 16 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.

For derivation of the following Itch NRS responses, no rounding will be performed. The imputed Itch NRS value will be compared directly to the observed mean baseline Itch NRS value to determine whether a response was achieved:

- Percentage of participants with Itch NRS of ≥ 4 -point at Baseline who achieve a ≥ 4 -point reduction from Baseline at Week 16.

Imputation of continuous data will parallel that of binary variable. The imputed values will be used for the following key secondary endpoints:

- Percentage change in EASI score from Baseline to Week 16.

- Percentage change in Itch NRS score from Baseline to Week 16.
- Change from baseline in DLQI score at Week 16.

Table KGBW.4.2. Seed Values for MCMC-MI for Induction Period

Analysis	Seed values
Proportion of participants achieving IGA score of 0 or 1 with a ≥ 2 -point improvement from baseline at Week 16	180345
Change and percentage change from baseline in EASI score at Week 16. EASI-75 and EASI-90 will leverage imputation from EASI score and therefore use the same seed number.	177100
Change and percentage change in Itch NRS from baseline to Week 16. Proportion of participants achieving at least a 4-point improvement from baseline at Weeks 16 will leverage imputation from Itch NRS and therefore use the same seed number.	119549
Change and percentage change from baseline in DLQI score at Week 16.	123456

Abbreviations: DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index score; IGA = Investigator's Global Assessment for AD; MCMC-MI = Markov chain Monte Carlo multiple imputation; NRS = numeric rating scale.

4.1.6.1.2. Tipping Point Analyses

In the combo cohort, the co-primary endpoints of EASI-75 and IGA score of 0 or 1 with ≥ 2 -point improvement from baseline at Week 16 will be assessed using the tipping point analysis. For each of these endpoints, the tipping point analysis will only be conducted if its analyses results cross the prespecified Bayesian criteria.

All participants who use rescue medication or discontinue treatment due to lack of efficacy will be imputed as nonresponders. Assumptions on missing data as a result of treatment discontinuation due to reasons other than lack of efficacy or any other intermittent missing data will be varied to investigate if there will be any tipping points.

For all the categorical endpoints described above that will be assessed using tipping point analysis, the following process will be used to determine the tipping point:

- Missing responses in the lebrikizumab groups will be imputed with a range of response probabilities, including probabilities of 0, 0.2, 0.4, 0.6, 0.8, and 1.0.
- For missing responses in the placebo group, a range of response probabilities (for example, probability = 0, 0.2 ... 1.0) will be used to impute the missing values. Multiple imputed dataset will be generated for each response probability.

Treatment differences between lebrikizumab and placebo are analyzed using Bayesian model specified in [Appendix 13](#) (Section 6.13) for aggregated number of responders.

The tipping point is identified as the response probability value within the placebo group that leads to a loss of success in pre-specified criteria (that is, posterior probability of treatment difference > 0) $> 90\%$) when evaluating lebrikizumab relative to placebo.

For tipping point analyses, the number of imputed data sets will be $m=25$ and the seed values to start the pseudorandom number generator of SAS are given in [Table KGBW.4.3](#).

Table KGBW.4.3. Seed Values for Tipping Point Analysis

Analysis	Seed value
Proportion of participants achieving IGA score of 0 or 1 with a ≥ 2 -point improvement from baseline at Week 16	123470
Proportion of participants achieving EASI-75 at Week 16	123471

Abbreviations: EASI-75 = at least 75% improvement from baseline in Eczema Area and Severity Index score;

IGA = Investigator's Global Assessment.

4.1.6.1.3. Nonresponder Imputation

The NRI method will be used to handle missing data relative to the supportive estimand for categorical endpoints (composite). Participants who receive rescue medication (that is, for combo cohort, high-potency TCS or systemic AD treatment; for mono cohort, any topical or systemic AD treatment defined in [Appendix 11](#) [Section 6.11]) or discontinue treatment, will be set to nonresponse subsequent to this time through Week 16. Intermittent missing values will also be set to nonresponse.

The NRI method imputes missing values as nonresponders and can be justified based on the composite strategy for handling ICEs. In this strategy, participants are defined as responders only if they meet the clinical requirements for response at the predefined time AND they remain on the assigned study treatment (in other words, not using rescue medications and not having missing values due to other reasons). Failing either criteria by definition makes them nonresponders.

Randomized participants without at least 1 postbaseline observation will also be defined as nonresponders for all visits for the NRI analysis.

4.1.6.1.4. Mixed-effects Model for Repeated Measures (MMRM)

MMRM analyses will be performed on continuous endpoints to mitigate the impact of missing data. This approach assumes missing observations are missing-at-random (missingness is related to observed data) and borrows information from participants in the same treatment arm taking into account both the missingness of data through the correlation of the repeated measurements.

The values subsequent to rescue medication use (that is, for combo cohort, high-potency TCS or systemic AD treatment; for mono cohort, any TCS or systemic AD treatment defined in [Appendix 11](#) [Section 6.11]) or treatment discontinuation will be made missing before applying the MMRM model. The MMRM model is described in Section 4.1.1.

4.1.6.1.5. Last Observation Carried Forward (LOCF)

In this analysis, the values subsequent to rescue medication use (that is, for the combo cohort, high-potency TCS or systemic AD treatment; for the mono cohort, any topical or systemic AD treatment defined in [Appendix 11](#) (Section 6.11), or treatment discontinuation will be made missing. All missing values will be imputed using LOCF. Baseline value will be used for imputation if there is no postbaseline observation.

4.1.6.2. Handling of Dropouts or Missing Data for Maintenance Period

For maintenance efficacy analysis relative to the maintenance primary estimand (Hybrid), the method of handling missing data including those as a result of intercurrent events will be MCMC-MI. The description of the maintenance MCMC-MI method can be found in Section 4.1.6.2.1.

For efficacy analysis relative to the maintenance supportive estimand for categorical endpoints (Composite), missing data including those as a result of intercurrent events will be imputed as nonresponder. The description of maintenance NRI can be found in Section 4.1.6.2.2.

For efficacy analysis relative to the maintenance supportive estimand for continuous endpoints (Hypothetical), missing data including those as a result of intercurrent events will be imputed using LOCF. The description of maintenance LOCF can be found in Section 4.1.6.2.3.

Table KGBW.4.4 describes the planned imputation methods for efficacy and health outcome endpoints for the Maintenance Period.

Table KGBW.4.4. Imputation Techniques for Various Variables during Maintenance Period

Type of Endpoints	Efficacy and Health Outcome Endpoints	Estimand (Analysis strategy for Intercurrent Events)	Missing Data Imputation Method (Analysis Method)
Categorical	IGA, EASI, and Itch NRS related categorical endpoints at prespecified timepoints	Maintenance Primary Estimand (Hybrid)	MCMC-MI (Descriptive statistics)
		Maintenance Supportive Estimand (Composite)	NRI (Descriptive statistics)
	Remaining categorical endpoints	Maintenance Supportive Estimand (Composite)	NRI (Descriptive statistics)
Continuous	EASI percentage change, Itch NRS percentage change	Maintenance Primary Estimand (Hybrid)	MCMC-MI (Descriptive statistics)
		Maintenance Supportive Estimand (Hypothetical)	LOCF (Descriptive statistics)
	Remaining continuous endpoints	Maintenance Supportive Estimand (Hypothetical)	LOCF (Descriptive statistics)

Abbreviations: EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment for AD; LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo multiple imputation; NRI = nonresponder imputation; NRS = numeric rating scale.

4.1.6.2.1. Maintenance Period MCMC-MI

The MCMC-MI will be used to handle missing data relative to the maintenance primary estimand (Hybrid) for both binary and continuous endpoints. Imputation will be conducted within each treatment group independently so the pattern of missing observations in one treatment group cannot influence missing value imputation in another. The SAS PROC MI with

MCMC option will be used to conduct the MCMC-MI. The imputation model will include the relevant baseline and postbaseline.

For each imputation process, 25 datasets with imputations will be calculated. The initial seed values are given in [Table KGBW.4.5](#). 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.

The imputation and analysis will be conducted on the MPP only.

The derivation of binary responses related to EASI, IGA and Itch NRS for the maintenance period will follow the derivation for the Induction Period. For the derivation of percentage change from baseline in EASI, the imputed values will be used directly to compare with baseline EASI.

Table KGBW.4.5. Seed Values for MCMC-MI for Maintenance Period

Analysis	Seed values
	Lebrikizumab 250 mg Q4W Lebrikizumab 250 mg Q8W
IGA	12345
EASI	12346
Itch NRS	12347

Abbreviations: EASI = Eczema Area and Severity Index score; IGA = Investigator's Global Assessment for AD; MCMC-MI = Markov chain Monte Carlo multiple imputation; NRS = numeric rating scale; Q2W = every 2 weeks; Q4W = every 4 weeks.

4.1.6.2.2. Maintenance Period NRI

The NRI method will be used to handle missing data relative to the maintenance supportive estimand for categorical endpoints (Composite). Participants who receive rescue medication (that is, high-potency TCS or systemic AD treatment as defined in [Appendix 11](#) [Section 6.11]), discontinue treatment, or transfer to escape arm will be set to nonresponse subsequent to this time through Week 52. Intermittent missing values will also be set to nonresponse.

Participants without at least 1 postbaseline observation will also be defined as nonresponders for all visits for the NRI analysis.

4.1.6.2.3. Maintenance Period LOCF

The LOCF will be used to handle missing data relative to the maintenance supportive estimand for continuous endpoints (Hypothetical). In this analysis, the values subsequent to rescue medication use (that is, high-potency TCS or systemic AD treatment defined in [Appendix 11](#) [Section 6.11]), treatment discontinuation or transfer to escape arm will be made missing. All missing values will be imputed using LOCF. Baseline value will be used for imputation if there is no postbaseline observation.

4.2. Participant Dispositions

The following participant disposition summaries will be provided (details of the analysis populations can be found in [Section 3](#)):

- Total number and percentage of participants entering each analysis population.
- The number and percentage of participants who entered the study, failed screening, were randomized at Baseline Visit (Visit 2, Week 0), completed Week 16, completed Week 52, and completed the safety Follow-Up Visit. Summary will be provided by the initial randomized treatment group (Analysis population: Intent-to-Treat [ITT]).
- The number and percentage of participants who completed the study, and the number and percentage of participants who discontinued the study at any time, by the initial randomized treatment group and primary reason for discontinuation (Analysis population: ITT).
- The number and percentage of participants who completed the Induction Period and the number and percentage of participants who discontinued from the Induction Period, by treatment group and primary reason for discontinuation (Analysis population: ITT).
- The number and percentage of participants who completed the maintenance period and the number and percentage of participants who discontinued from the maintenance period, by treatment group and primary reason for discontinuation (Analysis populations: MPP and MSP), in addition, the number and percentage of participants who entered the escape arm will be summarized for the MPP and the MSP.

All participants who were randomized (that is, in the ITT Population) and discontinued from study treatment during any period from the study will be listed together with the discontinuation reason, and the timing of discontinuation from the study will be reported.

4.3. Primary Endpoints Analysis

4.3.1. Definition of Endpoints

The co-primary endpoints are comprised of 2 separate endpoints:

- the proportion of participants achieving EASI-75 at Week 16 in lebrikizumab 250 mg Q2W versus placebo, and
- the proportion of participants achieving IGA score of 0 or 1 and a reduction of ≥ 2 -points from baseline to Week 16 in lebrikizumab 250 mg Q2W versus placebo.

Descriptions and derivations of these endpoints are shown in [Appendix 1](#) (Section [6.1](#)).

4.3.2. Main Analytical Approach

The primary estimand addresses the treatment response as directed. The analysis assumes that there is no treatment benefit from study interventions for participants who took rescue medication (as defined in [Appendix 11](#) [Section [6.11](#)]) or withdrew from the study due to lack of efficacy, therefore setting to the participant's baseline value subsequent to this time through Week 16. Other missing values will be imputed using MCMC-MI based on missing at random assumption (Section [4.1.6.1.1](#)).

For combo cohort, a Bayesian decision criterion will be used to assess the treatment effect by determining whether the CCI [REDACTED] for both co-primary endpoints (EASI-75 and IGA0/1 with 2-point reduction at Week 16). A Bayesian hierarchical model with a robust mixture prior will be used to dynamically borrow historical information on the log-odds scale from historical studies (Simpson et al. 2023; Katoh et al. 2025). Details pertaining to the structure of the Bayesian hierarchical model are described in [Appendix 13](#) (Section 6.13).

