

Protocol J2T-MC-KGBW (a)

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

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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

Protocol Number: J2T-MC-KGBW

Amendment Number: a

Compound: Lebrikizumab (LY3650150)

Brief Title:

Efficacy and Safety of Lebrikizumab with/without Topical Corticosteroid Treatment in Participants with Moderate-to-Severe Atopic Dermatitis

Study Phase: 3

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana, USA 46285

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Original Protocol	26-Oct-2023

Amendment [a]

This amendment is considered to be substantial, because of the change in sample size and statistical methodology, and revision to the primary and key secondary endpoints.

Overall Rationale for the Amendment:

The main purpose of this protocol amendment is to revise the co-primary and secondary objectives and endpoints in response to China National Medical Products Administration (NMPA) feedback. Sample size is adjusted according to China NMPA feedback on bridging strategy.

Changes specific to certain protocol sections and a brief rationale are provided in the below table. Other minor typographical corrections not affecting content have also been made in the document.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated objectives and endpoints, primary estimand, number of participants as the changes in Sections 3, 4.1 and 9.3.2.	Editorial consistency
1.2 Schema	Updated the patient number in combo cohort	Editorial consistency
1.2 Schema	Added “and/or TCI” for mono cohort washout period in footnote c	Editorial consistency
1.3 Schedule of Activities (SoA), Table 1	Removed “X” in Visit 2 for Medical history and Demography	Correction to avoid repeatable collection
1.3 Schedule of Activities (SoA), Table 1 and Table 2	Removed the sentence “BSA affected by AD will be derived from data collected as part of the EASI assessment.” in comment box of IGA, EASI (including BSA) scale	Correction
1.3 Schedule of Activities (SoA), Table 2	Added “[± 5 days]” to clarify the visit tolerance interval for the escape arm in the row of “Dispense and administer study intervention”	Clarification

Section # and Name	Description of Change	Brief Rationale
3 Objectives, Endpoints and Estimand	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”	Adjustment according to China NMPA feedback on bridging strategy
	Revised primary endpoint to co-primary endpoints: “Proportion of participants achieving at Week 16: • EASI-75 • IGA score of 0 or 1 with a reduction of ≥ 2 points from baseline at Week 16” Revised major secondary endpoints as below: “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:	Modification according to China NMPA requirement; Adjustment according to China NMPA feedback on bridging strategy

Section # and Name	Description of Change	Brief Rationale
	DLQI" Moved the above endpoints for mono cohort from "other secondary" to "major secondary"	
4.1 Overall Design	Updated the sample size for combo cohort	Adjustment according to China NMPA feedback on bridging strategy
5.2 Exclusion Criteria Exclusion criterion 13	Modified to "Have or have had active tuberculosis (TB) that has not been treated with a complete course of appropriate therapy as defined by the World Health Organization (WHO), the United States (US) Centers for Disease Control and Prevention (CDC) or local country guidelines"	Clarification to exclude participants with active TB history who have not been treated with a complete course of appropriate therapy
5.2 Exclusion Criteria, Exclusion criterion 14	Added "or local country guidelines" for appropriate LTBI therapy to follow	Clarification
6.3 Assignment to Study Intervention	Updated the patient number of combo cohort to "n=150"	Editorial consistency
6.4 Blinding	Added "A designated group will be unblinded to the treatment assignment of induction and maintenance period at Week 16 database lock. Another blinded group will continue with daily monitoring of the study." Added "except for the designated unblinded group" to clarify the blinded scope	Clarification
6.9.1 Permitted and Prohibited Treatments and Procedures	Added "and/or TCI" for mono cohort washout period. Added "Concomitant antihistamines are permitted and are prescribed by the investigator on an as-needed basis for individual patients. Non-sedative antihistamines are recommended, and if the sedative ones are to be used, they should be on a stable dose at the time of enrollment."	Clarification
7.2 Participant Discontinuation/With	Remove "if the participant, for any reason, requires treatment with another therapeutic agent that has been	Correction to avoid contradiction to the rescue medicine section

Section # and Name	Description of Change	Brief Rationale
drawal from the Study	demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent”	
8.1.1 Efficacy Assessments	Deleted “Assessors must be trained and certified by the sponsor prior to conducting this assessment.”	Correction
8.1.2 Participant Reported Outcomes and Health-Related Quality of Life	Added “Planned time points for these assessments are provided in the SoA (Section 1.3). Diaries and questionnaires that are missed by participants for less than 7 consecutive days at non-critical timepoints (i.e. except for Visit 2/Visit 10) are not regarded as protocol deviations.”	Clarification
8.2.6 Tuberculosis Testing	Added “the local country guidelines” for appropriate LTBI therapy to follow. Changed the monitoring frequency for TB to “every 3 to 4 months”.	Editorial consistency
8.2.9.1 Close Hepatic Monitoring 8.2.9.2 Comprehensive Hepatic Evaluation	Added “Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant’s clinical condition and lab results stabilize” for clinical and laboratory monitoring.	Clarification that if liver tests stabilize, lower frequency of monitoring is sufficient.
8.2.9.2 Comprehensive Hepatic Evaluation	Added “For participants with isolated ALP elevation $\geq 2.5 \times$ ULN without GGT elevation, consider testing for ALP isoenzymes and evaluating for extrahepatic sources such as bone disease (e.g., fractures, bone metastases, osteomalacia, Paget’s disease), or pregnancy.”	Added guidance for participants with isolated ALP elevation $\geq 2.5 \times$ ULN without GGT elevation
8.2.9.2 Comprehensive Hepatic Evaluation	Changed the frequency of clinical and laboratory monitoring to “2 to 3 times weekly” in comprehensive hepatic evaluation	Kept consistent frequency with close hepatic monitoring
8.2.10 Injection Site Reactions	Removed “In addition, all positive responses of injection-site pain will require an additional assessment using the Pain Visual Analog Scale (Williamson and Hoggart 2005).”	Correction to remove the suggested language only for exploratory medicine and pharmacology (EMP) protocols

Section # and Name	Description of Change	Brief Rationale
9.1. Statistical Hypotheses	Deleted statistical hypotheses and added clarification as “No formal statistical hypotheses are planned to be tested in this study.” Delete multiplicity adjustment related description.	Adjustment according to China NMPA feedback on bridging strategy
9.2 Analysis Sets	Added “without using rescue medication” to specify the requirement for Maintenance Period Primary Population Updated the description of analysis sets to separate the population sets of placebo responder and participants who escape at Week 16.	Clarification
9.3.1 General Considerations	Delete 2-sided alpha level and updated the statistical analyses to descriptive.	Adjustment according to China NMPA feedback on bridging strategy
9.3.2 Primary Endpoint(s)/Estimand(s) Analysis	Modified the primary analysis for the combo cohort to Bayesian model; specified the primary analysis for the mono cohort.	Adjustment according to China NMPA feedback on bridging strategy
9.3.3 Secondary Endpoint Analysis	Updated analysis method for secondary endpoint analysis.	Adjustment according to China NMPA feedback on bridging strategy
9.4 Interim Analysis	Deleted unblinding information and refer to Section 6.4.	Correction and editorial consistency
	Added “Additional database lock/snapshot may be conducted for regulatory interaction purpose.”	Added for potential regulatory interaction
9.5 Sample Size Determination	Updated sample size and its determination rationale.	Adjustment according to China NMPA feedback on bridging strategy
9.6 Data Monitoring Committee	Changed “blinded” to “unblinded”; deleted “have access to the treatment allocation code”	Correction
10.1.3 Informed Consent Process	Added “(or the acceptable age according to local regulations, whichever is older)” due to the age of adulthood varies by country.	Clarification that the re-consent to be obtained at the time of becoming an adult according to local regulation
10.9 Appendix 9: Provisions for Changes in Study Conduct During	Deleted unscheduled visit for central laboratory testing of PK and immunogenicity.	Clarification

Section # and Name	Description of Change	Brief Rationale
Exceptional Circumstances		
11 References	Delete "Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. <i>J Clin Nurs</i> . 2005;14:(7)798-804."	Editorial consistency

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1. Protocol Summary

1.1. Synopsis

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

Brief Title:

Efficacy and Safety of Lebrikizumab with/without Topical Corticosteroid Treatment in Participants with Moderate-to-Severe Atopic Dermatitis

Regulatory Agency Identifier Number(s): Not Applicable

Rationale:

The use of lebrikizumab for atopic dermatitis (AD) is supported by numerous preclinical studies demonstrating that AD is characterized by the increased expression of interleukin (IL)-13 in skin. Moreover, phase 3 clinical studies (Studies J2T-DM-KGAB [KGAB], J2T-DM-KGAC [KGAC], J2T-DM-KGAD [KGAD], J2T-DM-KGAE [KGAE] and J2T-DM-KGAA [KGAA]) with lebrikizumab demonstrated significant clinical benefit in participants with AD with a consistent safety profile across studies and a positive benefit risk assessment. Additional detailed discussion of the lebrikizumab studies is provided in the lebrikizumab Investigator's Brochure (IB).

Objectives, Endpoints, and Estimands:

Objectives		Endpoints
Combo Cohort	Mono Cohort	
Co-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 with a reduction of ≥ 2 points from baseline
Major Secondary		

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 in combination with TCS treatment	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	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
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Abbreviations: AD = atopic dermatitis; EASI = Eczema Area and Severity Index; EASI-75 = $\geq 75\%$ reduction from baseline in EASI score; EASI-90 = $\geq 90\%$ reduction from baseline in EASI score; IGA = Investigator's Global Assessment; NRS = numeric rating scale; Q2W = every 2 weeks; Q4W = every 4 weeks; TCS = topical corticosteroid.

Primary Estimand for Combo Cohort

The primary clinical question of interest is: what is the difference between treatment conditions, i.e., lebrikizumab + topical corticosteroid (TCS) versus (vs) placebo + TCS, in the target participant population in achieving successful responses at Week 16 without 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/Exclusion (I/E) criteria to reflect the targeted participant population for approval
- Endpoints: Proportion of participants achieving 75% reduction from baseline in Eczema Area and Severity Index score (EASI-75) at Week 16, and proportion of participants achieving Investigator's Global Assessment (IGA) score of 0 or 1 with a reduction of ≥ 2 points from baseline at Week 16.
- How to account for intercurrent events (ICEs)
 - Participants who require any use of rescue medication or discontinued treatment due to lack of efficacy prior to Week 16 will be considered as treatment failures, i.e., non-responder, after the ICEs. Therefore, composite strategy is used for these types of ICEs.
 - For participants who discontinue treatment due to any other reasons prior to Week 16, a hypothetical strategy will be used to estimate what the treatment effect would have been if participants continued with treatment. Therefore, hypothetical strategy is used for these types of ICEs.

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

Primary Estimand for Mono Cohort

The primary clinical question of interest is: what is the difference between treatment conditions, i.e., lebrikizumab vs placebo, in the target participant population, in achieving successful responses at Week 16 without 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 I/E criteria to reflect the targeted participant population for approval
- Endpoints: Proportion of participants achieving EASI-75 at Week 16, and proportion of participants achieving IGA score of 0 or 1 with a reduction of ≥ 2 points from baseline at Week 16.
- How to account for ICEs
 - a. Participants who require any use of rescue medication or discontinued treatment due to lack of efficacy prior to Week 16 will be considered as treatment failures, i.e., non-responder, after the ICEs. Therefore, composite strategy is used for these types of ICEs.
 - b. For participants who discontinue treatment due to any other reasons prior to Week 16, a hypothetical strategy will be used to estimate what the treatment effect would have been if participants continued with treatment. Therefore, hypothetical strategy is used for these types of ICEs.
- Population-level summary: difference in response proportions at Week 16 between treatment conditions

Overall Design:

This 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/without TCS treatment using a 16-week Induction Period and a 36-week Maintenance Period of lebrikizumab for participants with moderate to severe AD.

Enrolled participants will be assigned to either the combo cohort (lebrikizumab/placebo + TCS) or mono cohort (lebrikizumab/placebo) based on investigator's decision.

Either in the combo or mono cohort, participants will be randomized in a 2:1 ratio to lebrikizumab 250 mg every 2 weeks (Q2W) or placebo within cohort. The 16-week Induction Period will be double blinded. After completion of the Week 16 visit, Week 16 responders (achieving an Investigator's Global Assessment [IGA] of 0 or 1 and/or EASI-75) who were originally assigned to lebrikizumab 250 mg Q2W will be re-randomized in a 1:1 ratio to either lebrikizumab 250 mg every 4 weeks (Q4W) or lebrikizumab 250 mg every 8 weeks (Q8W)

within the cohort, and Week 16 responders who originally assigned to placebo in each cohort will continue to receive placebo for the Maintenance Period. Week 16 non-responders and participants who received rescue treatment in the Induction Period will move to the Escape Arm from Week 16. Treatment regimen assignment will remain blinded during the Maintenance Period.

Either in the combo or mono cohort, participants who do not maintain an EASI-50 response at certain time points in the Maintenance Period will be assigned to the Escape Arm and will 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 certain period of treatment will be terminated from the study.

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

Participants who terminate early or complete the 52-week treatment period will undergo a safety follow-up visit approximately 12 weeks after the last study intervention injection.

Brief Summary:

The purpose of this study is to evaluate the efficacy and safety of lebrikizumab compared with placebo when used with/without TCS in participants with moderate-to-severe AD.

Study details include:

- The study duration will be approximately 64 weeks (Screening: maximum duration of 30 days; treatment duration: 52 weeks; safety follow-up: 12 weeks from the last study intervention injection).
- The treatment duration will be up to 52 weeks including a 16-week Induction Period and 36-week Maintenance Period.
- The visit frequency will be every 2 weeks for Induction Period and then every 4 weeks for Maintenance Period. Participants who enter the Escape Arm will come to the clinic every 2 weeks for study intervention injection.

Study Population:

Participants are eligible for the study 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 American Academy of Dermatology (AAD) Consensus Criteria (Eichenfield et al. 2014); or have chronic eczema and meet the AAD criteria
- have an EASI score ≥ 16
- have an Investigator's Global Assessment (IGA) score ≥ 3 , and
- Have $\geq 10\%$ body surface area (BSA) of AD involvement

Number of Participants:

Approximately 280 participants, including approximately 58 adolescent participants (≥ 12 to < 18 years and weighing ≥ 40 kg), will be enrolled. China and Korea intend to participate in the study.

Intervention Groups and Duration:**Induction Period (16 weeks)**

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 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).

Maintenance Period (36 weeks) (either in the combo or mono cohort)

After completion of the Week 16 visit:

- Participants receiving lebrikizumab 250 mg Q2W
 - who achieve an IGA 0 or 1 and/or a $\geq 75\%$ reduction in EASI score ($\geq$ EASI-75) response at Week 16 will be randomly allocated to receive lebrikizumab 250 mg Q4W or Q8W, in a 1:1 fashion within the cohort;
 - who achieve neither an IGA 0 or 1 nor a 75% reduction in EASI score ($<$ EASI-75) response at Week 16 will enter the Escape Arm.
- Participants receiving placebo
 - who achieve an IGA 0 or 1 and/or an EASI-75 response ($\geq$ EASI-75) at Week 16 will continue to receive placebo;
 - who achieve neither an IGA 0 or 1 nor an EASI-75 response ($<$ 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 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 an 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.

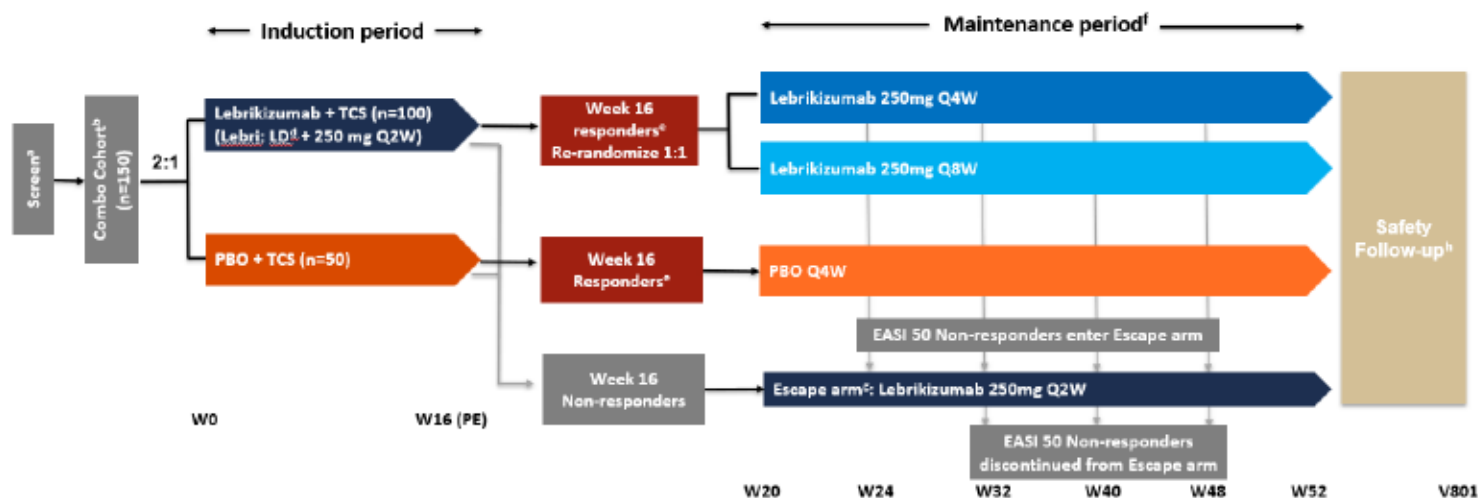
Ethical Considerations of Benefit/Risk:

Based on the cumulative knowledge, lebrikizumab has a positive benefit/risk profile and is assessed to be acceptable for testing in this phase 3 study, which will help fulfill an unmet need for adults and adolescents with AD who have not been able to achieve disease improvements with currently available treatment options.

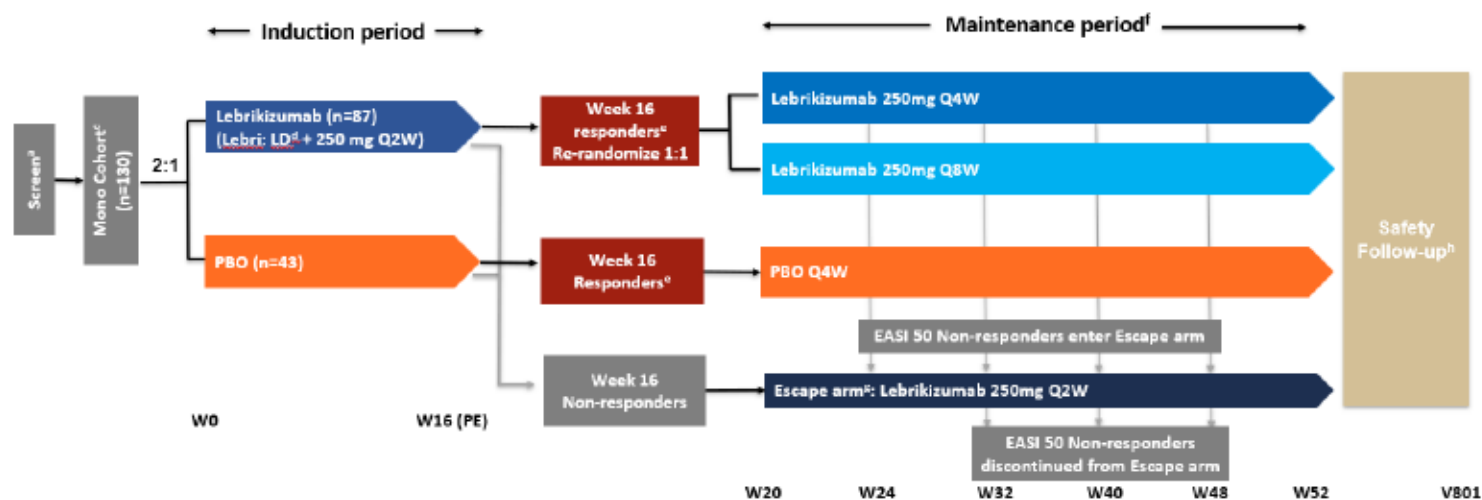
Data Monitoring Committee: Yes

1.2. Schema

Combo Cohort:



Mono Cohort:



Abbreviations: EASI = Eczema Area and Severity Index; F/U = follow up; IGA = Investigator's Global Assessment; LD = loading dose; PBO = placebo; PE = primary endpoint; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; W = week.