CCI [REDACTED]
[REDACTED]
[REDACTED]

Common risk difference will be estimated adjusted by randomization strata (disease severity: IGA 3 vs. 4, age: adolescent participants ≥ 12 to < 18 years vs. ≥ 18 years, and country: China vs. Korea [mono cohort only]) along with corresponding 95% CIs.

The analyses for co-primary outcomes of EASI-75 and IGA score of 0 or 1 are described in [Appendix 2](#) (Section 6.2).

4.3.3. Sensitivity Analyses

Sensitivity analyses are included to demonstrate robustness of analyses methods using different missing data imputations, analyses assumptions, and prior choices. Sensitivity analyses for the co-primary endpoints will be conducted using

- the tipping point analysis based on missing not at random assumption (Section 4.1.6.1.2),
- Bayesian analysis as described in [Appendix 13](#) (Section 6.13) with supportive estimand (composite strategy), and
- Bayesian analysis with different prior choice.

All sensitivity analysis are described in [Appendix 2](#) (Section 6.2).

4.3.4. Supplementary Analyses

Supplementary analyses of the co-primary endpoints will be conducted using the supportive estimand (Section 1.1).

4.4. Secondary Endpoints Analysis

4.4.1. Major Secondary Endpoints

4.4.1.1. Definition of Endpoint(s)

Major secondary endpoints are listed in Section 1.1 under Major Secondary.

Descriptions and derivations of these endpoints are shown in [Appendix 1](#) (Section 6.1).

Refer to Section 4.3.1.

4.4.1.2. Main Analytical Approach

The analyses for the major secondary outcomes are described in [Appendix 2](#) (Section 6.2).

4.4.1.3. Supplementary Analyses

Supplementary analyses for the major secondary endpoints will be conducted using supportive estimand, as described in [Appendix 2](#) (Section 6.2).

4.4.2. Supportive Secondary Endpoints

Other secondary endpoints are listed in Section 1.1 under Other Secondary.

Descriptions and derivations of these endpoints are shown in [Appendix 1](#) (Section 6.1).

The analyses for the other secondary endpoints are described in [Appendix 2](#) (Section 6.2).

4.5. Tertiary/Exploratory Endpoints Analysis

Not applicable.

4.6. 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 Clinical Data Interchange Standards Consortium (CDISC) standards, regulatory guidance (for example, FDA Clinical Review Template), and cross-industry standardization efforts (for example, Pharmaceutical Users Software Exchange [PhUSE] white papers from the Standard Analyses and Code Sharing Working Group provided in the PhUSE Computational Science Deliverables Catalog).

Safety evaluations will be based upon the following safety analysis populations with their associated study periods, unless specified otherwise:

- Safety Population (Induction Period)
- MPP (Maintenance Blinded Period), and
- all Lebrikizumab Safety Population (Combined Induction and maintenance periods, and Combined Induction and maintenance periods plus Follow-Up Period [selective analyses]).

These analysis populations, treatment groups, associated study periods, and the comparisons for each analysis population are fully defined in Section 3.

4.6.1. Extent of Exposure

Duration of exposure to study intervention will be summarized by treatment group. Drug interruption time period due to the use of systemic rescue therapies will not be removed from study drug exposure calculations as described in compound level safety standards.

The duration of exposure will be calculated as:

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

Note that date of last visit in the Induction Period will be defined as the first visit date in the Maintenance Period – 1.

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

- >0, ≥7, ≥14, ≥30, ≥60, ≥90, ≥112, ≥120 days for the Induction Period (for the Maintenance Period, use >0, ≥30, ≥60, ≥90, ≥120, ≥150, ≥180, ≥210, ≥240, ≥252 for the Combined Induction and Maintenance Periods, use >0, ≥7, ≥14, ≥30, ≥60, ≥90, ≥112, ≥120, ≥150, ≥183, ≥210, ≥273, ≥365 days). Note that participants may be included in more than 1 category.
- >0 to <7, ≥7 to <14, ≥14 to <30, ≥30 to <60, ≥60 to <90, ≥90 to <112, ≥112 to <120, ≥120 days (for the Maintenance Period, use >0 to <30, ≥30 to <60, ≥60 to <90, ≥90 to <120, ≥120 to <150, ≥150 to <180, ≥180 to <210, ≥210 to <240, ≥240 to <252 and ≥252 days, for the Combined Induction and Maintenance Periods, use >0 to <7, ≥7 to <14, ≥14 to <30, ≥30 to <60, ≥60 to <90, ≥90 to <112, ≥112 to <120, ≥120 to <150, ≥150 to <183, ≥183 to <210, ≥210 to <273, ≥273 to <365 and ≥365 days).

Additional exposure ranges may be considered if necessary. No p-values will be reported.

The summaries will also include the following information:

- Total exposure in participant years, calculated as:

Total exposure in participant years =

$$\frac{\text{Sum of duration of exposures for all participants in treatment group}}{365.25}$$

- Mean and median total dose: Total dose (in mg) is calculated by the number of active injections taken during the treatment period multiplied by dose. For participants in the Safety Population who were randomized to lebrikizumab 250 mg Q2W, or participants in the MPP who received lebrikizumab 250 mg Q4W or Q8W, the total dose (in mg) taken during the Induction Period or the Maintenance Period will be calculated as follows: Total lebrikizumab dose=Total number of active injections (including loading doses, if any) received in the Induction Period or the Maintenance Period ×250.
- Total number of injections received will be derived based on the response to the question “Was dose administered?” on the Exposure as Collected electronic case report form (eCRF) page.

The exposure for the All Lebrikizumab Safety Population during the Combined Induction and Maintenance Periods will be calculated as (Date of last study visit during Treatment Period – Date of first lebrikizumab injection +1 day) calculated for each treatment period where the participant receives lebrikizumab and then summed together (this excludes the duration of time that participants are receiving placebo during the Maintenance Period).

The exposure for the All Lebrikizumab Safety Population during the Combined Induction and Maintenance Periods plus Follow-Up Period will be calculated as the time between the first dose of lebrikizumab and the study treatment disposition visit plus any follow-up period.

4.6.2. Adverse Events

A TEAE is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period defined in Section 4.1.1 for the Induction Period and Section 4.1.2 for the Maintenance Period will be used as baseline. The Treatment Period will be used as the postbaseline period for the analysis. For events with a missing severity during the baseline period, it 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, it will be compared to the first injection time. If the start time of AE is missing, it will be assumed to be posttreatment.

The planned summaries for adverse events are provided in [Table KGBW.4.6](#), and are described more fully in compound level safety standards and in the adverse event-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 KGBW.4.6](#) will be presented for the following periods/analysis populations as indicated. Summary tables will include the number and percentage of participants reporting an event. For events that are gender-specific (as defined by MedDRA), the number of participants at risk will include only participants from the given gender.

- Induction Period (Safety Population, S)
- Maintenance Blinded Period (Maintenance Primary Population, M), and
- Combined Induction and Maintenance Periods, Combined Induction and Maintenance Periods Plus Follow-Up Period (selective analyses) (All Lebrikizumab Safety Population, A).

Table KGBW.4.6. Summary Tables and Listings Related to Adverse Events

Analysis	Population
Overview of AEs	S, MPP, MSP, A
Summary of TEAE by PTs	S, MPP
Summary of TEAE by PTs occurring in $\geq 1\%$ of participants	S, MPP
Summary of TEAE by PTs within SOC	S, MPP, A
Summary of TEAE PTs by maximum severity	S, MPP
Summary of SAE by PTs within SOC	S, MPP, A
Summary of AEs leading to treatment discontinuation by PTs within SOC	S, MPP, A
Summary of TEAE possibly related to study drug by PTs within SOC	S, MPP
Listing of SAEs (including Death)	ITT
Listing of primary AEs leading to study treatment discontinuation	ITT
Listing of AE (including AEs in the Maintenance Period and the Follow-Up Period)	S

Abbreviations: A = All Lebrikizumab Safety Population; AE = adverse event; ITT = intent-to-treat;

MPP = Maintenance Primary Population; MSP = Maintenance Period Secondary Population;

PT = preferred term; SAE = serious adverse event; S = Safety Population; SOC = System Organ Class;

TEAE = treatment-emergent adverse event.

Statistical comparisons will be performed for Safety Population using Fisher's exact test. OR will be provided.

4.6.2.1. Common Adverse Events

The number and percentages of participants with TEAEs will be summarized by treatment using MedDRA preferred terms (PTs) for the common TEAEs (occurred in $\geq 1\%$ before rounding in total lebrikizumab column in the table).

4.6.2.2. Deaths, Other Serious Adverse Events, and other Notable Adverse Events

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

4.6.3. Device Product Complaints

A listing of all product complaints by subcategory, inclusive of device product complaints that led to an AE or could have led to an SAE had intervention not been taken may be included. Additional summaries may be provided as deemed appropriate.

4.6.4. Additional Safety Assessments

4.6.4.1. 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 the table below.

Table KGBW.4.7. Analysis for Clinical Laboratory Evaluations

Analysis	Population
Box plots of observed values by visit. Box plots for change values by visit.	S, MPP, A
Change from baseline to last observations. ANCOVA model with treatment and baseline value in the model.	S, MPP
Scatter plots of baseline-by-maximum values and baseline-by-minimum values.	S, MPP
Treatment-emergent abnormal high lab values (that is, participants shifting from a normal/low maximum baseline value to a high maximum postbaseline value) or abnormal low lab values (that is, participants shifting from normal/high minimum baseline value to a low minimum postbaseline value).	S, MPP, A
Shift tables showing the number of participants who shift from each category of maximum (minimum) baseline observation to each category of maximum (minimum) postbaseline observation. Categories may be low, normal, or high with cut-offs defined in the compound level safety standards.	S, MPP
Listing of abnormal findings for laboratory analyte measurements, including qualitative measures.	S

Abbreviations: A = All Lebrikizumab Safety Population; ANCOVA = analysis of covariance; MPP = Maintenance Primary Population; S = Safety Population.

4.6.4.2. 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 as described in the table below. For vital signs, treatment-emergent low and high are based on a combination of a specified value and a change or percentage change for adults and adolescents as defined in the compound level safety standards.

Table KGBW.4.8. Analysis Related to Vital Signs

Analysis	Population
Box plots for observed values by visit.	S, MPP, A
Box plots for change from baseline values by visit.	S, MPP, A
Scatterplots of baseline-by-maximum values and baseline-by-minimum values.	S, MPP
Tables with the number and percentage of participants who shift from normal/high to low (that is, treatment-emergent low) and the number and percentage of participants who shift from normal/low to high (that is, treatment-emergent high). The limits are defined in the compound level safety standards.	S, MPP, A

Abbreviations: A = All Lebrikizumab Safety Population; MPP = Maintenance Primary Population; S = Safety Population.

4.6.4.2.1. Adolescent Standardized Growth

Z-score, and standardized percentile of weight, height, and BMI (body mass index) at each visit will be calculated. Because of the short duration of controlled period and the small number of adolescent participants, only All Lebrikizumab Safety Population will be described during the Combined Induction and Maintenance Periods.

The z-score and percentile calculations are based on algorithms and data provided by the National Center for Health Statistics. The details are provided in the Centers for Disease Control and Prevention (CDC) website ([WWW]).

The following summaries and plots will be provided:

Table KGBW.4.9. Analysis Related to Adolescent Standardized Growth

Analysis	Population
Summaries for baseline, mean change of actual measure, z-score and standardized percentile of weight, height, and BMI.	A
Scatter plot of participants' mean weight, height, and BMI standardized percentile versus lebrikizumab exposure time.	A

Abbreviations: A = All Lebrikizumab Safety Population; BMI = body mass index.