- a. Enrollment will be stopped in either combo or mono cohort once the participant number reaches the planned number.
- b. Participants in combo cohort: daily use of mid-potency TCS (low potency TCS and/or TCI for sensitive areas) will be initiated at least 7 days prior to baseline (not allowed to be tapered or stopped during the Screening Period) until Week 16.
- c. Participants in mono cohort: a washout period of TCS and/or TCI for 7 days prior to baseline is required.
- d. LD: 500 mg at baseline and Week 2 as loading dose.
- e. Week 16 responder is defined as having an IGA of 0 or 1 and/or an EASI-75 response (75% reduction in EASI from baseline to Week 16).
- f. Low to mid-potency TCS can be used when needed per the investigator's opinion during Maintenance Period.
- g. 500 mg at Week 16 and Week 18 as loading dose for participants who receive placebo during Induction period.
- h. The safety follow-up visit will occur approximately 12 weeks after last study intervention injection.

1.3. Schedule of Activities (SoA)

Table 1. Induction Period: Screening through Week 16

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
Informed consent/assent	X										
Inclusion and exclusion criteria	X	X									
Medical history	X										
Demography	X										
Review of immunization record	X										Adolescents only
IWRS entry	X	X	X	X	X	X	X	X	X	X	
Randomization		X								X	
Dispense background TCS	X	X	X	X	X	X	X	X	X	X	Combo cohort only
Weigh (tube with cap) and record returned background TCS			X	X	X	X	X	X	X	X	Combo cohort only
Dispense and administer study intervention		X	X	X	X	X	X	X	X	X	Administered by site personnel. At Visits 2 and 3: 2 injections At Visit 10 for participants in the Escape Arm: 2 injections All other visits: 1 injection
Safety											
Vital signs	X	X	X	X	X	X	X	X	X	X	

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
Physical examination including height and weight	X									X	Complete physical examination will perform at screening. Symptom-directed physical assessment will perform at other times as shown here and as needed based on participant status and standard of care. May be performed by qualified personnel per local regulations. Assess for TB risk factors, and for signs and symptoms of active TB, including an assessment of peripheral lymph nodes. See Sections 8.2.1
12-lead ECG (single)	X										A local ECG will be collected according to instructions in Section 8.2.3. Abnormalities recorded as AEs.
Chest x-ray (posterior-anterior view)	X										Will be performed locally at screening (Section 8.2.5). Abnormalities recorded as AEs.
Prior therapy	X										
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	
Investigator Scales											
IGA, EASI (including BSA)	X	X	X	X	X	X	X	X	X	X	
SCORing Atopic Dermatitis (objective) (SCORAD)		X	X	X	X	X	X	X	X	X	
Health Outcome Measures and Other Questionnaires											

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
Itch NRS, Sleep-Loss Scale, Skin Pain NRS (daily)	X	X (Will be collected daily via an electronic participant diary)									The baseline for the daily assessments will be the average score of the 7 days prior to randomization.
POEM (weekly)	X	X (Will be collected weekly via an electronic participant diary)									The baseline for the weekly assessments will be the score acquired closest to randomization.
SCORing Atopic Dermatitis (subjective) (SCORAD)		X	X	X	X	X	X	X	X	X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
DLQI		X				X				X	Only for participants ≥16 years of age at baseline. Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
CDLQI		X				X				X	Only for participants <16 years of age at baseline. Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
EQ-5D-5L		X								X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
WPAI-AD		X				X				X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
HADS	X	X		X		X		X		X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
ACQ-5	X	X								X	Participants who report comorbid asthma prior to enrollment only. Will be collected as paper form. Will be completed by the participant prior to any clinical assessments on days of study visits.
Laboratory Testing											
TB test (PPD TST, T-SPOT® or QuantiFERON®-TB Gold)	X										See Sections 8.2.6 and 10.2 for description of TB testing.
Hematology, clinical chemistry	X	X		X		X		X		X	See Section 10.2, Clinical Laboratory Tests, for details.

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
Pregnancy test	serum	urine	urine	urine	urine	urine	urine	urine	urine	urine	For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests will be performed locally and not captured in eCRF.
FSH	X										For female participants who are >40 to ≤55 years of age.
HIV, HCV, HBV screening tests	X										For participants who are positive for HCV antibody, a follow-up test for circulating HCV RNA is required. Participants who are positive for HCV antibody and negative for HCV RNA may be enrolled.
HBV DNA	X							X			For participants who are HBsAg negative and positive for HbcAb, further testing for HBV DNA is required at screening. If screening HBV DNA is negative, defined as undetectable HBV DNA, the participant is not excluded, and HBV DNA monitoring is required per the schedule. (Section 8.2.7).
Urinalysis	X	X								X	

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
Lebrikizumab PK samples				X				X		X	PK samples should be collected prior to dosing on days of dosing. Additional samples can be collected for any participants experiencing a hypersensitivity reaction during study (Section 8.2.11).
Immunogenicity samples		X		X						X	Immunogenicity samples should be collected prior to dosing on days of dosing. Additional sample can be collected for any participants experiencing a hypersensitivity reaction during study (Section 8.2.11).

Table 2. Maintenance Period: Week 18 to Week 52/Escape Arm

	Maintenance Period										Safety F/U	Comments
Visit Number	11	12	13	14	15	16	17	18	19	20/ET	801	
Weeks from Randomization	18	20	24	28	32	36	40	44	48	52/ET	12 weeks after Last Dose	
Days from Randomization	126	140	168	196	224	252	280	308	336	364		
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	
IWRS entry	X	X	X	X	X	X	X	X	X	X	X	
Dispense background TCS	X	X	X	X	X	X	X	X	X			Combo cohort only

	Maintenance Period										Safety F/U	Comments
Visit Number	11	12	13	14	15	16	17	18	19	20/ET	801	
Weeks from Randomization	18	20	24	28	32	36	40	44	48	52/ET	12 weeks after Last Dose	
Days from Randomization	126	140	168	196	224	252	280	308	336	364		
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	
Weigh (tube with cap) and record returned background TCS	X	X	X	X	X	X	X	X	X	X		Combo cohort only
Dispense and administer study intervention	X (only escape arm)	X (every 4 weeks [± 5 days] for Lebrikizumab Q4W and Q8W arms through Week 48; every 2 weeks [± 5 days] for Escape arm through Week 50)										Administered by site personnel. At Visit 11, for participants in the Escape Arm: 2 injections. All other visits: 1 injection. Participants in the Escape arm will come to the site every 2 weeks for study intervention administration.
Safety												
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Physical examination including height and weight				X			X			X		Symptom-directed physical assessment will perform as shown here and as needed based on participant status and standard of care. May be performed by qualified personnel per local regulations. Assess for TB risk factors, and for signs and symptoms of active TB, including an assessment of peripheral lymph nodes. See Section 8.2.1.
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	
Investigator Scales												
IGA, EASI (including BSA)	X	X	X	X	X	X	X	X	X	X	X	

	Maintenance Period										Safety F/U	Comments
Visit Number	11	12	13	14	15	16	17	18	19	20/ET	801	
Weeks from Randomization	18	20	24	28	32	36	40	44	48	52/ET	12 weeks after Last Dose	
Days from Randomization	126	140	168	196	224	252	280	308	336	364		
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	
SCORing Atopic Dermatitis (objective) (SCORAD)	X	X	X	X	X	X	X	X	X	X	X	
Health Outcomes Measures and Other Questionnaires												
Itch NRS, Sleep-Loss Scale, Skin Pain NRS	X (Will be collected daily via an electronic participant diary)											
POEM (weekly)	X (Will be collected weekly via an electronic participant diary)											
SCORing Atopic Dermatitis (subjective) (SCORAD)	X	X	X	X	X	X	X	X	X	X	X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
DLQI				X			X			X	X	Only for participants ≥16 years of age at baseline. Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
CDLQI				X			X			X	X	Only for participants <16 years of age at baseline. Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
EQ-5D-5L										X		Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.

	Maintenance Period										Safety F/U	Comments
Visit Number	11	12	13	14	15	16	17	18	19	20/ET	801	
Weeks from Randomization	18	20	24	28	32	36	40	44	48	52/ET	12 weeks after Last Dose	
Days from Randomization	126	140	168	196	224	252	280	308	336	364		
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	
WPAI-AD				X			X			X		Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
HADS		X	X	X	X	X	X	X	X	X	X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
ACQ-5										X		Participants who report comorbid asthma prior to enrollment only. Will be collected as paper form. Will be completed by the participant prior to any clinical assessments on days of study visits.
Laboratory Testing												
Hematology, clinical chemistry		X		X		X		X		X		See Section 10.2, Clinical Laboratory Tests, for details.
Pregnancy test	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	Urine pregnancy tests will be performed locally and not captured in the eCRF. If required per investigator judgment, local regulations, and/or institutional guidelines, additional pregnancy testing can occur during the study treatment period.
HBV DNA			X			X			X		X	If screening HBV DNA is negative, defined as undetectable HBV DNA, the participant is not excluded, and

	Maintenance Period										Safety F/U	Comments
Visit Number	11	12	13	14	15	16	17	18	19	20/ET	801	
Weeks from Randomization	18	20	24	28	32	36	40	44	48	52/ET	12 weeks after Last Dose	
Days from Randomization	126	140	168	196	224	252	280	308	336	364		
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	
												HBV DNA monitoring is required per the schedule (Section 8.2.7).
Urinalysis					X					X		
Lebrikizumab PK samples			X		X				X	X	X	PK samples should be collected prior to dosing on days of dosing. Additional sample can be collected for any participants experiencing a hypersensitivity reaction during the study (Section 8.2.11).
Immunogenicity samples					X					X	X	Immunogenicity samples should be collected prior to dosing on days of dosing. Additional sample can be collected for any participants experiencing a hypersensitivity reaction during the study (Section 8.2.11).

Abbreviations: ACQ-5 = Asthma Control Questionnaire-5; AE = adverse event; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eCOA = electronic clinical outcome assessment; eCRF = electronic case report form; ET = early termination; FSH = follicle-stimulating hormone; HADS = Hospital Anxiety Depression Scale; HBcAb = hepatitis B core antibody; HbsAb = hepatitis B surface antibody; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGA = Investigator's Global Assessment; IWRS = interactive web response system; NRS = numeric rating scale; PK = pharmacokinetic; POEM = Patient-Oriented Eczema Measure; PPD = purified protein derivative; Q4W = every 4 weeks; Q8W = every 8 weeks; SCORAD = SCORing Atopic Dermatitis; TB = tuberculosis; TCS = topical corticosteroid; WPAI-AD = Work Productivity and Activity Impairment-Atopic Dermatitis.

2. Introduction

Lebrikizumab is a monoclonal immunoglobulin (Ig) G4 antibody (huIgG4) currently under investigation for the treatment of AD.

2.1. Study Rationale

The use of lebrikizumab for AD is supported by numerous preclinical studies demonstrating that AD is characterized by the increased expression of IL-13 in skin. Moreover, phase 3 clinical studies (Studies KGAB, KGAC, KGAD, KGAE and KGAA) with lebrikizumab demonstrated significant clinical benefit in participants with AD with a consistent safety profile across trials and a positive benefit risk assessment. Additional detailed discussion of the lebrikizumab studies is provided in the lebrikizumab Investigator's Brochure (IB).

2.2. Background

AD is a complex disease that is determined by genetic, environmental, and immunologic factors (Werfel et al. 2016; Simon et al. 2019). Genetic studies of AD (Bieber 2012; Auriemma et al. 2013; Weidinger et al. 2018) have shown that genes encoding for cytokines involved in the regulation of the immune system (IL-4, IL-5, and IL-13) are strongly associated with the development of AD (Novak et al. 2002; He et al. 2003; Hummelshoj et al. 2003). In addition, variants of genes that encode for proteins involved in skin barrier function such as filaggrin (FLG) and loricrin (LOR) are also associated with AD (Van Bever and Llanora. 2011). Since FLG plays a central role in skin barrier integrity, loss of function mutations of the FLG gene are considered a major contributor to the development of early childhood AD (Bieber 2008; Tanei 2009; Bieber 2012; Flohr and Irvine 2013).

Reduced epithelial barrier function, which represents the first line of protection against the environment, is thought to lead to sensitization to environmental allergens, associated with elevated IgE (present in about 50% to 80% of all patients with AD, particularly in children [Werfel et al. 2016]) and consistent with the presence in the skin of Type 2 cytokines (IL-4, IL-5, IL-9, IL-13, IL-25, IL-31, IL-33, and thymic stromal lymphopoietin) and inflammation. Type 2 cytokines increase epidermal thickening, sensitization, inflammation, and pruritus and decrease the expression of antimicrobial peptides and the barrier proteins FLG, LOR, and involucrin. IL-13 in particular can reduce epithelial integrity and barrier function through downregulation of FLG, LOR, and involucrin (Kim et al. 2008) and can act on keratinocytes in the skin to downregulate their differentiation (Howell et al. 2008). IL-13 also induces T-cell chemoattractants that mediate T-cell infiltration into AD lesions (Purwar et al. 2006) and may also induce IL-5 expression and eosinophil infiltration through the induction of eosinophil chemoattractants (Esche et al. 2004). Increased expression of IL-13 has consistently been reported in AD skin lesions and is associated with disease severity (Hamid et al. 1996; Jeong et al. 2003; Tazawa et al. 2004; La Grutta et al. 2005; Neis et al. 2006; Choy et al. 2012; Suárez-Fariñas et al. 2013). The elevation of IL-13 expression in the nonlesional skin of patients with AD supports the evaluation of anti-IL-13 therapies in patients with AD (Suárez-Fariñas et al. 2011).

Epidemiology of Pediatric Atopic Dermatitis

Atopic dermatitis is one of the most common chronic medical diseases; 15% to 30% of children and 2% to 10% of adults are affected, and the prevalence appears to have increased over the past 2 to 3 decades (Williams et al. 2008), with some geographic variability. With respect to disease severity, about 67% of pediatric patients with AD have mild disease, 14% to 26% have moderate disease, and 2% to 7% have severe disease (Silverberg 2017). Approximately 85% of all cases of AD begin before age 5, with up to 70% of children having spontaneous remission before adolescence (Illi et al. 2004; Bieber 2008; Hua et al. 2014). With the improvement of living environments, the prevalence of AD in China has increased during the past decade (AD working group, CSD. 2020). The prevalence of AD in Chinese adults was approximately 6% based on a cross-sectional survey conducted in 2017 (Mao et al. 2023).

Clinical Manifestations

Clinically, AD is characterized by xerosis, erythematous crusted eruption (dermatosis), lichenification, and intense pruritus (Bieber 2008), which, along with the distribution, chronicity, and history of skin lesions, form the basis for making a diagnosis of AD. Flares are frequently triggered by exposure to environmental factors, irritants, and allergens (Bieber and Novak 2009). Several clinical patterns, with differing distributions of skin lesions in distinct age groups, have been noted (Weidinger and Novak 2016; Weidinger et al. 2018).

The infantile stage (up to 2 years of age) is characterized by eczema that is usually localized to the face, scalp, and extensor aspects of the arms and legs. The lesions are characterized by pruritic red eczematous plaques, erythema, papules, vesicles, excoriations, oozing, and formation of crusts.

The adult stage (from age 2 years to puberty and onward) is less predictable. Affected patients may have had only a few outbreaks since infancy, or they may have had a chronic relapsing course. Lesions frequently localize to the face and neck (head-and-neck dermatitis), as well in the flexures of the elbows and knees, and a considerable portion of patients (around 30%) develop atopic hand eczema, which may interfere with workplace activities. Like affected children, adolescents and adults commonly have lichenification of the flexures and have facial dermatitis.

Patients with AD have a high disease burden, and their quality of life is significantly affected. In one study, AD was shown to have a greater negative effect on patient mental health than diabetes and hypertension (Zuberbier et al. 2006). Patients with moderate-to-severe AD have a higher prevalence of social dysfunction and sleep impairment, which are directly related to the severity of the disease (Williams et al. 2008). Depression, anxiety, and social dysfunction not only affect patients with AD but also affect their caregivers (Zuberbier et al. 2006). Compared with patients with psoriasis, another common and debilitating skin disease, patients with AD have lower physical vitality, social functioning, role-emotional, and mental health scores as measured by the Medical Outcomes Study Short Form-36 Health Survey (SF-36) and the Dermatology Life Quality Index (DLQI) or the Children's Dermatology Life Quality Index (CDLQI) (Kiebert et al. 2002).

Treatment for Atopic Dermatitis

The therapeutic approach to AD consists primarily of trigger avoidance, skin hydration with bathing, and use of moisturizers and anti-inflammatory therapies consisting predominantly of TCS. In many patients, treatment with TCS provides some measure of symptomatic relief but does not always adequately control the disease. In patients with persistent moderate-to-severe disease not responding adequately to TCS, the step-up options include topical calcineurin inhibitors (TCIs), phototherapy, and immunosuppressive agents such as oral corticosteroids, cyclosporine, azathioprine, methotrexate (MTX), and mycophenolate mofetil (MMF). Recently, in June 2020, a clinically efficacious and relatively safe treatment, anti-IL-4R monoclonal antibody, dupilumab, was approved for the treatment of adult and adolescent patients with moderate-to-severe AD in China. Despite these treatments, there remains a major disease burden for those with AD and a significant unmet medical need for treatment.

2.3. Benefit/Risk Assessment

As of 01 May 2023, cumulatively, approximately 8344 participants have been enrolled into the lebrikizumab clinical program, of which approximately 6912 participants have received lebrikizumab. Lebrikizumab has been given to 552 healthy people and 6360 study participants with AD, asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and Hodgkin's lymphoma. Approximately 2562 have been treated with lebrikizumab in the phase 2 and phase 3 AD programs.

The use of lebrikizumab for the treatment of AD is supported by numerous preclinical studies demonstrating that AD is characterized by the increased expression of IL-13 in skin. Moreover, phase 2 efficacy studies of lebrikizumab (J2T-DM-KGAG [KGAG]/TREBLE, J2T-DM-KGAH [KGAH]/ARBAN and J2T-DM-KGAF [KGAF]/DRM06-AD01) demonstrated significant clinical benefit in participants with AD. The top-line results from the 2 monotherapy phase 3 studies of lebrikizumab (Studies KGAB and KGAC) achieved the primary and all key secondary endpoints, including skin clearance and itch improvement at Week 16. A third completed pivotal phase 3 trial of lebrikizumab in combination with topical steroids (Study KGAD) also met all primary and key secondary endpoints at Week 16.

Potential risks associated with lebrikizumab include conjunctivitis, eosinophilia and eosinophilic conditions, herpes zoster and herpes infections (Section 8.3.3), anaphylaxis and hypersensitivity reactions (Section 8.2.11), keratitis, injection site reactions (ISRs) (Section 8.2.10) and other infections (Section 8.3.3.1).

In the initial 16-week placebo-controlled period of Studies KGAB and KGAC, the incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) among patients treated with lebrikizumab was similar with those patients treated with placebo, which was consistent with that of the previous phase 2 lebrikizumab studies in AD. The most common adverse events (AEs) included conjunctivitis, nasopharyngitis, and headache for lebrikizumab-treated patients. Four deaths were reported in the lebrikizumab treatment group, none of which were assessed by the investigator as related to treatment. Discontinuations due to AEs were similar in the lebrikizumab group (1.4%) compared to placebo (1.7%). The safety profile of lebrikizumab observed in the 3 phase 3 studies was found to be consistent with prior lebrikizumab studies in AD.

No serious immediate hypersensitivity or anaphylaxis events were reported in the phase 3 studies (Studies KGAB, KGAC and KGAD). No parasitic or opportunistic infections were reported. No eosinophilic related events were reported.

Participants will be monitored for these events and will be provided appropriate intervention or supportive care as needed. If events occur, additional testing and data collection may be required as described further in Sections 8.3.3.1 and 8.2.11.

Additionally, to monitor participant safety during the course of the study, the sponsor will conduct trial-level safety reviews at periodic intervals throughout the study.

In summary, in the context of the cumulative knowledge for lebrikizumab, the benefit/risk balance is assessed to be acceptable for testing in this Phase 3 study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of lebrikizumab may be found in the IB.

3. Objectives, Endpoints, and Estimands

Objectives		Endpoints
Combo Cohort	Mono Cohort	
Co-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 with a reduction of ≥ 2 points from baseline
Major Secondary		
To compare the efficacy and health outcome measures of lebrikizumab 250 mg Q2W to placebo during the 16-week Induction (Week 0 to 16) Period in participants with moderate-to-severe AD when used in combination with TCS treatment	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	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 250 mg Q2W during the 16-week Induction (Week 0 to 16) and 36-week Maintenance (Week 16 to 52) Periods in participants with moderate-to-severe AD when used in combination with TCS treatment	To evaluate the efficacy and health outcome measures of lebrikizumab 250 mg Q2W during the 16-week Induction (Week 0 to 16) and 36-week Maintenance (Week 16 to 52) Periods 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 - 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 and 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 ≥ 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 - DLQI - CDLQI - POEM - WPAI-AD - HADS - EQ-5D-5L index
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		- Change from baseline in ACQ-5 score to Week 16 in participants who have self-reported comorbid asthma - Number of Skin Pain-Free days (Skin Pain NRS = 0)
To evaluate the efficacy of lebrikizumab 250 mg Q2W during the 16-week Induction (Week 0 to 16) 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 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 - 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; ADA = anti-drug antibody; 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 and Severity Index; EASI-50 = $\geq 50\%$ reduction from baseline in EASI score; EASI-75 = $\geq 75\%$ reduction from baseline in EASI score; EASI-90 = $\geq 90\%$ reduction from baseline in EASI score; HADS = Hospital Anxiety Depression Scale; IGA = Investigator's Global Assessment; NRS = numeric rating scale; POEM = Patient-Oriented Eczema Measure; Q2W = every 2 weeks; SAE = serious adverse event; SCORAD = SCORing Atopic Dermatitis; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid; TE = treatment-emergent; TEAE = treatment-emergent adverse event; WPAI-AD = Work Productivity and Activity Impairment-Atopic Dermatitis.