4.6.4.3. Immunogenicity

An individual sample is potentially examined multiple times in a hierarchical procedure to produce a sample anti-drug antibody (ADA) assay result and may yield a sample neutralizing ADA (NAb) assay result. Treatment-emergent ADA (TE ADA) are defined as those with a titer ≥ 2 -fold (1 dilution) greater than the minimum required dilution if no ADA were detected at baseline (treatment-induced ADA) or those with a ≥ 4 -fold (2 dilutions) increase in titer compared to baseline if ADA were detected at baseline (treatment-boosted ADA). A participant

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 for the Safety Population. The summary of TE ADA and NAb status will be produced for the 3 populations (that is, Safety Population for the Induction Period, MPP for the combined Induction and Maintenance Periods, and All Lebrizumab Safety Population for the combined Induction and Maintenance Periods plus Follow-Up Period), where the postbaseline period for reporting is the same as described for AEs in Section 4.1. Additional assessments of the relationship between immunogenicity and efficacy/safety may be performed in this study.

4.6.4.4. 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 adverse events of special interest (AESI) relevant to these special safety topics will be identified by 1 or more Standardized MedDRA Query(ies) (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 special safety topics will be summarized for the Safety Population and All Lebrizumab Safety Population during their associated study periods as described in Section 4.1.3.

Full details of the search terms and rules for deriving special safety topics 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.

4.6.4.4.1. Hepatic Safety

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

Table KGBW.4.10. Tables Related to Hepatic Safety

Analysis	Population
ALT and AST: The number and percentage of participants with a measurement greater than or equal to 3 times (3X), 5 times (5X), and 10 times (10X) the performing lab upper limit of normal (ULN) during the treatment period for all participants with a postbaseline value and for subsets based on various levels of baseline value. TBL and ALP: The number and percentage of participants with a measurement greater than or equal to 2 times (2X) the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value and for subsets based on various levels of baseline value.	S, A

Analysis	Population
Plot of maximum postbaseline ALT vs. maximum postbaseline total bilirubin.	Safety Population for All Periods: ever on lebri and never on lebri

Abbreviations: A = All Lebrikizumab Safety Population; ALP = serum alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate transaminase; lebri = lebrikizumab; S = Safety Population; TBL = total bilirubin.

4.6.4.4.2. *Eosinophilia and Eosinophil-Related Disorders*

In addition to the standard laboratory analysis (Section 4.6.4.1), eosinophilia and eosinophil-related AE will be summarized. Details regarding eosinophil-related PTs are in Compound Level Safety Standard.

Table KGBW.4.11. Tables Related to Eosinophilia and Eosinophil-Related AE

Analysis	Population
Shift table summarizing the number and percentage of participants within each maximum baseline category versus each maximum postbaseline category by treatment.	S, A
Summary of eosinophil-related TEAE by PT.	S, A

Abbreviations: A = All Lebrikizumab Safety Population; AE = adverse event; PT = preferred term; S = Safety Population; TEAE = treatment-emergent adverse event.

4.6.4.4.3. *Infections, Including Herpes Infections, and Relevant Parasitic Infections*

Infections will be defined using the PTs from the MedDRA Infections and Infestations System Organ Class (SOC). The MedDRA terms used to identify infections considered to be opportunistic infections (OI) in participants 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 KGBW.4.12. Summary Tables and Listings Related to Infection-Related AE

Analysis	Population
Summary of treatment-emergent infections by maximum severity	S, A
Summary of serious infections by PT	S, A
Summary of infection AEs resulting in permanent study drug discontinuation by PT	S, A
Summary of treatment-emergent potential OI by PT nested with categories for narrow terms and broad terms separately.	S, MPP, A
Summary of treatment-emergent adverse events – herpes and parasitic infections	S, MPP, A
Summary of treatment-emergent adverse events – skin infections by maximum severity	S, A
Summary and/or listing of infection follow-up form	S
A listing of participants with potential OI, serious infection, herpes and parasitic infections (including events in the Maintenance Period and the Follow-Up Period)	S

Abbreviations: A = All Lebrikizumab Safety Population; AE = adverse event; MPP = Maintenance Primary Population; OI = opportunistic infections; PT = preferred term; S = Safety Population; TEAE = treatment-emergent adverse event.

4.6.4.4.4. Conjunctivitis

Conjunctivitis are events of special interest and will be identified using PTs in the cluster definitions outlined in the Compound Level Safety Standards.

Table KGBW.4.13. Summary Tables and Listings Related to Conjunctivitis

Analysis	Population
Summary of TEAE of conjunctivitis cluster and keratitis cluster by maximum severity	S, MPP, A
Summary and/or listing of conjunctivitis and eye inflammation follow-up form	S
A listing of participants with conjunctivitis cluster events (including events in the Maintenance Period and the Follow-Up Period).	S

Abbreviations: A = All Lebrikizumab Safety Population; MPP = Maintenance Primary Population;

S = Safety Population; TEAE = treatment-emergent adverse event.

4.6.4.4.5. Hypersensitivity

Potential hypersensitivity reactions will be determined using the following SMQs: anaphylactic reaction, hypersensitivity, and angioedema. Potential hypersensitivity will be categorized as immediate (that is, occurring the same day as drug administration) and non-immediate (that is, occurring after the day of study drug administration but prior to subsequent drug administration).

Table KGBW.4.14. Summary Tables and Listings Related to Hypersensitivity

Analysis	Population
For immediate hypersensitivity: (1) combined narrow/algorithmic search (that is, any narrow term from any one of the SMQs, or anaphylaxis algorithm); (2) narrow search (that is, any narrow term) by SMQ; (3) broad search (that is, any narrow or broad term) by SMQ; and (4) TEAEs (occurring on the day of study drug administration) by PT not in any of the 3 SMQs	S, A
For nonimmediate hypersensitivity: (1) combined narrow search (that is, any narrow term from any one of the SMQs); (2) narrow search (that is, any narrow term) by SMQ; and (3) broad search (that is, any narrow or broad term) by SMQ	S, A

Abbreviations: A = All Lebrikizumab Safety Population; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; S = Safety Population; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse events.

4.6.4.4.6. *Injection Site Reactions*

Injection site reactions (ISRs) 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 Injection Site Reaction, excluding certain PTs related to joints as described in the Compound Level Safety Standards.

Table KGBW.4.15. Tables Related to Injection Site Reactions

Analysis	Population
Summary of TEAE of ISR overall, and by PT	S, MPP, A

Abbreviations: A = All Lebrikizumab Safety Population; ISR = injection site reaction; MPP = Maintenance Primary Population; PT = preferred term; S = Safety Population; TEAE = treatment-emergent adverse event.

4.6.4.4.7. *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 as below.

Table KGBW.4.16. Summary Tables Related to Malignancies

Analysis	Population
Summary of TEAE of malignancies within categories of NMSC and malignancy excluding NMSC	S, A

Abbreviations: A = All Lebrikizumab Safety Population; NMSC = non-melanoma skin cancer; TEAE = treatment-emergent adverse event; S = Safety Population.

4.6.4.4.8. *Atopic Dermatitis Exacerbation*

AD exacerbation will be defined using PTs specified in the Compound Level Safety Standards and summarized below.

Table KGBW.4.17. Summary Tables Related to Atopic Dermatitis Exacerbation

Analysis	Population
Summary of TEAE of atopic dermatitis exacerbation	S, A

Abbreviations: A = All Lebrikizumab Safety Population; S = Safety Population; TEAE = treatment-emergent adverse event.

4.6.4.4.9. Suicide/Self-Injury

Suicide/self-injury will be defined as described in the Compound Level Safety Standards and summarized below.

Table KGBW.4.18. Summary Tables Related to Suicide/Self-Injury Standardized Medical Dictionary for Regulatory Activities Query

Analysis	Population
Summary of TEAE of Suicide/self-injury SMQ	S, A

Abbreviations: A = All Lebrikizumab Safety Population; MedDRA = Medical Dictionary for Regulatory Activities; S = Safety Population; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.

4.7. Other Analyses

4.7.1. Other Variables and/or Parameters

Additional analyses may be performed to analyze the biomarkers specified in protocol addendum.

4.7.2. Subgroup Analyses

Subgroup analyses will be conducted for the co-primary and major secondary endpoints of IGA score of 0 or 1, EASI-75, EASI-90 and 4-point improvement in Itch NRS at Week 16 in the ITT Population using MCMC-MI approach as in the primary analysis (Section 4.1.6.1.1). A logistic regression analysis with treatment, subgroup, and treatment-by-subgroup interaction as factors will be used. The treatment-by-subgroup interaction will be tested using the Firth correction (Firth 1993) for combo cohort. Treatment group differences will be evaluated within each subgroup using the chi-square test, regardless of whether the interaction is statistically significant. If any group within the subgroup (for example, yes, no) is <10% of the total population, only descriptive statistics will be provided for that subgroup (that is, no inferential testing).

Forest plots may be created to illustrate the treatment differences with 95% CIs between each of the lebrikizumab treatment groups and placebo group, by each subgroup category.

The following subgroups will be analyzed:

- Age group (Adolescents (12<18), Adults ≥18)
- Age group (Adolescents (12<18), Adults ≥18 to < 65, ≥65 to <75, ≥75)
- Sex (male, female)
- Country (China, Korea, [mono cohort only])
- Weight category (<60 kg, ≥60 to <100 kg, ≥100 kg)

- BMI category (Underweight [$<18 \text{ kg/m}^2$], Normal [≥ 18.5 and $<25 \text{ kg/m}^2$], Overweight [≥ 25 and $<30 \text{ kg/m}^2$], Obese [≥ 30 and $<40 \text{ kg/m}^2$], Extreme obese [$\geq 40 \text{ kg/m}^2$])
- Duration since AD onset category (0 to <2 years, 2 to <5 years, 5 to <10 years, 10 to <20 years, ≥ 20 years)
- Baseline IGA (3 versus 4)
- Baseline EASI (≥ 16 to ≤ 21 , >21 to ≤ 50 , >50 to ≤ 72)
- Baseline Itch NRS (<4 versus ≥ 4), and
- Prior use of systemic treatment (yes, no).

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

4.8. Interim Analyses

All analysis occurred at database lock (DBL) before studying close out is defined as Interim analysis in this section.

Primary outcome DBL: The first DBL and unblinding will occur, and the interim analysis will be performed after the last participant completes Week 16 (or ET visit) or a cut-off date determined by study team, whichever is later. This DBL will include all data collected by the cut-off date. Both Induction period and maintenance period treatment assignment will be unblinded at the time of this interim lock for submission purpose. For efficacy analysis at primary outcome DBL, only patients completed or discontinued at each visit will be included in the maintenance period efficacy analysis. Patients who do not have the chance to complete maintenance visits will not be included in the patients analyzed at such visits.

The study will not be terminated early based on efficacy following this interim analysis. The sponsor or designee could unblind a small team to prepare for regulatory interactions, safety updates, and disclosures if needed, while the investigator, study-site personnel, and Lilly study members who are site facing and the participants will be blinded to treatment assignment until the final DBL.

In the first DBL, a tiered DBL approach will be employed. Two tiers of raw data transfers will be performed for this tiered DBL. The first-tier raw data transfer includes all data except for some laboratory data (for example, PK, and immunogenicity data) while only the remaining laboratory data will be added to the database in the second-tier raw data transfer. All the planned efficacy and safety analyses will be conducted after the first-tier raw data transfer to start preparation of the relevant sections of regulatory submission documents in China earlier than the remaining laboratory-related sections of the documents which will be started after the second-tier raw data transfer. The detailed plan of the tiered DBL is described in the Data Management Plan. Mitigation plan of perceived bias and validation/verification activities for the tiered DBL are described in the Blinding and Unblinding Plan (BUP).

Week 52 DBL: The second DBL will occur, and the interim analysis, including the Maintenance Period, will be performed at the time the last participant completes Week 52 or the ET visit (that is, a cut-off date). This DBL will include all data collected by the cut-off date.

Final DBL: The final DBL will then be conducted after all participants have completed the Follow-Up Period.

Depending on the regulatory submission timeline, the second DBL and the final DBL may be combined, (that is, 1 final DBL will occur after all participants have either completed the Follow-Up Period or discontinued the study early).

Details for the blinding and unblinding procedure is described in KGBW blinding and unblinding plan. Personnel who will be unblinded at primary outcome DBL will be specified in blinding and unblinding of key study team personnel.

4.8.1.Data Monitoring Committee

An independent DMC composed of members who are independent of the study sponsor and study investigators will monitor participant safety by conducting formal reviews of accumulated unblinded safety data.

The DMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the participants enrolled in the study. The DMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the DMC are described in the DMC charter.

4.9. Changes to Protocol-Planned Analyses

Deleted number of skin pain-free days in other secondary endpoints.