Primary Estimand for Combo Cohort

The primary clinical question of interest is: what is the difference between treatment conditions, i.e., lebrikizumab + TCS vs placebo +TCS, in the target participant population in achieving successful responses at Week 16 without 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 I/E criteria to reflect the targeted participant population for approval
- Endpoints:** Proportion of participants achieving EASI-75 at Week 16, and proportion of participants achieving IGA score of 0 or 1 with a reduction of ≥ 2 points from baseline at Week 16
- How to account for intercurrent events (ICEs)**

- a. Participants who require any use of rescue medication or discontinued treatment due to lack of efficacy prior to Week 16 will be considered as treatment failures, i.e., non-responder, after the ICEs. Therefore, composite strategy is used for these types of ICEs.
 - b. For participants who discontinue treatment due to any other reasons prior to Week 16, a hypothetical strategy will be used to estimate what the treatment effect would have been if participants continued with treatment. Therefore, hypothetical strategy is used for these types of ICEs.
- **Population-level summary:** difference in response proportions at Week 16 between treatment conditions

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 Mono Cohort

The primary clinical question of interest is: what is the difference between treatment conditions, i.e., lebrikizumab vs placebo, in the target participant population in achieving successful responses at Week 16 without 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 I/E criteria to reflect the targeted participant population for approval
- **Endpoints:** Proportion of participants achieving EASI-75 at Week 16, and proportion of participants achieving IGA score of 0 or 1 with a reduction of ≥ 2 points from baseline at Week 16
- **How to account for ICEs**
 - a. Participants who require any use of rescue medication or discontinued treatment due to lack of efficacy prior to Week 16 will be considered as treatment failures, i.e., non-responder, after the ICEs. Therefore, composite strategy is used for these types of ICEs.
 - b. For participants who discontinue treatment due to any other reasons prior to Week 16, a hypothetical strategy will be used to estimate what the treatment effect would have been if participants continued with treatment. Therefore, hypothetical strategy is used for these types of ICEs.
- **Population-level summary:** difference in response proportions at Week 16 between treatment conditions

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

4. Study Design

4.1. Overall Design

Study Design

This 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/without TCS treatment using a 16-week induction period and a 36-week maintenance period of lebrikizumab for participants with moderate-to-severe AD.

Study Population

Participants are eligible for the study 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 (Section 10.8, Appendix 8)
- have an EASI score ≥ 16
- have an IGA score ≥ 3 , and
- Have $\geq 10\%$ BSA of AD involvement

Investigators should review vaccination status in adolescent participants (≥ 12 to < 18 years) and determine the benefit/risk of their participation. Prior to initiating therapy, consider completion of all age-appropriate immunizations according to current local immunization guidelines. No change in 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 (see exclusion criterion [27]).

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 SC injection 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 vs ≥ 18 years) and disease severity (IGA 3 vs 4). For mono cohort, participants will be stratified by age (adolescent participants ≥ 12 to < 18 years vs ≥ 18 years), disease severity (IGA 3 vs 4), and country (China vs Korea). TCS and/or TCI 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 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 (Section 6.1.1).

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 0 or 1 and/or a $\geq 75\%$ reduction in EASI score ($\geq$ EASI-75) response at Week 16 will be randomly allocated to receive lebrikizumab 250 mg Q4W or Q8W, in a 1:1 fashion within the cohort;
 - who achieve neither an IGA 0 or 1 nor a 75% reduction in EASI score ($<$ EASI-75) response at Week 16 will enter the Escape Arm.
- Participants receiving placebo
 - who achieve an IGA 0 or 1 and/or an EASI-75 response ($\geq$ EASI-75) at Week 16 will continue to receive placebo;
 - who achieve neither an IGA 0 or 1 nor an EASI-75 response ($<$ 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, see Section 6.9.1 for details.

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, see Section 6.9.1 for details.

Escape Arm from Week 16:

- Participants who achieve neither an IGA 0 or 1 nor an EASI-75 response (<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 an 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) (Section 1.3).

Efficacy, Health Outcomes, and Safety Assessments

The efficacy, health outcomes and safety assessments are described in Sections 8.1 and 8.2, respectively.

Serum samples will be collected for pharmacokinetic (PK) analysis and immunogenicity (Section 8.5 and 8.8).

4.2. Scientific Rationale for Study Design

Participants enrolled

Unmet need in AD patients

Participants with moderate-to-severe, chronic AD will be enrolled in this study due to the unmet need for this population.

Inclusion of adolescent participants

In this phase 3 study, adolescent participants aged ≥ 12 to < 18 years and weighing ≥ 40 kg will be included and receive the same dose of lebrikizumab as for adults. The justification for this approach is that both adult and adolescent patients have similar disease characteristics,

characterized by prominent Type 2 skin inflammation and similar clinical manifestations. Furthermore, both adolescents and adults tend to have similar efficacy outcomes in response to therapies, including dupilumab (Simpson et al. 2018; Treister and Lio. 2019). PK modeling and simulations of lebrikizumab dosing revealed similar kinetics for adults and adolescent patients. The maximal exposures were predicted to be slightly (35% or less) higher in adolescent patients than in adults for any given dose due to the lower adolescent weight ranges and lebrikizumab exposure dependence on weight; however, the safety profile in adolescent patients, based on the exposure-response relationship analysis and on partial extrapolation, is comparable to that observed in adults.

Blinding and randomization

The study design and randomization scheme used is designed to minimize participant exposure to placebo.

- Induction Period: 2:1 ratio of lebrikizumab 250 mg Q2W to placebo Q2W (either in the combo or mono cohort), and
- Maintenance Period: only Week 16 responders in placebo group (either in the combo or mono cohort) from Induction Period will continue to receive placebo.

Double-blind treatment duration

The 16-week duration of the double-blind Induction Period for primary evaluation will allow for sufficient comparison between treatment groups while minimizing possible AEs related to the worsening of AD that could be experienced by participants receiving placebo treatment.

The rerandomization of lebrikizumab induction responders during the Maintenance Period will allow for further comparison between the treatment groups while minimizing possible AEs related to the worsening of AD that could be experienced by participants receiving placebo treatment.

Dosing

Justification for dose is detailed in Section 4.3.

Outcomes

The outcomes used in the study are selected to provide clinically meaningful measures to participants and investigators that are easily described and practical for use in patients with moderate-to-severe AD.

4.2.1. Patient Input into Design

Not applicable.

4.3. Justification for Dose

4.3.1. Rationale for Induction Dosage Recommendation

Initial modeling informed the dose regimens evaluated in the phase 2b dose-ranging Study KGAF, which included appropriate loading dose regimens to rapidly provide steady-state concentrations of lebrikizumab. The loading dose of 500 mg at Week 0 and Week 2 allows

steady-state concentrations to be achieved by Week 4 versus Week 12 when lebrikizumab 250 mg Q2W is administered without a loading dose. Results from Study KGAF also demonstrated a dose-response relationship with the largest improvement compared to placebo observed in patients treated with lebrikizumab 250 mg Q2W through Week 16. Therefore, lebrikizumab 500 mg at Week 0 and Week 2 followed by 250 mg Q2W was selected as the loading and induction dose for Phase 3 to enable a rapid response. The next highest dose, lebrikizumab 250 mg Q4W, also demonstrated significant improvement compared to placebo. Therefore, both lebrikizumab 250 mg Q2W and 250 mg Q4W were selected as maintenance doses in the global phase 3 study to determine whether a lower dosing frequency was adequate once response was achieved, or whether the induction dosing frequency should be continued.

Results from the phase 3 program (Studies KGAB, KGAC and KGAD) demonstrated that treatment with lebrikizumab 250 mg Q2W through Week 16 provided improvements compared to placebo across numerous clinically relevant measures of efficacy including skin inflammation related to AD, pruritus, and quality-of-life (QoL) measured by DLQI. Therefore, the same induction dosing regimen will be used in this study.

Adolescent participants

As adult and adolescent patients with AD have similar disease characteristics and have similar efficacy outcomes in response to therapies (Simpson et al. 2020; Treister and Lio. 2019), the same dose of lebrikizumab was used in adolescent participants (≥ 12 to < 18 years of age and weighing ≥ 40 kg) as adults.

Population PK analyses determined that lebrikizumab concentrations were slightly higher for adolescents compared to adults, due to the lower body weight. However, simulations show significant overlap in the lebrikizumab concentrations between adolescents and adults. The average concentration at steady state ($C_{avg,ss}$) for adolescents and adults after lebrikizumab 250 mg Q2W dosing was CCI. The $C_{avg,ss}$ for adolescents and adults after 250 mg Q4W dosing was CCI. The resulting PK exposure for adolescents was CCI higher than adults, driven by their lower mean body weight. The observed Week 16 concentrations from the phase 3 studies showed a similar trend.

This difference in exposure did not translate to a clinically relevant difference in efficacy results in adolescents compared to adults (adolescents versus adults receiving lebrikizumab 250 mg Q2W in Studies KGAB and KGAC at Week 16: 47% vs 37% achieved IGA 0,1 and 62% vs 55% achieved EASI-75). Further, subgroup analyses for clinical safety suggested that the safety profile of lebrikizumab was similar across adults and adolescents with no clinically relevant impact on adolescent growth.

4.3.2. Rationale for Maintenance Dosage Recommendation

Participants in Studies KGAB and KGAC who were treated with lebrikizumab and achieved protocol-defined clinical response at Week 16 maintained higher response rates when continuing on lebrikizumab 250 mg treatment, with either Q4W or Q2W dosing, compared to those who switched to placebo (lebrikizumab withdrawal).

Similarly, participants in Study KGAD who were treated with lebrikizumab + TCS and achieved protocol-defined clinical response at Week 16 showed maintenance of treatment effects in Study KGAA.