5. Sample Size Determination

The study plan is to enroll approximately 280 participants in total, with 150 participants in combo cohort and 130 (90 Chinese and 40 Korean) participants in mono cohort.

Combo Cohort:

Approximately 150 Chinese participants (including approximately 35 adolescents) will be randomized at a 2:1 ratio to lebrikizumab Q2W and placebo (100 participants: 50 participants).

According to operation characteristics via simulation, 150 participants could provide:

- probability of study success (that is, achieving Bayesian decision criterion) is greater than 90% if true assumption of the co-primary endpoint EASI-75 response rates at Week 16 are 63% for lebrikizumab Q2W and 30% for placebo, co-primary endpoint IGA score 0 or 1 response rates at Week 16 are 34% for lebrikizumab Q2W and 16% for placebo, based on historical lebrikizumab phase 3 study results (Simpson et al. 2023), and
- a false-positive rate of 5%, assuming lebrikizumab EASI-75 and IGA score 0 or 1, response is placebo-like, at 30% and 16% respectively, with a 0.4 correlation between EASI-75 and IGA score 0 or 1 response.

The probabilities above are evaluated based on Bayesian decision criterion: posterior probability of risk difference between lebrikizumab and placebo is greater than 0 is greater than 90%, that is, $\Pr(\text{lebrikizumab-placebo} > 0) > 90\%$ for both co-primary endpoints. Details of this method is provided in [Appendix 13](#) (Section 6.13).

Mono Cohort: Approximately 130 (90 Chinese and 40 Korean) participants in mono cohort, including approximately 23 adolescents (15 Chinese and 8 Korean), will be randomized at 2:1 ratio to lebrikizumab Q2W and placebo (87 participants: 43 participants). The sample size calculation in mono cohort is aimed to show 50% effect size of global studies (Studies KGAB and KGAC) with >95% probability for the co-primary endpoint EASI-75 (that is, >95% chance to observe a treatment difference in EASI-75 response to be greater than 18.8%, assuming true response rates of EASI-75 at Week 16 between lebrikizumab Q2W and placebo are 55.6% and 18.0%) and IGA score of 0 or 1 with 2-point reduction (that is, >95% chance to observe a treatment difference in IGA score 0 or 1 with 2-point to be greater than 13%, assuming the true response rates between lebrikizumab Q2W and placebo are 38.8% and 13%).

6. Supporting Documentation

6.1. Appendix 1: Description and Derivation of Efficacy and Health Outcome Endpoints

The description and derivation rule of efficacy and health outcomes measures are described in [Table KGBW.6.1](#).

Table KGBW.6.1. Description and Derivation of Efficacy/Health Outcome Measures and Endpoints

Measure	Description	Variable	Derivation/Comment	Missing rule
Investigator's Global Assessment (IGA)	The IGA is a static assessment and rates the severity of the participant'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.
		Change from baseline in IGA score	Change from baseline: observed IGA score – baseline IGA score	Missing if baseline or observed value is missing.
		IGA (0,1) with ≥ 2 -point improvement	Observed score of 0 or 1 and change from baseline ≤ -2	Missing if baseline or observed value is missing.
		IGA (0)	Observed score of 0	Single item, missing if missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
		Time to loss of IGA response, that is, developing an IGA score ≥ 2 with 2 points deterioration of achieved IGA response at Week 16	Date of first time developing an IGA score ≥ 2 with 2 points deterioration of achieved IGA response at Week 16 – date of Week 16 + 1	If a participant has not experienced loss of response by completion or early discontinuation of the Maintenance Blinded Period, the participant will be censored at the date of their last visit during the Maintenance Blinded Period. If a participant has not experienced loss of response by the time of systemic rescue, the participant will be censored at the date of systemic rescue.

Measure	Description	Variable	Derivation/Comment	Missing rule
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 <u>extent</u> 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 <u>severity</u> 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 <u>4 body</u> 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 head and neck, trunk, upper limbs, and lower limbs as follows: $\text{EASI}_{\text{region}} = r * (\text{erythema} + \text{edema/papulation} + \text{excoriation} + \text{lichenification}) * (\text{value from percentage involvement})$ 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, $r = 0.1$ for head and neck, $r = 0.2$ for upper limbs, $r = 0.3$ for trunk, and $r = 0.4$ for lower limbs. Then, total EASI score is as follows: $\text{EASI} = \text{EASI}_{\text{head and neck}} + \text{EASI}_{\text{trunk}} + \text{EASI}_{\text{upper limbs}} + \text{EASI}_{\text{lower limbs}}$	N/A – partial assessments cannot be saved.
		Change from baseline in EASI ($\text{EASI}_{\text{region}}$) score	Change from baseline: observed EASI ($\text{EASI}_{\text{region}}$) score – baseline EASI ($\text{EASI}_{\text{region}}$) score % change from baseline: $100 \times \frac{\text{Observed score} - \text{Baseline}}{\text{Baseline}}$	Missing if baseline or observed value is missing.
		Percentage change from baseline EASI score		
		Each symptom score and percentage involvement score by body regions in EASI.	The following scores by body regions (that is, head and neck, trunk, upper limbs, and lower limbs): Erythema score Edema/papulation score Excoriation score Lichenification score Percentage involvement score	Missing if missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
		Change from baseline in each symptom score and percentage involvement score by body regions in EASI.	Change from baseline: observed score – baseline score	Missing if baseline or observed value is missing.
		EASI-50	% Improvement in EASI score from baseline $\geq 50\%$: % change from baseline ≤ -50	Missing if baseline or observed value is missing.
		EASI-75	% Improvement in EASI score from baseline $\geq 75\%$: % change from baseline ≤ -75	Missing if baseline or observed value is missing.
		EASI-90	% Improvement in EASI score from baseline $\geq 90\%$: % change from baseline ≤ -90	Missing if baseline or observed value is missing.
		Time to loss of EASI-50	Date of first time % change from baseline in EASI score > -50 – date of Week 16 + 1	If a participant has not experienced loss of response by completion or early discontinuation of the Maintenance Blinded Period, the participant will be censored at the date of their last visit during the Maintenance Blinded Period.

Measure	Description	Variable	Derivation/Comment	Missing rule
				If a participant has not experienced loss of response by the time of systemic rescue, the participant will be censored at the date of systemic rescue.
		Time to loss of EASI-75	Date of first time % change from baseline in EASI score > -75 – date of Week 16 + 1	If a participant has not experienced loss of response by completion or early discontinuation of the Maintenance Blinded Period, the participant will be censored at the date of their last visit during the Maintenance Blinded Period. If a participant has not experienced loss of response by the time of systemic rescue, the participant will be censored at the date of systemic rescue.

Measure	Description	Variable	Derivation/Comment	Missing rule
Body Surface Area (BSA)	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 participant palm = 1% rule.	BSA	BSA Total = BSAhead and neck + BSAtunk +BSAext + BSAlower ext	N/A – partial assessments cannot be saved.
		Change from baseline in BSA	Change from baseline: observed BSA score – baseline BSA score.	Missing if baseline or observed value is missing.
SCORing Atopic Dermatitis (SCORAD)	SCORAD is a validated clinical tool for assessing the extent and intensity of atopic dermatitis. There are 3 components to the assessment: The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 102% (assigned as “A” in the overall SCORAD calculation). The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as “B” in the overall SCORAD calculation).	SCORAD	SCORAD = A/5 + 7B/2 + C, where A is extent of disease, range 0-102 B is disease severity, range 0-18 C is subjective symptoms, range 0-20	Missing if components A and B are missing or if component C is missing. Partial assessments performed by physician cannot be saved and partial assessments performed by participant cannot be saved.
		Change from baseline in SCORAD. Percentage change from baseline in SCORAD	Change from baseline: observed SCORAD score – baseline SCORAD score % change from baseline: $100 \times \frac{\text{Observed score} - \text{Baseline}}{\text{Baseline}}$	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
	Subjective assessment of itch and of sleeplessness is recorded for each symptom by the participant or relative on a VAS, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20 (assigned as “C” in the overall SCORAD calculation).	SCORAD75	% Improvement in SCORAD from baseline $\geq 75\%$: % change from baseline ≤ -75	Missing if baseline or observed value is missing.
		SCORAD90	% Improvement in SCORAD from baseline $\geq 90\%$: % change from baseline ≤ -90	Missing if baseline or observed value is missing.
Itch Numeric Rating Scale (NRS)	The Itch NRS is a an 11-point scale used by participants to rate their worst itch severity over the past 24 hours with 0 indicating “No itch” and 10 indicating “Worst itch imaginable.” Assessments will be recorded daily by the participant using an electronic diary.	Itch NRS prorated weekly mean score	The prorated weekly mean is based on previous 7 days. If a participant 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. eCOA data are mapped to study visit per Appendix 10 (Section 6.10).	Weekly mean score missing if the participant has no Itch NRS responses within the week.
		Change from baseline in Itch NRS pro-rated weekly mean score. Percentage change from baseline in Itch NRS prorated weekly mean score.	Change from baseline: observed Itch NRS prorated weekly mean score – baseline Itch NRS weekly mean score % change from baseline: $100 \times \frac{\text{Observed score} - \text{Baseline}}{\text{Baseline}}$	Missing if baseline or observed value is missing.
		4-point Itch improvement in Itch NRS prorated weekly mean score	Change from baseline ≤ -4 in Itch NRS prorated weekly mean score	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
Skin Pain Numeric Rating Scale (NRS)	Skin Pain NRS is a participant-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing “no pain” and 10 representing “worst pain imaginable.” Overall severity of a participant’s skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours.	Skin Pain NRS prorated weekly mean score	The prorated weekly mean is based on previous 7 days. If a participant 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. eCOA data are mapped to study visit per Appendix 10 (Section 6.10)	Weekly mean score missing if the participant has no Skin Pain NRS responses within the week.
		Change from baseline in Skin Pain NRS prorated weekly mean score	Change from baseline: observed Skin Pain NRS prorated weekly mean score – baseline Skin Pain NRS weekly mean score % change from baseline:	Missing if baseline or observed value is missing.
		Percentage change from baseline in Skin Pain NRS prorated weekly mean score	$100 \times \frac{\text{Observed score} - \text{Baseline}}{\text{Baseline}}$	
		4-point Skin Pain NRS improvement in Skin Pain NRS prorated weekly mean score	Change from baseline ≤ -4 in Skin Pain NRS prorated weekly mean score.	Missing if baseline or observed value is missing.
Sleep-loss due to itch	Sleep-loss due to itch will be assessed by the participant. Participants 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 participant using an electronic diary.	Sleep-loss prorated weekly mean score	The prorated weekly mean is based on previous 7 days. If a participant has at least one daily score within the week, the weekly mean is the prorated average of daily scores within the given week. Single item; range 0 to 4. eCOA data are mapped to study visit per Appendix 10 (Section 6.10).	Weekly mean score missing if the participant has no Sleep-loss responses within the week.

Measure	Description	Variable	Derivation/Comment	Missing rule
		Change from baseline in Sleep-loss prorated weekly mean score	Change from baseline: observed Sleep-loss prorated weekly mean score – baseline Sleep-loss weekly mean score	Missing if baseline or observed value is missing.
		Percentage change from baseline in Sleep-loss prorated weekly mean score	% change from baseline: $100 \times \frac{\text{Observed score} - \text{Baseline}}{\text{Baseline}}$	
		2-point improvement in Sleep-loss prorated weekly mean score	Change from baseline in Sleep-loss prorated weekly mean score ≤ -2	Missing if baseline or observed value is missing.
Patient-Oriented Eczema Measure (POEM)		POEM	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.
		Change from baseline in POEM	Change from baseline: observed POEM – baseline POEM	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
	The POEM is a 7-item, validated, questionnaire used by the participant to assess disease symptoms over the last week. The participant 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.	4-point improvement	Change from baseline ≤ -4	Missing if baseline or observed value is missing. 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. Missing if DLQI total score is missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
Dermatology Life Quality Index (DLQI)	DLQI is a validated, dermatology-specific, patient-reported measure that evaluates participant's health-related QoL. 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 Not relevant = 0 Scores range from 0-30 with higher scores indicating greater impairment of quality of life. A DLQI total score of 0 to 1 is considered as having no effect on a participant's health-related QoL (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	A DLQI total score is calculated by summing all 10 question responses and has a range of 0-30 (less to more impairment) (Finlay and Khan 1994; Basra et al. 2008).	Score of 1 unanswered question = 0; If 2 or more questions are missing, the total score is missing. Note: #7B could be a valid missing while #7A is not "No." That is, #7 should be considered as 1 question.
		DLQI (0,1)	A DLQI (0,1) response is defined as a postbaseline DLQI total score of 0 or 1. A DLQI total score of 0 to 1 is considered as having no effect on a participant's health-related QoL (Khilji et al. 2002; Hongbo et al. 2005).	Missing if DLQI total score is missing.
		4-point improvement	Change from baseline ≤ -4	Missing if baseline or observed value is missing.
		DLQI total score and domain scores change from baseline	Calculated as: observed DLQI (total score or domain scores) – baseline DLQI (total score or domain scores)	If 1 question in a domain is missing, that domain 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.

Measure	Description	Variable	Derivation/Comment	Missing rule
		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: #7A. Has your skin prevented you from working or studying? #7B. If No: how much has your skin been a problem at work or studying?	If the answer to question #7A is missing, this domain is missing. If #7A is No, and #7B is missing, this domain is missing.
		DLQI personal relationships domain	Sum of responses of questions #8 and #9: #8. How much has your skin created problems with your partner or any of your close friends or relatives? #9. How much has your skin caused any sexual difficulties?	If 1 question in a domain is missing, that domain is missing.
		DLQI treatment domain	Response of question #10: #10. How much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Single item, missing if missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
Children's Dermatology Life Quality Index (CDLQI)	The CDLQI is designed to measure the impact of any skin disease on the lives of children. Participants ≤ 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 et al. 2010).	Score of 1 unanswered question = 0; If 2 or more questions are missing, the total score is missing.
		CDLQI (0,1)	A CDLQI (0,1) response is defined as a postbaseline CDLQI total score of 0 or 1.	Missing if CDLQI total score is missing.
		4-point improvement	Change from baseline ≤ -4	Missing if baseline or observed value is missing.
		CDLQI total score and domain scores change from baseline	Calculated as: observed CDLQI (total score or domain scores) – baseline CDLQI (total score or domain scores)	If 1 question in a domain is missing, that domain 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	Responses of questions 9: #9. Over the last week, how much has your sleep been affected by your skin problem?	Single item, missing if missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
		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 <u>Last week,</u> was it school time? OR was it holiday time? If school time: Over the last week, how much did your skin problem <u>affect</u> your school work? If holiday time: How much over the last week, has your skin problem interfered with your enjoyment of the <u>holiday</u>?	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.
		Employment status	Question (Q)1	Single item, missing if missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
Work Productivity and Activity Impairment: Atopic Dermatitis (WPAI-AD)	The Work Productivity and Activity Impairment Questionnaire – Atopic Dermatitis (WPAI-AD) records impairment due to AD during the past 7 days. The WPAI-AD consists of 6 items grouped into 4 domains: absenteeism (work time missed), presenteeism (impairment at work/reduced on the job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism), and activity impairment. Scores are calculated as impairment percentages (Reilly et al. 1993), with higher scores indicating greater impairment and less productivity.	Change in employment status	Employed at baseline and remained employed: Q1 = 1 at postbaseline visit and at baseline visit. Not employed at baseline and remain unemployed: Q1 = 0 at postbaseline visit and at baseline visit.	Missing if baseline or observed value is missing.
		Percentage of absenteeism	Percent work time missed due to problem: $(Q2/[Q2 + Q4])*100$	If Q2 or Q4 is missing, then missing. Missing if baseline or observed value is missing.
		Change from baseline in absenteeism	Change from baseline: observed absenteeism – baseline absenteeism	Missing if baseline or observed value is missing.
		Percentage of presenteeism	Percent impairment (reduced productivity while at work) while working due to problem: $(Q5/10)*100$	If Q5 is missing, then missing.
		Change from baseline in presenteeism	Change from baseline: observed presenteeism – baseline absenteeism	Missing if baseline or observed value is missing.
		Overall work impairment	Percent overall work impairment (combines absenteeism and presenteeism) due to problem: $(Q2/[Q2 + Q4] + ([1 - Q2/[Q2+Q4]]*[Q5/10]))*100$	If Q2, Q4, or Q5 is missing, then missing.
		Change from baseline in work impairment	Change from baseline: observed overall work impairment – baseline overall work impairment	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
		Percentage of activity impairment	Percent activity impairment (performed outside of work) due to problem: $(Q6/10)*100$	If Q6 is missing, then missing.
		Change from baseline in activity impairment	Change from baseline: observed activity impairment – baseline activity impairment	Missing if baseline or observed value is missing.
Hospital Anxiety Depression Scale (HADS)	The Hospital Anxiety Depression Scale (HADS) is a 14-item self-assessment scale that determines the levels of anxiety and depression that a participant is experiencing over the past week. The HADS utilizes a 4-point Likert scale (e.g., 0 to 3) for each question and is intended for ages 12 to 65 years (Zigmond and Snaith 1983; White et al. 1999). Scores for each domain (anxiety and depression) can range from 0 to 21, with higher scores indicating greater anxiety or depression (Zigmond and Snaith 1983; Snaith 2003).	HADS domain scores for anxiety and depression	Anxiety domain score is sum of the seven anxiety questions, range 0 to 21; Depression domain score is sum of the seven depression questions, range 0 to 21.	N/A – partial assessments cannot be saved.
		Change from baseline in HADS total score, anxiety and depression domain scores	Change from baseline: observed HADS total/domain score – baseline HADS total/domain score	Missing if baseline or observed value is missing.
Asthma Control Questionnaire (ACQ-5)		ACQ-5 total score	An ACQ-5 total score is the mean score of all 5 questions.	If more than 1 question is missing, the ACQ-5 total score is missing.
		Change from baseline in ACQ-5 score	Change from baseline: observed ACQ-5 total score – baseline ACQ-5 total score	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
	Participants who report comorbid asthma prior to enrollment will complete the Asthma Control Questionnaire in addition to other patient-reported outcomes in this trial. The ACQ-5 has been shown to reliably measure asthma control and distinguish participants with well-controlled asthma (score ≤ 0.75 points) from those with uncontrolled asthma (score ≥ 1.5 points). It consists of 5 questions that are scored on a 7-point Likert scale with a recall period of 1 week. The total ACQ-5 score is the mean score of all questions; a lower score represents better asthma control.	Minimal Clinically Important Difference (MCID) of 0.5	Change from baseline ≤ -0.5	Missing if baseline or observed value is missing.
European Quality of Life–5 Dimensions–5 Levels (EQ-5D-5L)	EQ-5D comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ VAS records the patient’s self-rated health on a vertical visual analogue scale. The scores on these five dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles	EQ-5D mobility EQ-5D self-care EQ-5D usual activities EQ-5D pain/discomfort EQ-5D anxiety/depression	Five health profile dimensions, each dimension has 5 levels: 1 = no problems 2 = slight problems 3 = moderate problems 4 = severe problems 5 = extreme problems. It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as a primary score.	Each dimension is a single item, missing if missing.
		EQ-5D VAS	Single item. Range 0 to 100. 0 represents “worst health you can imagine” 100 represents “best health you can imagine”	Single item, missing if missing.

Measure	Description	Variable	Derivation/Comment	Missing rule
		Change from baseline in EQ-5D VAS	Change from baseline: observed EQ-5D VAS score – baseline EQ-5D VAS score	Missing if baseline or observed value is missing.
		EQ-5D-5L UK Population-based index score (health state index)	Derive EQ-5D-5L UK Population-based index score according to the link by using the UK algorithm to produce a patient-level index score between -0.59 and 1.0 (continuous variable).	N/A – partial assessments cannot be saved on the eCOA tablet.
		Change from baseline in EQ-5D-5L UK Population-based index score.	Change from baseline: observed EQ-5D-5L UK score – baseline EQ-5D-5L UK Score.	Missing if baseline or observed value is missing.
Topical corticosteroid (TCS) or topical calcineurin inhibitor (TCI) Use	Mid-potency TCS and low-potency TCS will be provided by the Sponsor for use in this trial (Combo cohort). Participants are to be instructed to return all used and unused TCS medication (tubes) to the study site for accountability purposes.	Time (days) to TCS/TCI-free use from Baseline to Week 16 for the Induction Period, and from Baseline to Week 52 for the Combined Induction and Maintenance Blinded Periods	Days from the first study drug injection to the day participant stop using all TCS/TCI (if a participant starts and stops using low or mid potency TCS/TCI multiple times, use the last stop date as the stop date for this participant.)	If do not stop using the TCS/TCI, the participant will be censored at the date of their last visit.

Measure	Description	Variable	Derivation/Comment	Missing rule
		Proportion of TCS/TCI-free days from Baseline to Week 16 for the Induction Period, from Week 16 to Week 52 for Maintenance Period, and from Baseline to Week 52 for the Combined Induction and Maintenance Blinded Periods	100*(Number of the total TCS/TCI free days divided by total number of days during the treatment period)	N/A
		Mean gram quantity (tube weights) of low and moderate-potency TCS used from Baseline to Week 16 for the Induction Period, and from Baseline to Week 52 for the Combined Induction and Maintenance Blinded Periods	Weight all tubes after participants returned by potency. The total weight of TCS used calculated as total standard weight of each tube by supplier minus the total weight of the used tube. If a returned tube is not returned, then the tube can be classified as partially used, fully used, unused, or unknown. Partially used will be defined as 50% used whereas fully used and unused tubes will be defined as 100% and 0% used, respectively. Unknown will be treated as missing.	Missing data will be treated as missing.

Abbreviations: ACQ-5 = Asthma Control Questionnaire-5; AD = atopic dermatitis; eCOA = electronic Clinical Outcome Assessment; MCID = Minimal Clinically Important Difference; N/A = not applicable; NRS = numeric rating scale; Q = question; QoL = quality of life; VAS = visual analog scale.

6.2. Appendix 2: Description of Efficacy and Health Outcome Analyses

The description of efficacy and health outcomes analysis for different populations are described in details in [Table KGBW.6.2](#).

Table KGBW.6.2 Description of Efficacy and Health Outcome Analyses

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
Investigator's Global Assessment (IGA)	Proportion of participants achieving IGA (0,1) with a $\geq$ 2-point improvement	Primary Estimand (Hybrid)	Bayesian analysis with MCMC-MI	ITT	Leb 250 mg Q2W vs. PBO; Week 16	Primary analysis
			Common risk difference analysis with MCMC-MI	ITT	Week 16 and all scheduled visits in the Induction Period	Supplementary analysis: Week 16 Secondary analysis: other timepoints
			Bayesian analysis with MCMC-MI	ITT	Leb 250 mg Q2W vs. PBO; Week 16	Sensitivity analysis with tipping point method and different prior choice.
		Supportive Estimand (Composite)	Common risk difference analysis with NRI	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Supplementary analysis
			Bayesian analysis with NRI	ITT	Leb 250 mg Q2W vs. PBO; Week 16;	Sensitivity analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
	Proportion of participants achieving both IGA (0,1) with a ≥ 2 -point improvement and a ≥ 4 -point improvement in Itch NRS prorated weekly mean score	Supportive Estimand (Composite)	Common risk difference analysis with NRI	ITT with baseline Itch NRS ≥ 4	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Secondary analysis
	Maintenance of IGA (0,1): Proportion of participants maintaining IGA (0,1) with a ≥ 2 -point improvement from baseline among those re-randomized participants who achieved IGA (0,1) with a ≥ 2 -point improvement from baseline at Week 16	Maintenance Primary Estimand (Hybrid)	Descriptive statistics with MCMC-MI	MPP who have achieved IGA (0,1) with a ≥ 2 -point improvement from baseline at Week 16	No comparisons.	Secondary analysis
		Maintenance Supportive Estimand (Composite)	Descriptive statistics with NRI		All scheduled visits in the Maintenance Period	Supplementary analysis
	Time to loss of IGA (0,1)	N/A	KM method	MPP who have achieved IGA (0,1) with a ≥ 2 -point improvement from baseline at Week 16	No comparisons.	Secondary analysis
	Proportion of participants with IGA (0,1) with a ≥ 2 -point improvement from baseline	N/A	Descriptive statistics	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
	Proportion of participants with IGA (0,1) with a ≥ 2 -point improvement from baseline after lebrikizumab re-treatment	N/A	Descriptive statistics	Maintenance Period W20-52 Escape Population	No comparisons. Every 4 weeks after escape and re-treated by lebrikizumab 250mg Q2W	Secondary analysis
Eczema Area and Severity Index (EASI)	Change from baseline in EASI (EASI _{region}) score Percentage change from baseline in EASI score.	Primary Estimand (Hybrid)	ANCOVA with MCMC-MI for EASI score only	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period.	Major secondary analysis: percentage change at Week 16; Secondary analysis: other timepoints.
		Supportive Estimand (Hypothetical)	MMRM for EASI score and EASI _{region} score, respectively	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Supplementary analysis for EASI score Secondary analysis for EASI _{region} score
		Maintenance Primary Estimand (Hybrid)	Descriptive statistics with MCMC-MI for EASI score only	MPP	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
		Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF for EASI score and EASI _{region} score, respectively			Supplementary analysis for EASI score Secondary analysis for EASI _{region} score
		N/A	Descriptive statistics for EASI score only	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
	Change from baseline in each symptom score (that is, erythema, edema/papulation, excoriation, lichenification) and percentage involvement score by body regions (that is, head and neck, trunk, upper limbs, and lower limbs)	Supportive Estimand (Hypothetical)	MMRM	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Secondary analysis
		Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF	MPP	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis
	Proportion of participants achieving EASI-75 Proportion of participants achieving EASI-90	Primary Estimand (Hybrid)	Bayesian analysis with MCMC-MI (EASI-75 only)	ITT	Leb 250 mg Q2W vs. PBO; Week 16	Primary analysis: EASI-75 at Week 16
			Common risk difference analysis with MCMC-MI	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Supplementary analysis: EASI-75 at Week 16; Major secondary analysis: EASI-90 at Week 16; Secondary analysis: other timepoints
			Bayesian analysis with MCMC-MI (EASI-75 only)	ITT	Leb 250 mg Q2W vs. PBO; Week 16	Sensitivity analysis with tipping point method and different prior choice.