These clinical findings are supported by exposure-response (E-R) modeling suggesting that adequate clinical response can be maintained with the less frequent maintenance dosing of 250 mg Q4W, and high levels of efficacy were predicted based on the model.

In general, the safety profile was consistent and similar between lebrikizumab 250 mg Q2W and Q4W during the maintenance period. Therefore, the 250 mg Q4W was selected as the maintenance dosing regimen for future studies.

Evaluation of a maintenance dose option of lebrikizumab 250 mg Q8W

The high levels of EASI response observed with the 250 mg Q2W and Q4W regimens in the maintenance period of Studies KGAB and KGAC prompted further exploration into other options for maintenance dosing regimens for lebrikizumab. In addition, the placebo (lebrikizumab withdrawal) arm in the maintenance period exhibited a durable and prolonged efficacy response after the last dose of lebrikizumab at Week 14, with a slow and gradual decline in response noted by Week 52. The long half-life of lebrikizumab (24.5 days, minimum to maximum of 10 to 55 days in Population PK report) also supports the concept of a longer dosing interval in the maintenance phase.

The E-R modeling and simulations suggested that 250 mg Q8W is a reasonable maintenance dosing option for patients who have achieved adequate clinical response in the induction period. For patients with adequate clinical response at Week 16, the predicted EASI-75 response rates at Week 52 were at a high level for both Q4W and Q8W, 80% and 73%, respectively. Other dosing regimens were explored, but the 250 mg Q8W regimen was selected since it was predicted to maintain EASI-75 response rates within 10% of those predicted for 250 mg Q4W.

Although lebrikizumab 250 mg Q8W dosing is not yet studied in clinical trials, lower doses of lebrikizumab, including 125 mg Q4W, were evaluated in the phase 2 AD studies and also phase 3 asthma studies. Based on the linear and dose proportional PK of lebrikizumab, the $C_{avg,ss}$ for lebrikizumab 250 mg Q8W would be equal to 125 mg Q4W.

Therefore, the 250 mg Q8W is selected as an additional maintenance dosing regimen for evaluation in this phase 3 study.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all required phases of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study.

5. Study Population

Participant eligibility for enrollment in the study is based on the criteria listed in this section. The inclusion and exclusion criteria used to determine eligibility should only apply at screening or other specified visits, and not continuously throughout the study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be ≥ 12 years of age inclusive, at the time of signing the informed consent/assent.

Type of Participant and Disease Characteristics

2. Have chronic AD (according to American Academy of Dermatology Consensus Criteria) (Eichenfield et al. 2014) that has been present for ≥ 1 year before the screening visit (Visit 1); or have chronic eczema and meet the AAD criteria (Section 10.8).
3. Have moderate-to-severe AD, including all of the following:
 - a. EASI score ≥ 16 at the baseline visit (Visit 2)
 - b. IGA score ≥ 3 (scale of 0 to 4) at the baseline visit (Visit 2), and
 - c. Have $\geq 10\%$ BSA of AD involvement at the baseline visit (Visit 2).
4. Have a documented history provided by a physician and/or investigator of inadequate response to existing topical medications within 6 months preceding screening as defined by at least 1 of the following:
 - a. Inability to achieve good disease control, defined as mild disease or better (for example, IGA ≤ 2) after use of at least a medium-potency TCS for at least 4 weeks, or for the maximum duration recommended by the product prescribing information (for example, 14 days for super-potent TCS), whichever is shorter. TCS may be used with or without TCIs and/or topical Janus kinase (JAK) inhibitors.
 - b. Participants who failed systemic therapies intended to treat AD within 6 months preceding screening, such as cyclosporine, MTX, azathioprine, and MMF, will also be considered as surrogates for having inadequate response to topical therapy.
5. Are willing and able to comply with all clinic visits and study-related procedures and questionnaires.

Weight

6. Adolescents body weight must be ≥ 40 kg at baseline.

Sex

7. Male and/or female
- Males may participate in this trial. No male contraception is required except in compliance with specific local government study requirements.
 - Females of childbearing potential and females not of childbearing potential may participate in this trial.

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Section 10.4.

Informed Consent

8. Are capable of giving signed informed consent as described in Section 10.1, Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

NOTE: Month and year of birth will be collected from participants <18 years old.

NOTE: During clinical studies, adequate informed consent for continued participation will be obtained from adolescent participants once a child reaches the age of legal consent.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

- Have a history of anaphylaxis as defined by National Institute of Allergy and Infectious Disease criteria (Sampson et al. 2006).
- Have uncontrolled chronic disease that might require bursts of oral corticosteroids, for example, comorbid severe uncontrolled asthma (defined by a history of ≥ 2 asthma exacerbations within the past 12 months requiring systemic [oral and/or parenteral] corticosteroid treatment or hospitalization for >24 hours at Visit 1 and 2).
- Have a current or recent acute, active infection. For at least 30 days before screening (Visit 1) and up to the randomization visit (Visit 2), participants must have no symptoms or signs of confirmed or suspected infection, and must have completed any appropriate anti-infective treatment.

Note: Participants who have an upper respiratory infection, a vaginal candida infection, or an oral candida infection and who are being treated only symptomatically and not requiring systemic anti-infectives may be considered for enrollment if other study eligibility criteria are met. Enrollment of participants with other uncomplicated local infections should be discussed with the sponsor's designated medical monitor.

12. Have had any of the following types of infection within 3 months prior to the screening visit (Visit 1) or develops any of these infections before the randomization visit (Visit 2):
 - Serious (requiring hospitalization, or intravenous or equivalent oral antibiotic treatment, or both)
 - Opportunistic (as defined in Section 10.7 [Winthrop et al. 2015])
Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.
 - Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
 - Recurring (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis).
Note: Participants with only recurrent mild and uncomplicated orolabial herpes, or genital herpes, or both may be discussed with the sponsor's designated medical monitor and considered for enrollment if other study eligibility criteria are met.
13. Have or have had active tuberculosis (TB) that has not been treated with a complete course of appropriate therapy as defined by the World Health Organization (WHO), the United States (US) Centers for Disease Control and Prevention (CDC) or local country guidelines (Section 8.2.6).
14. Have or have had latent tuberculosis infection (LTBI) that has not been treated with a complete course of appropriate therapy as defined by the WHO, the US CDC or local country guidelines, unless such treatment is underway (Section 8.2.6).
15. Have a current infection with HBV (that is, positive for HBsAg and/or polymerase chain reaction (PCR) positive for HBV DNA [Section 8.2.7]).
16. Have a current infection with HCV (that is, positive for HCV RNA [Section 8.2.8]).
17. Have human immunodeficiency virus (HIV) infection.
18. Have presence of skin comorbidities (for example, sclerosis, psoriasis, or lupus erythematosus) that may interfere with study assessments.
19. Have a diagnosis or history of malignant disease within 5 years before screening visit, with the following exceptions:
 - a. basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years, and
 - b. cervical carcinoma in situ, with no evidence of recurrence within 5 years before screening visit.
20. Have severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the participant's participation in the study or any other medical or psychological

condition that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant because of his/her participation in this clinical study, may make the participant's participation unreliable, or may interfere with study assessments.

Prior/Concomitant Therapy

21. Have received a dose of lebrikizumab in any prior lebrikizumab clinical study.
22. Have had an important side effect from TCS (for the combo cohort only) (for example, intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects), as assessed by the investigator or treating physician, that would prevent further use.
23. Had treatment with high-potency TCS, JAK inhibitors (topical) or phosphodiesterase-4 inhibitor within 7 days prior to the baseline visit (Visit 2).
24. Had treatment with any of the following agents within 4 weeks prior to the baseline visit:
 - a. immunosuppressive/immunomodulating drugs (for example, systemic corticosteroids, cyclosporine, MMF, interferon γ [IFN- γ], JAK inhibitors, azathioprine, MTX), or
 - b. Phototherapy or photochemotherapy for AD.
25. Had treatment with the following prior to the baseline visit:
 - a. dupilumab or other IL-4/IL-13 inhibitors
 - b. an investigational intervention within 8 weeks or within 5 half-lives (if known), whichever is longer
 - c. B-cell-depleting biologics, including rituximab, within 6 months, or
 - d. other biologics within 5 half-lives (if known) or 16 weeks, whichever is longer.
26. Have regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit.
27. Have received a live vaccine, including attenuated live vaccines, within 12 weeks prior to screening or plans to receive such vaccines during the study.

Note: The following are not considered live vaccines: RNA vaccines, vaccines with inactive viral elements, and/or nonreplicating viral vector vaccines.

28. Have received oral herbal therapy for AD within 4 weeks of baseline (Week 0; Visit 2).

Prior/Concurrent Clinical Study Experience

29. Participated in a prior lebrikizumab clinical study.

Diagnostic assessments

30. Have any of the following specific abnormalities in screening laboratory tests:

- a. serum creatinine, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 2 \times$ upper limit of normal (ULN)
- b. alkaline phosphatase (ALP) $\geq 2 \times$ ULN
- c. total bilirubin (TBL) $\geq 1.5 \times$ ULN
- d. hemoglobin < 10.0 g/dL (< 100.0 g/L)
- e. total white blood cell (WBC) count < 2500 cells/ μ L ($< 2.50 \times 10^3/\mu$ L or < 2.50 GI/L)
- f. neutropenia (absolute neutrophil count [ANC] < 1200 cells/ μ L) ($< 1.20 \times 10^3/\mu$ L or < 1.20 GI/L)
- g. lymphopenia (lymphocyte count < 750 cells/ μ L) ($< 0.75 \times 10^3/\mu$ L or < 0.75 GI/L), or
- h. thrombocytopenia (platelets $< 100,000/\mu$ L) ($< 100 \times 10^3/\mu$ L or < 100 GI/L).

NOTE: For each aforementioned test, a single repeat analysis is allowed during screening, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

- 31. Have screening electrocardiogram (ECG) abnormalities that, in the opinion of the investigator, are clinically significant and indicate an unacceptable risk for the participant's safety in the study.
- 32. Have other clinically significant laboratory test results at screening, in the opinion of the investigator, indicate unacceptable risk for the participant's safety in the study.

Other Exclusions

- 33. Pregnant or breastfeeding women or women planning to become pregnant or breastfeed during the study.
- 34. Have donated more than a single unit of blood within 4 weeks before screening visit or intend to donate blood during the study.
- 35. Are Lilly employees or are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the consolidated standard of reporting trials (CONSORT) publishing requirements and to respond to

queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should re-sign an ICF and be assigned a new participant number for every screening/rescreening event.