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
		Supportive Estimand (Composite)	Common risk difference analysis with NRI	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Supplementary analysis
			Bayesian analysis with NRI	ITT	Leb 250 mg Q2W vs. PBO; Week 16	Sensitivity analysis
	Proportion of participants achieving EASI-50	Supportive Estimand (Composite)	Common risk difference analysis with NRI	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Secondary analysis
	Proportion of participants achieving both EASI-75 and a ≥ 4-point improvement in Itch NRS prorated weekly mean score	Supportive Estimand (Composite)	Common risk difference analysis with NRI	ITT with baseline Itch NRS ≥ 4	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period.	Secondary analysis
	Proportion of participants maintaining EASI-50 (only for Maintenance Supportive Estimand [Composite]) and EASI-75 or achieving EASI-90 among those re- randomized participants who achieved EASI-75 at Week 16	Maintenance Primary Estimand (Hybrid)	Descriptive statistics with MCMC-MI	MPP who have achieved EASI-75 at Week 16	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis
		Maintenance Supportive Estimand (Composite)	Descriptive statistics with NRI			Supplementary analysis
	Time to loss of EASI-75	N/A	KM method	MPP who have achieved EASI-75 at Week 16	No comparisons.	Secondary analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
	Proportion of participants with EASI-75	N/A	Descriptive statistics	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis
	Proportion of participants with EASI-75 after lebrikizumab re-treatment	N/A	Descriptive statistics	Maintenance Period W20-52 Escape Population	No comparisons. Every 4 weeks after escape and re-treated by lebrikizumab 250 mg Q2W.	Secondary analysis
Body Surface Area (BSA) Affected by AD	Change from baseline in BSA	Supportive Estimand (Hypothetical)	MMRM	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period.	Secondary analysis
		Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF	MPP	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis
		N/A	Descriptive statistics	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
Itch Numeric Rating Scale (NRS)	Change from baseline in Itch NRS prorated weekly mean score.	Primary Estimand (Hybrid)	ANCOVA with MCMC-MI	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period.	Secondary analysis
	Percentage change from baseline in Itch NRS prorated weekly mean score.	Supportive Estimand (Hypothetical)	MMRM	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period.	Supplementary analysis
		Maintenance Primary Estimand (Hybrid)	Descriptive statistics with MCMC-MI	MPP	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
		Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF			Supplementary analysis
		N/A	Descriptive statistics	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis
	Proportion of participants achieving at least 4-point improvement in Itch NRS prorated weekly mean score in participants who had baseline Itch NRS ≥ 4	Primary Estimand (Hybrid)	Common risk difference analysis with MCMC-MI	ITT with baseline Itch NRS ≥ 4	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Major secondary analysis at Week 16; Secondary analysis: other timepoints
		Supportive Estimand (Composite)	Common risk difference analysis with NRI	ITT with baseline Itch NRS ≥ 4	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period.	Supplementary analysis
	Proportion of participants maintaining ≥ 4 -point reduction from baseline among those participants with Itch NRS of ≥ 4 -point at baseline who achieved ≥ 4 -point reduction from baseline at Week 16	Maintenance Primary Estimand (Hybrid)	Descriptive statistics with MCMC-MI	MPP with Itch NRS of ≥ 4 -points at baseline and who achieved ≥ 4 -point reduction from baseline at Week 16	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis
		Maintenance Supportive Estimand (Composite)	Descriptive statistics with NRI			Supplementary analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
	Proportion of participants with ≥ 4 -point reduction from baseline among those participants with Itch NRS of ≥ 4 -point at baseline	N/A	Descriptive statistics	Maintenance W16 Escape Population with Itch NRS of ≥ 4 -points at baseline	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
	Proportion of participants with ≥ 4 -point reduction from baseline after lebrikizumab re-treatment among those participants with Itch NRS of ≥ 4 -point at baseline	N/A	Descriptive statistics	Maintenance W20-52 Period Escape Population with Itch NRS of ≥ 4 -points at baseline	No comparisons. Every 4 weeks after escape and re-treated by lebrikizumab 250mg Q2W	Secondary analysis
Skin Pain Numeric Rating Scale (NRS)	Change from baseline in Skin Pain NRS	Supportive Estimand (Hypothetical)	MMRM	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period.	Secondary analysis
	Percentage change from baseline in Skin Pain NRS score	Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF	MPP	No comparisons. All scheduled visits in the Maintenance Period.	Supplementary analysis
	Proportion of participants with ≥ 4 -point reduction from baseline among those participants with Skin Pain NRS of ≥ 4 -point at baseline	Supportive Estimand (Composite)	Common risk difference analysis with NRI	ITT with baseline Skin Pain NRS score ≥ 4	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period.	Secondary analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
	Proportion of participants maintaining ≥ 4 -point reduction from baseline among those participants with Skin Pain NRS of ≥ 4 -point at baseline and who achieved ≥ 4 -point reduction from baseline at Week 16	Maintenance Supportive Estimand (Composite)	Descriptive statistics with NRI	MPP with Skin Pain NRS of ≥ 4 -points at baseline and who achieved ≥ 4 -point reduction from baseline at Week 16	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
	Proportion of participants with ≥ 4 -point reduction from baseline among those participants with Skin Pain NRS of ≥ 4 -point at baseline	N/A	Descriptive statistics	Maintenance W16 Escape Population with baseline Skin Pain NRS score ≥ 4	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
Sleep-loss Scale score	Change from baseline in Sleep-loss prorated weekly mean score.	Supportive Estimand (Hypothetical)	MMRM	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Secondary analysis
	Percentage change from baseline in Sleep-loss prorated weekly mean score.	Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF	MPP	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis
	Proportion of participants achieving at least 2-point improvement in Sleep-loss prorated weekly mean score in participants who had baseline Sleep-loss ≥ 2	Supportive Estimand (Composite)	Common risk difference analysis with NRI	ITT with baseline Sleep-loss ≥ 2	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Secondary analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
	Proportion of participants achieving at least 2-point improvement in Sleep-loss prorated weekly mean score in participants who had baseline Sleep-loss ≥ 2	Maintenance Supportive Estimand (Composite)	Descriptive statistics with NRI	MPP with baseline Sleep-loss ≥ 2	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis
	Proportion of participants achieving at least 2-point improvement in Sleep-loss prorated weekly mean score in participants who had baseline Sleep-loss ≥ 2	N/A	Descriptive statistics	Maintenance W16 Escape Population with baseline Sleep-loss ≥ 2	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis
(Children) Dermatology Life Quality Index (DLQI/CDLQI)	Change from baseline in DLQI total scores.	Primary Estimand (Hybrid)	ANCOVA	ITT	Leb 250 mg Q2W vs. PBO; Week 16	Secondary analysis
	Change from baseline in DLQI total and domain scores Change from baseline in CDLQI total and domain scores	Supportive Estimand (Hypothetical)	MMRM	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period.	Secondary analysis
		Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF	MPP	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis
		N/A	Descriptive statistics	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
	Proportion of participants achieving at least 4-point improvement in DLQI total score in participants who had baseline DLQI total score ≥ 4	Supportive Estimand (Composite)	Common risk difference analysis with NRI	ITT with baseline DLQI/CDLQI total score ≥ 4	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period.	Secondary analysis
		Maintenance Supportive Estimand (Composite)	Descriptive statistics with NRI	MPP with baseline DLQI/CDLQI total score ≥ 4 who have achieved ≥ 4 -point improvement in DLQI/CDLQI total score at Week 16	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
		N/A	Descriptive statistics	Maintenance W16 Escape Population with baseline DLQI/CDLQI total score ≥ 4	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
	Proportion of participants achieving DLQI (0,1)/CDLQI (0,1)	Supportive Estimand (Composite)	Common risk difference analysis with NRI	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Secondary analysis
		Maintenance Supportive Estimand (Composite)	Descriptive statistics with NRI	MPP	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
		N/A	Descriptive statistics	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period	No comparisons. All scheduled visits in the Maintenance Period

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
SCORing Atopic Dermatitis (SCORAD)	Change from baseline in SCORAD Percentage change from baseline in SCORAD	Supportive Estimand (Hypothetical)	MMRM	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Secondary analysis
		Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF	MPP	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
		N/A	Descriptive statistics	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
	Proportion of participants achieving SCORAD75 Proportion of participants achieving SCORAD90	Supportive Estimand (Composite)	Common risk difference analysis with NRI	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Secondary analysis
		Maintenance Supportive Estimand (Composite)	Descriptive statistics with NRI	MPP	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
		N/A	Descriptive statistics	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
	Percentage change in SCORAD from baseline in participants who achieved EASI-75 at Week 16	Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF	MPP who have achieved EASI-75 at Week 16	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
	Patient-Oriented Eczema Measure (POEM)	Supportive Estimand (Hypothetical)	MMRM	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Secondary analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
		Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF	MPP	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
		N/A	Descriptive statistics	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
Work Productivity and Activity Impairment: Atopic Dermatitis (WPAI-AD)	Change from baseline in: - absenteeism - presenteeism - overall work impairment - impairment in activities	Supportive Estimand (Hypothetical)	MMRM	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Secondary analysis
		Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF	MPP	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
		N/A	Descriptive statistics	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
Hospital Anxiety Depression Scale (HADS)	Change from baseline in HADS anxiety score Change from baseline in HADS depression scores.	Supportive Estimand (Hypothetical)	MMRM	ITT	Leb 250 mg Q2W vs. PBO; Week 16 and all scheduled visits in the Induction Period	Secondary analysis
		Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF	MPP	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
		N/A	Descriptive statistics	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
Asthma Control Questionnaire (ACQ-5)	Change from baseline in ACQ-5 score.	Supportive Estimand (Hypothetical)	ANCOVA with LOCF	ITT with self-reported comorbid asthma	Leb 250 mg Q2W vs. PBO; Week 16 in the Induction Period.	Secondary analysis
		Maintenance Supportive Estimand (Hypothetical)	Descriptive statistics with LOCF	MPP with self-reported comorbid asthma	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
European Quality of Life–5 Dimensions–5 Levels (EQ-5D-5L)	Change from baseline in - EQ-5D VAS - EQ-5D-5L UK Population-based index score - EQ-5D-5L China Population-based index score (China population only)	Supportive Estimand (Hypothetical)	ANCOVA with LOCF	ITT	Leb 250 mg Q2W vs. PBO; Week 16 in the Induction Period	Secondary analysis
		Maintenance Supportive Estimand (Hypothetical)	ANCOVA with LOCF	MPP	No comparisons. All scheduled visits in the Maintenance Period	Secondary analysis
		NA	Descriptive stats	Maintenance W16 Escape Population	No comparisons. All scheduled visits in the Maintenance Period.	Secondary analysis
Topical corticosteroid (TCS) or topical calcineurin inhibitor (TCI) Use	Time (days) to TCS/TCI-free use from Baseline to Week 16	N/A	KM method with log-rank test	ITT	Leb 250 mg Q2W vs. PBO;	Secondary analysis
	Time (days) to TCS/TCI-free use from Baseline to Week 52	N/A	KM method	MPP	No comparisons.	Exploratory analysis
	Proportion of TCS/TCI-free days from Baseline to Week 16	N/A	Descriptive statistics with observed data	ITT	Leb 250 mg Q2W vs. PBO; Baseline through Week 16 in the Induction Period.	Secondary analysis
	Proportion of TCS/TCI-free days from Week 16 to Week 52	N/A	Descriptive statistics with observed data	MPP	No comparisons. Week 16 to Week 52 in the Maintenance period.	Exploratory analysis