**5.5. Criteria for Temporarily Delaying
Enrollment/Randomization/Administration of Study Intervention of
a Participant**

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Lebrikizumab drug product and placebo are provided as sterile liquids and contain no preservatives. Each single-use, 2-mL pre-filled syringe (PFS) is assembled with a needle safety device (NSD) to form the 2-mL PFS-NSD drug product presentation.

The lebrikizumab drug product is formulated as 125 mg/mL.

The placebo has similar composition to the active drug product with the exception of absence of the drug substance lebrikizumab.

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

Dosing schedules

The [Table 3](#), [Table 4](#) and [Table 5](#) below describe the dosing schedules of lebrikizumab and placebo for the Induction and Maintenance periods and the Escape Arm.

Table 3. Lebrikizumab Dosing Schedule During Induction Period (Either the Combo or Mono Cohort)

Treatment Assignment in Induction Period (Blinded)	Loading Dose (Baseline and Week 2)	Weeks 4, 6, 8, 10, 12 and 14
Lebrikizumab 250 mg Q2W	Baseline: 2 active injections Week 2: 2 active injections	1 active injection
Placebo	Baseline: 2 placebo injections Week 2: 2 placebo injections	1 placebo injection

Abbreviations: SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks.

Notes: Injections are given SC.

Table 4. Lebrikizumab Dosing Schedule During Maintenance Period (Either the Combo or Mono Cohort)

Treatment Assignment in Induction Period (Blinded)	Treatment Assignment in Maintenance Period	Weeks 16, 24, 32, 40 and 48	Weeks 20, 28, 36 and 44
Lebrikizumab 250 mg Q2W	Lebrikizumab 250 mg Q4W	1 active injection	1 active injection
	Lebrikizumab 250 mg Q8W	1 active injection	1 placebo injection
Placebo	Placebo	1 placebo injection	1 placebo injection

Abbreviations: SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.

Notes: Injections are given SC.

Participants Entering Escape Arm at Week 16 (either the combo or mono cohort)

Participants who achieve neither an IGA 0 or 1 nor an EASI-75 response (<EASI-75) at Week 16 will enter the Escape Arm.

Participants in the combo cohort who require high-potency topical or systemic rescue treatment for AD during the Induction Period will be eligible for treatment in the Escape Arm. Participants in the mono cohort who require topical or systemic rescue treatment for AD during the Induction Period will be eligible for treatment in the Escape Arm.

Participants receiving systemic rescue medication in the Induction Period will be required to washout for 5 half-lives prior to initiating treatment in the Escape Arm.

Participants who are eligible for the Escape Arm at Week 16 will receive blinded loading doses at Week 16 and 18, based on their prior treatment assignment, followed by 250 mg lebrikizumab Q2W through Week 50 in the Escape Arm in an open-label fashion. Participants not achieving an EASI-50 response at 2 consecutive visits in the Escape Arm after Week 32 of treatment will be terminated from the study.

Table 5. Lebrikizumab Dosing Schedule for Escape Arm (Either the Combo or Mono Cohort)

Treatment Assignment in Induction Period	Treatment Assignment in Maintenance Period	Escape Arm (Blinded: Week 16 and 18)	Escape Arm (Unblinded after Week 20)
Participants Entering Escape Arm at Week 16			
Lebrikizumab 250 mg Q2W	Escape Arm (Lebrikizumab 250 mg Q2W)	Week 16: 1 active and 1 placebo injection Week 18: 1 active and 1 placebo injection	One active injection Q2W during Weeks 20 to 50
Placebo	Escape Arm (Lebrikizumab 250 mg Q2W)	Week 16: 2 active injections Week 18: 2 active injections	

Abbreviations: SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks.

Notes: Injections are given SC.

Participants Entering Escape Arm at Week 24, 32, 40 or 48 (either combo or mono cohort)

Participants who do not maintain an acceptable response (have an EASI score <50% of baseline) at Week 24, 32, 40 or 48 in the Maintenance Period will be eligible for treatment in the Escape Arm and will receive 250 mg lebrikizumab Q2W through Week 50 in the Escape Arm in an open-label fashion. Participants not achieving an EASI-50 response at 2 consecutive visits after 8 weeks of treatment in the Escape Arm will be discontinued from the study.

6.1.1. Background Medication (Topical Treatment for AD) for Combo Cohort

Background TCS is allowed for the combo cohort during the Induction Period as described below.

All participants in the combo cohort will be instructed to use a mid-potency TCS (0.1% hydrocortisone butyrate cream, or equivalent-potency TCS) for AD symptoms starting ≥ 7 days prior to the baseline visit (Day 1). Low-potency TCS (0.05% desonide cream, or equivalent-potency TCS) and/or TCI may be used for sensitive areas only (that is, face, neck, intertriginous, and genital areas) ≥ 7 days prior to the baseline visit (Day 1). Background medication is not allowed to be tapered or stopped until the baseline visit (Day 1).

At baseline (Week 0, Visit 2), participants in the combo cohort will receive 0.1% hydrocortisone butyrate cream (or equivalent-potency TCS) and 0.05% desonide cream (or equivalent-potency TCS). See “Choice of Background Topical Corticosteroid” below. 0.1% hydrocortisone butyrate cream (mid-potency TCS) should be applied at least once daily to affected areas until lesions are under control (clear or almost clear). Patients should then switch to 0.05% desonide cream (low-potency TCS) and treat previously affected areas once daily for 7 days and then stop. 0.05% desonide cream (low-potency TCS) may also be used to replace 0.1% hydrocortisone butyrate cream (mid-potency TCS) on areas of thin skin (face, neck, folds, and genital areas) and areas with skin atrophy.

The investigator must keep an accurate record of the number of tubes received, dispensed/used, and returned to the sponsor or designee. The sponsor or designee will provide forms to facilitate inventory control. All accountability forms and treatment logs must be retained in the site study file, and these records must be available for inspection at any time by the sponsor or by regulatory agencies.

Each container will be labeled as required per local country requirements.

Choice of Background Topical Corticosteroid

Where possible, a mid-potency TCS (0.1% hydrocortisone butyrate cream) and/or a low-potency TCS (0.05% desonide cream) will be provided by the sponsor for use as background TCS for participants in the combo cohort. In the event of these specific TCS being unavailable, an alternate, equivalent-potency TCS may be prescribed by the investigator (see below). Topical corticosteroid use, when supplied by the sponsor, should be recorded via weight of returned tubes as indicated in the SoA (Section 1.3). In the event that the sponsor is unable to supply TCS, commercially available 0.1% hydrocortisone butyrate cream and/or 0.05% desonide cream may be prescribed by the investigator.

- Where providing 0.1% hydrocortisone butyrate cream and/or 0.05% desonide cream is not possible, an equivalent-potency TCS cream and/or ointment that is in line with local practices can be prescribed by the investigator.

- If the TCS supplied by the sponsor is not considered suitable for an individual participant, an equivalent-potency TCS cream and/or ointment that is in line with local practices can be prescribed by the investigator.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention

Participants will be assigned to either the combo cohort (lebrikizumab/placebo + TCS) (n=150) or mono cohort (lebrikizumab/placebo) (n=130) based on the investigator's decision. Enrollment will be stopped in either cohort once the participant number reaches the planned number in that cohort.

The randomization ratio and stratification factors are described in Section 4.1. The blinding scheme is described in Section 6.1.

Either in the combo or mono cohort, participants who achieve an IGA 0 or 1 and/or an EASI-75 response ($\geq$ EASI-75) at Week 16 and do not use rescue therapy during the Induction Period are defined as responders. The responders originally assigned to lebrikizumab 250 mg Q2W (either in the combo or mono cohort) will be re-randomized to either lebrikizumab 250 mg Q4W or lebrikizumab 250 mg Q8W in 1:1 ratio within the cohort. The responders originally assigned to placebo (either in the combo or mono cohort) will continue placebo treatment in Q4W frequency in the double-blind Maintenance Period from Visit 10 (Week 16).

Either in the combo or mono cohort, participants who achieve neither an IGA 0 or 1 nor an EASI-75 response ($<$ EASI-75) at Week 16 and participants who require rescue treatment for AD during the Induction Period will be eligible for treatment in the Escape Arm. Participants who are eligible for the Escape Arm will receive blinded loading doses at Week 16 and Week 18, based on their prior treatment assignment, followed by 250 mg lebrikizumab Q2W through Week 50 in the Escape Arm in an open-label fashion.

All participants will be centrally assigned to randomized study intervention using an interactive web response system (IWRS). Before the study is initiated, the login information and directions

for the IWRS will be provided to each site. Study intervention will be dispensed at the study visits as summarized in the SoA (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor clinical research physician (CRP) for the participant to continue in the study.

6.4. Blinding

This is a double-blind study.

Initial randomization (study treatment administered between Weeks 0 and 16) and re-randomization for Week 16 responders will remain blinded to study site personnel and participants until the final clinical trial database lock has occurred.

Randomization will be blinded to sponsor until the clinical trial database through Week 16 has locked.

A designated group will be unblinded to the treatment assignment of induction and maintenance period at Week 16 database lock. Another blinded group will continue with daily monitoring of the study.

Re-randomization for Week 16 responders originally assigned to lebrikizumab 250 mg Q2W (either in the combo or mono cohort) will be blinded to sponsor, except for the designated unblinded group, until Week 52 or final (if combined with Week 52) database lock has occurred.

Emergency unblinding

Emergency unblinding for AEs may be performed through the IWRS. This option may be used only if the participant's well-being requires knowledge of the participant's intervention assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

The investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that the unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify the sponsor as soon as possible.

If, because of emergency unblinding, a participant's study intervention assignment is unblinded to the participant or to blinded site personnel who are performing assessments, including the investigator, the participant must be discontinued from study intervention (Section 7.1.1).

6.5. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

6.6. Dose Modification

Dose modifications of lebrikizumab are not allowed in this study.

6.7. Continued Access to Study Intervention after the End of the Study

Lebrikizumab will not be provided after participants exit this study.

6.8. Treatment of Overdose

For this study, any dose of lebrikizumab greater than 500 mg (baseline and Week 2) and 250 mg Q2W (Week 4 and beyond) will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate.

6.9. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the

- reason for use
- dates of administration including start and end dates, and
- dosage information including dose and frequency for concomitant therapy of special interest.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Permitted and Prohibited Treatments and Procedures

All participants in the mono cohort are required to have a TCS and/or TCI washout period for 7 days prior to the baseline visit (Visit 2).

Participants should not apply emollients or other topical treatments on the day of their study visit prior to the procedures to allow adequate assessment of skin dryness.