Measure	Variable	Estimand (Section 1.1)	Analysis Method (Section 4)	Population (Section 3)	Comparison/Time Point	Analysis Type
	Proportion of TCS/TCI-free days from Baseline to Week 52	N/A	Descriptive statistics with observed data	MPP	No comparisons. Baseline through Week 52 in the Combined Induction and Maintenance Periods.	Exploratory analysis
	Mean weight of TCS use by potency (tube weights) from Baseline to Week 16	N/A	Descriptive statistics with observed data Two-sample t-test and ANOVA including treatment group and stratification factors with observed data.	ITT	Leb 250 mg Q2W vs. PBO; Baseline through Week 16 in the Induction Period	Secondary analysis
	Mean weight of TCS use by potency (tube weights) from Baseline to Week 52	N/A	Descriptive statistics with observed data	MPP	No comparisons. Baseline through Week 52 in the Combined Induction and Maintenance Periods	Exploratory analysis

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; KM = Kaplan-Meier; Leb = lebrikizumab; LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo multiple imputation; MMRM = mixed-effects model for repeated measures; MPP = Maintenance Primary Population; N/A = not applicable; NRI = nonresponder imputation; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; VAS = visual analog scale; W = week.

6.3. Appendix 3: Demographic and Baseline characteristics

Participant demographic variables and baseline characteristics will be summarized by treatment group for the ITT Population, the MPP, and the Maintenance W16 Escape Population. The summary will also be created by treatment group in the ITT Population by participants who experienced or did not experience conjunctivitis adverse events defined using Customized MedDRA Query (CMQ) PTs as described in the Compound Level Safety Standards during the Induction Period. In addition, participant disease characteristics at Week 16 will be summarized by treatment group for the MPP. The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages. No formal statistical comparisons will be made between treatment groups unless otherwise specified.

The following demographic information will be included:

- Age
- Age group (Adolescents (12<18), Adults ≥18)
- Age group (Adolescents (12<18), Adults ≥ 18 - <65, ≥65 - <75, ≥75)
- Sex (male, female)
- Race (Asian, Not Reported)
- Country (China, Korea)
- Weight (kg)
- Weight category (<60 kg, ≥60 to <100 kg, ≥100 kg)
- Height (cm)
- BMI (kg/m²)
- BMI category: Underweight (<18.5 kg/m²), Normal (≥18.5 and <25 kg/m²), Overweight (≥25 and <30 kg/m²), Obese (≥30 and <40 kg/m²), Extreme obese (≥40 kg/m²)

By-participant listings of basic demographic information for the ITT Population will be provided.

The following baseline disease/clinical characteristics will be included:

- Age at onset (years): calculated as the difference between date of onset of AD and the date of birth.
- Duration since AD onset (years): calculated as the difference between date of Informed Consent and the date of onset of AD
- Duration since AD onset category (0 to <2 years, 2 to <5 years, 5 to <10 years, 10 to <20 years, ≥20 years)
- Anatomical area affected by atopic dermatitis:
 - Head
 - Trunk (internal/medial axillae and groin)
 - Upper extremities (includes external axillae)
 - Lower extremities (includes buttocks and feet)
 - At least 2 areas

- AD treatment used in the past defined in [Appendix 11](#) (Section 6.11)
 - None
 - Topical corticosteroids
 - Topical calcineurin inhibitors
 - Crisaborole
 - Systemic corticosteroids
 - Immunosuppressant
 - Biologics
 - Phototherapy
 - Photochemotherapy
- IGA score: 3 versus 4
- EASI score
- SCORAD
- BSA
- Itch NRS
- Itch NRS: $< 4, \geq 4$
- Sleep loss due to itch
- Sleep loss due to itch $< 2, \geq 2$
- Skin pain NRS
- POEM
- DLQI
- CDLQI
- Work Productivity and Activity Impairment – Atopic Dermatitis (WPAI-AD)
 - Employment status: Employed, Not employed
 - Absenteeism
 - Presenteeism
 - Overall work impairment
 - Activity impairment
- HADS
 - Total score
 - Anxiety domain score
 - Depression domain score
- Asthma Control Questionnaire (ACQ-5) (among participants who report comorbid asthma)

6.4. Appendix 4: Medical History

Medical histories are defined as the conditions/events recorded on the *Pre-Existing Conditions and Medical History Details* eCRF with a start date prior to the first study drug injection.

The number and percentage of participants with medical histories will be summarized for the overall ITT Population by treatment group and by treatment and age groups for the ITT Population using the MedDRA PT nested within SOC.

The number and percentage of participants with specific medical history events of interest pre-specified on the *Prespecified Medical History* eCRF (Conjunctivitis, herpes zoster, chicken-pox and asthma) will be summarized for the overall ITT Population, the MPP, and the Maintenance Week 16 Escape Population by treatment group and by treatment and age groups.

6.5. Appendix 5: Treatment Compliance

Treatment compliance with investigational product will be summarized for participants who have at least one dose for the Safety Population in the Induction Period and for the MPP during the blinded Maintenance Period. Treatment compliance for each participant will be calculated as:

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

- 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 response to the question “Was dose administered?” on the *Exposure as Collected* eCRF page.

The number of injections expected at each visit and total number of injections up to each visit during the Induction Period are as follows:

Visit	W0	W2	W4	W6	W8	W10	W12	W14 ^a
# injections at each visit	2	2	1	1	1	1	1	1
Total # injections up to each visit	2	4	5	6	7	8	9	10

Abbreviation: W = week.

^a Last injection during the Induction Period occurs on Week 14.

The number of injections expected at each visit and total number of injections up to each visit during the blinded Maintenance Period are as follows:

Timepoint	W16	W20	W24	W28	W32	W36	W40	W44	W48
Visit	W16	W20	W24	W28	W32	W36	W40	W44	W48
# injections at each visit	1	1	1	1	1	1	1	1	1
Total # injections up to each visit	1	2	3	4	5	6	7	8	9

Abbreviation: W = week.

A participant will be considered compliant if he or she received $\geq 75\%$ of the expected number of injections in the respective treatment period 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.

6.6. Appendix 6: 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 each treatment period to allow medications to be classified as concomitant for each treatment period.

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

Prior medication for AD will be summarized for the ITT Population. Concomitant medication during the Induction Period and the Maintenance Period will be presented separately for the ITT Population and the MPP.

Specific AD treatment during the Induction and the Maintenance Periods will be presented by treatment groups for the ITT Population and the MPP separately based on the information collected on *Concomitant Therapy* eCRF page. This will include: (1) topical AD treatment (including TCS, TCI and crisaborole), (2) systemic AD treatment (including oral corticosteroids, immunosuppressant, biologics and phototherapy). The TCS will be presented by potency. Definition of these drugs of interest is described in [Appendix 11](#) (Section 6.11).

6.6.1. Rescue Medication for Atopic Dermatitis (AD)

Rescue therapy were collected from “Concomitant Therapy” and defined as below:

Induction period:

Rescue medication for AD in combo cohort is defined as:

- any **high-potency** TCS as defined in [Appendix 11](#) (Section 6.11)
- any systemic medication as defined in [Appendix 11](#) (Section 6.11)

Rescue medication for AD in mono cohort is defined as:

- any potency TCS or other topical AD treatment as defined in [Appendix 11](#) (Section 6.11)
- any systemic medication as defined in [Appendix 11](#) (Section 6.11)

Maintenance period:

Rescue medication for AD in combo cohort and mono cohort is defined as:

- any **high potency** TCS as defined in [Appendix 11](#) (Section 6.11)
- any systemic medication as defined in [Appendix 11](#) (Section 6.11)

Participants who use these rescue medications will be summarized. The summary will be provided for any rescue medication use, with TCS and systemic therapy summarized separately for the Induction Period on the ITT Population, the Maintenance Blinded Period on the MPP, and the Maintenance Escape Period on the Maintenance W16 Escape Population, respectively.

A summary of percentage of participants in the ITT Population, the MPP, and the Maintenance W16 Escape Population rescued by visit will be provided for the Induction Period, Maintenance Blinded Period, and Maintenance Escape period, respectively. KM curves for time to first rescue use in induction period may be generated.

6.7. Appendix 7: 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 participant's rights, safety, or well-being.

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

The number and percentage of participants having important protocol deviation (IPD[s]) will be summarized within category and subcategory of deviation by treatment group for the Induction Period on the ITT Population and for the Maintenance Period on All Maintenance Population.

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

6.8. Appendix 8: Clinical Trial Registry Analyses

Additional analyses will be performed (if not already available from the study CSR) for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements, which include:

Summary of AEs, provided as a dataset, will be converted to an XML file. Both serious adverse events (SAEs) and 'Other' AEs are summarized by treatment group and 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 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 fewer than 5% of participants 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.

6.9. Appendix 9: Unblinding Plan

Unblinding details are specified in the BUP.

6.10. Appendix 10: Study Visit Mapping for Itch NRS, Skin Pain NRS and Sleep-loss and POEM

Itch NRS, Skin Pain NRS and sleep loss are collected via eCOA; entries will be mapped to study week by the following:

Week	Start Day	End Day
Baseline	Date of First Injection ^a - 7	Date of First Injection - 1
Week 1	Max (Date of First Injection, Week 2 Assessment Date - 14)	Week 2 Assessment Date - 8
Week 2	Week 2 Assessment Date - 7	Week 2 Assessment Date - 1
Week 4	Week 4 Assessment Date - 7	Week 4 Assessment Date - 1
Week 6	Week 6 Assessment Date - 7	Week 6 Assessment Date - 1
Week 8	Week 8 Assessment Date - 7	Week 8 Assessment Date - 1
Week 10	Week 10 Assessment Date - 7	Week 10 Assessment Date - 1
Week 12	Week 12 Assessment Date - 7	Week 12 Assessment Date - 1
Week 14	Week 14 Assessment Date - 7	Week 14 Assessment Date - 1
Week 16	Week 16 Assessment Date - 7	Week 16 Assessment Date - 1
Week 20	Week 20 Assessment Date - 7	Week 20 Assessment Date - 1
Week 24	Week 24 Assessment Date - 7	Week 24 Assessment Date - 1
Week 28	Week 28 Assessment Date - 7	Week 28 Assessment Date - 1
Week 32	Week 32 Assessment Date - 7	Week 32 Assessment Date - 1
Week 36	Week 36 Assessment Date - 7	Week 36 Assessment Date - 1
Week 40	Week 40 Assessment Date - 7	Week 40 Assessment Date - 1
Week 44	Week 44 Assessment Date - 7	Week 44 Assessment Date - 1
Week 48	Week 48 Assessment Date - 7	Week 48 Assessment Date - 1
Week 52	Week 52 Assessment Date - 7	Week 52 Assessment Date - 1

^a If 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 an assessment could be mapped to different weeks, it will be mapped to the earlier week. Derivation of the weekly mean scores for Itch NRS, Skin Pain NRS and Sleep-loss could be found in [Appendix 1](#) (Section 6.1). If at least 1 of the 7 days contains nonmissing daily assessments, postbaseline weekly score will be calculated using prorated weekly average. If the range of 7 days are all missing daily assessments, then the weekly score is missing.

POEM is collected every week via eCOA, the visit week mapping will follow the following rule: the last collected POEM data before or on the visit date would be used, the evaluation window is injection date - 7 to injection date - 1 for baseline (if missing, use the last nonmissing POEM score before baseline) and assessment date - 7 to assessment date - 1 for postbaseline. For

example, if a participant gets an injection/assessment on the 14th, the scale completed between the 13th and the 7th would be used.

6.11. Appendix 11: Definition of Topical and Systemic Atopic Dermatitis Therapy

The atopic dermatitis therapy for different cohort and period is defined in [Appendix 6](#) (Section 6.6). The topical treatments and systemic treatments are defined as following:

1. Topical AD Treatment (including corticosteroids, TCI and crisaborole)

Route of topical treatments includes: Topical and Transdermal.

Topical Corticosteroids (TCS):

- High-potency TCS: ATC code is D07AC, D07AD, D07BC, D07BD, D07CC, D07CD, D07XC, D07XD
- Low or Moderate-potency TCS: ATC code is D07, excluding D07AC, D07AD, D07BC, D07BD, D07CC, D07CD, D07XC, D07XD
- For TCS recorded in CRF “Concomitant Therapy”, with preferred term as: MOMETASONE, MOMETASONE FUROATE, DESONIDE, METHYLPREDNISOLONE ACEPONATE, use potency collected by CRF page instead of the ATC code.

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/chemotherapy)

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, Baricitinib, Upadacitinib 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’ or ‘UV’ then medicals to manually review to confirm whether the medication in question is indeed ‘Phototherapy’ or ‘Photochemotherapy.’

6.12. Appendix 12: Details of Combining Estimates and Test Statistics for Categorical Endpoints with Multiple Imputation

Following the implementation of MCMC-MI imputation as specified in Section 4.1.6.1.1, the 25 data sets with imputations should be set together and sorted by imputation number. The following sections describe the processes for combining inferences for the individual imputed data sets into 1 inference for reporting. All calculations are performed in SAS software version 9.4.

Summarize Unadjusted Response Rate

The response rates, overall and by treatment arm, and their associated SEs are computed for each imputed data set using PROC FREQ with the *riskdiff* option specified for the appropriate column in the TABLES statement. 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% CI bounds output by PROC MIANALYZE are percents (that is, they are in terms of the response rate). To obtain the number of responders, the estimated percent is multiplied by the number of individuals in the analysis population and rounded to the nearest integer.

Compute Stratified Measures of Association

The common risk difference, common OR, and CMH test statistic are computed for each imputed data set using PROC FREQ with the *riskdiff* option for the appropriate column (for risk difference) and the *cmh* option (for OR and CMH test statistic) specified in the TABLES statement. Each of these analyses are stratified by age group, and baseline disease severity via inclusion of these variables in the TABLES statement with the treatment and outcome variables.

Note that the PROC FREQ output corresponding to the Mantel-Haenszel method is used for the risk difference, and the output corresponding to the General Association statistic is used for the CMH statistic. PROC MIANALYZE is then called separately for each of these measures, with further details in the sections below.

Common Risk Difference

No transformation is necessary before using PROC MIANALYZE to combine the risk difference estimates and their associated SEs across the 25 imputed data sets. This procedure outputs an estimate of the common risk difference and the associated 95% CI bounds.

Common Odds Ratio

The OR from each imputed data set is first transformed using the natural logarithm. The SE for each log OR ($SE_{\log OR}$) is derived from the OR 95% CI bounds (LB_{OR} , UB_{OR}) according to the following equation: $SE_{\log OR} = (\ln(UB_{OR}) - \ln(LB_{OR})) / (2 \times 1.96)$. The log OR and derived SE are then combined using PROC MIANALYZE, which outputs a combined estimate of the log OR and the associated 95% CI. Finally, these measures can be exponentiated to transform them back to the OR scale.

Cochran-Mantel-Haenszel Test

The CMH test statistic (CMH) from each imputed data set is transformed using the Wilson-Hilferty transformation and standardized so that it has approximately a standard Normal distribution (Ratitch et al. 2013). In particular, the transformed CMH statistic is computed as follows:

$$CMH_{WH} = \frac{\left(\frac{CMH}{df}\right)^{\frac{1}{3}} - \left(1 - \frac{2}{9 \times df}\right)}{\sqrt{\frac{2}{9 \times df}}}, \text{ where } df \text{ is the degrees of freedom of the CMH statistic.}$$

Then the SE for each is 1, and PROC MIANALYZE is used to output a combined estimate of the transformed CMH statistic. Note that the two-sided p-value output by PROC MIANALYZE is not used directly, but instead the one-sided p-value is computed manually using both the t statistic and two-sided p-value output by PROC MIANALYZE: if t statistic is greater than 0, then one-sided p-value is computed as half of the two-sided p-value; otherwise, the one-sided p-value is computed as 1 – half of the two-sided p-value. The resulting one-sided p-value is reported as the pooled p-value for the CMH test.

6.13. Appendix 13: Details of Bayesian Hierarchical Model with Mixture Prior for Combo cohort Co-primary Endpoints

Bayesian model details:

1. Bayesian hierarchical model:

Let y_{ij} be the number of events for arm $i = 1, 2$ (lebrikizumab + TCS vs. placebo + TCS) and endpoint $j = 1, 2$ (EASI-75 and IGA[0/1] with 2-point reduction); n_i the total number of participants in each arm; and p_{ij} the response rates for each arm i and endpoint j . Number of responders n_i and response rate p_{ij} follows binomial distribution as below:

$$y_{ij} \sim \text{Binomial}(n_i, p_{ij})$$

Construct a linear model for p_{ij} after logit transformation:

$$\text{logit}(p_{ij}) = \alpha_j + \beta_j(i - 1)$$

with α_j defined as the log-odds of the placebo rate and β_j defined as the log-odds ratio comparing lebrikizumab + TCS to placebo + TCS for endpoint j . Construct prior distribution for α_j and β_j .

2. Constructing the prior distributions:

Informative priors were designed using results from global studies via above Bayesian hierarchical model. To reduce the risk from the conflict between KGBW results and prior information, a robust mixture prior was constructed to incorporate non-informative prior component and informative prior component derived from other trials' results. Therefore, less borrowing will occur when informative prior deviates from Study KGBW trial results, so that to avoid the domination of informative prior.

a. Mixture prior

- 1) For the placebo rate, no information will be borrowed from the historical data; therefore, a weakly informative prior will be used for α_j :

$$\alpha_j \sim N(0, 4)$$

- 2) In contrast, a mixture model will be used to construct the prior distribution for β_j . Bayesian Dynamic borrowing via mixture prior has been increasingly utilized in clinical development for integrating existing trial data into a new clinical trial (Greenhouse and Wasserman 2024). This approach will enable dynamic borrowing of the historical data on the log-odds scale such that more data will be borrowed if the results across KGBW and the historical studies are consistent. The prior distribution for β_j is as follows:

$$\pi(\beta_j) = w_1 \times N(0, 2) + w_2 \times N(\mu_{j,D}, \sigma_{j,D}^2) + w_3 \times N(\mu_{j,L}, \sigma_{j,L}^2)$$

- $w_1 \times N(0, 2)$ is non-informative on the log-odds scale and is used to add probability mass to the tails to robustify the prior, by assuming no difference between 2 treatment arm.
- Informative component: Two informative prior components $w_2 \times N(\mu_{j,D}, \sigma_{j,D}^2)$, $w_3 \times N(\mu_{j,L}, \sigma_{j,L}^2)$ is constructed based on global phase 3 study KGAD and Japan phase 3 study KGAL data, respectively. $\mu_{j,D}, \mu_{j,L}, \sigma_{j,D}^2, \sigma_{j,L}^2$ in the model are listed in the table below:



Note: LOR : Log Odds Ratio; Dupixent experienced patients were excluded in the calculation of treatment effect FOR study KGAD, to keep consistent with KGBW's inclusion and exclusion criteria; Rate and rate difference was calculated after MCMC-MI, unadjusted rate difference were reported.

- Three prior weights $w_{1,2,3}$ followed a categorical distribution which pre-specified as $w_{1,2,3} = I(p = \{0.5, 0.25, 0.25\})$ Setting the prior of weight as 0.5, 0.25, 0.25 aims to restrict the information used in the prior to less than a half of the total information.

In the constructed Bayesian hierarchical model, the weight of each component is not a fixed value, the posterior distribution of weight will be adjusted according to the observed treatment response date. When the observed results deviates from the global results toward “no treatment difference”, weight of non-informative prior will be increased when fitting the posterior distribution of weight, so that the result will not be dominated by the global results. When observed results are close to the global results, weight of informative component will be increased while fitting the posterior distribution.

3. Likelihood: according to the Bayesian model specified in part 1, for endpoint j, we have:

$$\begin{aligned} \text{logit}(p_i) &= \alpha + \beta(i - 1) \\ p_i &= \frac{\exp \{\alpha + \beta(i - 1)\}}{1 + \exp \{\alpha + \beta(i - 1)\}}, i = 1, 2 \quad (1) \end{aligned}$$

For $p_{i=1,2}$, the likelihood function could be specified as:

$$L(p_i, y_i) = \prod_{i=1}^2 \binom{n_i}{y_i} p_i^{y_i} (1 - p_i)^{n_i - y_i}$$

y_i = the number of responders, n_i = sample size in each arm, p_i could be linked to α and β via Equation (1).

4. Posterior distribution

The posterior distribution for β_j cannot be expressed in a closed form method due to the inclusion of weights in the model. Thus, the R2jags package in R, which utilizes a Gibbs sampling method, will be used to obtain samples from the posterior distribution. Statistics to be output are calculated by samples extracted in each iteration.

5. Output statistics

CCI
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

6. R programming example

```

library(R2jags) # for jags model and bayesian analysis, version 0.7-1
library(bayestestR) # for credible interval computation, version 0.13.1

EASI75_Jags_Model <- "model{
  # Likelihoods
  yL ~ dbin(pL, nL)
  yP ~ dbin(pP, nP)
  logit(pL) <- theta0 + theta1*w[1] + theta1_inf1*w[2] + theta1_inf2*w[3]
  logit(pP) <- theta0

  # Priors
  theta0 ~ dnorm(0, 1/4)
  theta1 ~ dnorm(0, 1/2)
  theta1_inf1 ~ CCI
  theta1_inf2 ~ CCI
  catpar ~ dcat(weights[1:3])
  w[1] <- ifelse(catpar==1, 1, 0)
  w[2] <- ifelse(catpar==2, 1, 0)
  w[3] <- ifelse(catpar==3, 1, 0)

  # Treatment effects of interest
  pd <- pL - pP
  lor <- theta1*w[1] + theta1_inf1*w[2] + theta1_inf2*w[3]
  log(or) <- lor
}"

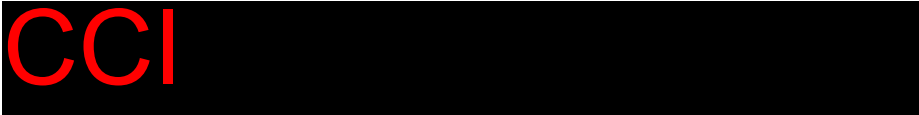
# jags_data_easi as input data, which contains final responders and corresponding sample
size

#(yL, yP, and nP, nL), here as an example set PBO responder as 15, LY responder as 60:
CCI

```

```
#posterior distribution fitting using jags() function, set n.burnin=20000, niter=70000, to
ensure a #robust final output
set.seed(1) #ensure reproducibility
load.module("glm",quiet=T)
params = c("pd") # params to output
jags_res_easi =jags(data = jags_data_easi, n.burnin = 20000, n.iter = 70000, n.thin = 1,
jags.module = "glm", n.chains = 4, parameters.to.save = params, model.file =
textConnection(EASI75_Jags_Model))

# output statistics
samps_easi <- jags_res_easi$BUGSoutput$sims.matrix[,-1]
res_easi <- data.frame(PrRD0 = mean(samps_easi[, "pd"]>0), RD =
mean(samps_easi[, "pd"]), PrOR1 = mean(samps_easi[, "or"]>1)) #output
```

A large black rectangular redaction box covering the bottom portion of the code. The letters 'CCI' are printed in red on the left side of the redacted area.

7. References

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