The use of concomitant medications for other medical conditions (for example, hypertension, diabetes, acute infections) is permitted during this study. Inhaled corticosteroids and bronchodilators to control asthma are permitted.

Concomitant antihistamines are permitted and are prescribed by the investigator on an as-needed basis for individual patients. Non-sedative antihistamines are recommended, and if the sedative ones are to be used, they should be on a stable dose at the time of enrollment.

The introduction of medications or therapies for other medical conditions known to affect AD (for example, high-potency TCS, topical/oral JAK inhibitors, topical/oral phosphodiesterase-4 inhibitor, systemic corticosteroids, MMF, IFN- γ , cyclosporine, azathioprine, MTX, phototherapy, biologics or photochemotherapy) are not permitted during the study.

During the Maintenance Period, a low-potency TCS (0.05% desonide cream, or equivalent-potency TCS) and/or a mid-potency TCS (0.1% hydrocortisone butyrate cream, or equivalent-potency TCS) can be used when needed per the investigator's opinion.

The use of systemic corticosteroids for the treatment of AD is prohibited and requires temporary/permanent discontinuation of study intervention. If used for treatment of an AE (for example, worsening of an existing condition such as asthma exacerbation), the corticosteroid will still be treated as rescue medication per Section 6.9.3.

Acute infections can be treated with systemic antibiotics, use of which must be recorded in the electronic case report form (eCRF). However, chronic treatment with systemic antibiotics is not permitted.

The use of a tanning booth/parlor is not permitted during the study.

Cannabinoid, dupilumab and other IL-4/IL-13 inhibitors treatments for AD are prohibited. Planned or anticipated major medical procedures or surgeries should be avoided during the study. See Section 6.9.3 for details on approved rescue medications and timing of use.

Prior to therapeutic intervention, the investigator must review the study participant's vaccination record to evaluate the risk of under-immunization to the adolescent participant.

6.9.2. Moisturizers

A stable dose of non-medicated moisturizers should be used for ≥ 7 days prior to the baseline visit (Visit 2) and daily during the study. If daily applications are missed, it will not be considered a protocol violation.

6.9.3. Rescue Medicine

The goal of this phase 3 study is to demonstrate the efficacy and safety of lebrikizumab when used with/without TCS for AD. However, add-on rescue therapies may be needed if the participant experiences clinical worsening of symptoms that are intolerable.

All rescue treatment usage must be recorded in the eCRF.

Induction Period

Combo cohort:

The use of high-potency topical or systemic treatments for AD is prohibited from baseline through Week 16 in the combo cohort. Participants who experience intolerable AD symptoms

and require treatment should preferably be started on high-potency TCS treatments prior to instituting systemic treatments for AD symptoms, in accordance with best practice.

If systemic treatments (for example, oral corticosteroids, phototherapy, cyclosporine) are required by Week 16, study intervention must be temporarily discontinued through Week 16. The participant should continue to attend all study visits through Week 16 and be assessed for efficacy and safety according to the SoA (Section 1.3). Participants requiring high-potency TCS or systemic rescue medication who complete the study through Week 16 will be eligible to enter the Escape Arm after the Week 16 visit has been completed. Participants who required systemic treatment must wait for the washout (≥ 5 half-lives of the treatment) prior to entering the Escape Arm.

Mono cohort:

The use of topical or systemic treatments for AD is prohibited from baseline through Week 16 in the mono cohort. Participants who experience intolerable AD symptoms and require treatment should preferably be started on topical treatments (e.g., mid-potency TCS) prior to instituting systemic treatments for AD symptoms, in accordance with best practice.

If systemic rescue treatments (e.g., oral corticosteroids, phototherapy, cyclosporine, etc.) are required, study intervention must be temporarily discontinued through Week 16. The participant should continue to attend all study visits through Week 16 and be assessed for efficacy and safety according to the SoA (Section 1.3). Participants requiring topical or systemic rescue medication who complete the study through Week 16 will be eligible to enter the Escape Arm after the Week 16 visit has been completed. Participants who required systemic rescue medication must wait for rescue medication washout (≥ 5 half-lives of the medication) prior to entering the Escape Arm.

Maintenance Period

Either in the combo or mono cohort, intermittent use of low to mid-potency TCS treatments for AD is permitted during the Maintenance Period but high-potency TCS treatments must be communicated to the investigator and documented as concomitant medications. Participants who may require short-term systemic treatment for symptoms of AD during the Maintenance Period will be assessed on a case-by-case basis and must be discussed with the medical monitor prior to initiating treatment. Participants requiring long-term systemic treatment for symptoms of AD in the Maintenance Period must be discontinued from the study.

Escape Arm

Either in the combo or mono cohort, intermittent use of additional low to mid-potency TCS for AD is permitted for participants who are in the Escape Arm. Participants who may require high-potency TCS or short-term systemic treatment for symptoms of AD while in the Escape Arm will be assessed on a case-by-case basis and must be discussed with the medical monitor prior to initiating treatment. Participants requiring long-term systemic treatment for symptoms of AD in the Escape Arm (for example, non-responders) must be discontinued from the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or the study as a whole are handled as part of Section 10.1, Appendix 1.

7.1. Discontinuation of Study Intervention

7.1.1. Permanent Discontinuation

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention (treatment), thereby discontinuing the treatment period, and will remain in the study to complete procedures for

- an early termination (ET) visit, and
- posttreatment follow-up visits, as shown in the SoA (Section 1.3).

Possible reasons for permanent discontinuation of study intervention include, but are not limited to, the reasons listed here:

Participant decision: The participant asks to stop receiving study intervention.

Pregnancy: The participant becomes pregnant (Sections 8.2.13 and 8.3.2).

Hypersensitivity: The investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration. In this case, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor's designated medical monitor.

Malignancy: The participant develops a malignancy (except for successfully treated basal or squamous cell skin carcinoma).

HIV or AIDS: The participant develops HIV infection or acquired immune deficiency syndrome (AIDS).

Active TB or untreated LTBI: The participant develops active TB or has untreated LTBI (Section 8.2.6). For temporary discontinuation of study intervention while the participant is being treated for LTBI, see Section 7.1.2.

HBV: The participant tests positive for HBV DNA (Section 8.2.7).

Note: The HBV DNA result is to be confirmed if initial test result is positive but below the level of quantification (Section 7.1.2). Prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study intervention, the participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis. The timing of discontinuation from study intervention relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

HCV: The participant tests positive for HCV RNA (Section 8.2.8).

Clinically significant ECG finding: Discontinuation of study intervention may occur after consultation with the sponsor's designated medical monitor (Section 8.2.3).

Liver test abnormality: Section 8.2.9.3 describes temporary interruption of study intervention based on liver test abnormalities. If, after temporary interruption of study intervention, liver test results fail to return to baseline or near baseline and a self-limited nondrug etiology is not identified, study intervention is to be permanently discontinued.

Abnormal hematology laboratory values: The participant has any of the following results:

- total WBC count $<2.00 \times 10^3/\mu\text{L}$
- absolute neutrophil count (ANC) $<0.5 \times 10^3/\mu\text{L}$
- absolute lymphocyte count (ALC) $<0.5 \times 10^3/\mu\text{L}$
- platelet count $<50.0 \times 10^3/\mu\text{L}$

For laboratory values that meet permanent discontinuation thresholds, study intervention should be discontinued. However, if, in the opinion of the investigator, the laboratory abnormality is due to intercurrent illness, laboratory tests may be repeated. When the laboratory value returns to baseline and the intercurrent illness or other identified factor has resolved, then the investigator may restart study intervention after consultation with the sponsor's designated medical monitor.

Other AEs or changes in laboratory values: The participant has an AE, an SAE, or a clinically significant change in a laboratory value that, in the opinion of the investigator, merits the permanent discontinuation of study intervention and appropriate measures being taken.

Noncompliance: The investigator decides the participant is noncompliant with study intervention administration or any other study procedure.

Unblinding: If an investigator, blinded site personnel, or blinded designees who are performing assessments, or the participant is unblinded to the participant's intervention assignment because of an emergency unblinding as described in Section 6.4, the participant must be permanently discontinued from study intervention. In cases where there are ethical reasons for the participant to continue in the study and continue to receive study intervention, the investigator must obtain specific approval from the sponsor's designated medical monitor for the participant to continue.

7.1.2. Temporary Discontinuation

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to the study intervention. Except in cases of emergency, it is recommended that the investigator consult with Lilly (or its designee) before temporarily interrupting therapy for reasons other than those predefined in this section.

For the abnormal laboratory findings and clinical events (regardless of relatedness) listed in Table 6, specific guidance is provided for temporarily interrupting treatment and when treatment may be restarted. Retest frequency and timing of follow-up laboratory tests to monitor the abnormal finding is at the discretion of the investigator. Investigational product that was

temporarily interrupted because of an AE or abnormal laboratory value not specifically covered in Table 6 may be restarted at the discretion of the investigator.

If systemic treatments (for example, oral corticosteroids, phototherapy, cyclosporine) are required in the Induction Period, study intervention must be temporarily discontinued through Week 16. These participants can be eligible to continue in the Escape Arm after completion of Week 16 but must wait for the washout (≥ 5 half-lives of the treatment) prior to entering the Escape Arm.

Table 6 lists some reasons for temporary interruption (withholding) of study intervention and conditions necessary for resumption of study intervention.

Table 6. Criteria for Temporary Interruption of Study Intervention

Temporarily interrupt study intervention if the participant...	Conditions for resuming study intervention
ANC < 1000 cells/ μ L ($< 1.00 \times 10^3/\mu$ L or < 1.00 GI/L)	ANC ≥ 1200 cells/ μ L ($\geq 1.20 \times 10^3/\mu$ L or ≥ 1.20 GI/L)
Platelet count $< 75,000/\mu$ L ($< 75 \times 10^3/\mu$ L or < 75 GI/L)	Platelet count $\geq 100,000/\mu$ L ($\geq 100 \times 10^3/\mu$ L or ≥ 100 GI/L)
Hemoglobin < 8 g/dL (< 80.0 g/L)	Hemoglobin ≥ 10 g/dL (≥ 100.0 g/L)
has hepatic events or liver test abnormalities as described in Section 8.2.9.3	As described in Section 8.2.9, resumption of study intervention can be considered only in consultation with the sponsor's designated medical monitor and only if the liver test results return to baseline or near baseline values and if a self-limited nondrug etiology is identified
is a candidate for LTBI treatment and is treated for LTBI	Withhold study intervention for at least the first 4 weeks of LTBI treatment. Study intervention may be resumed - after participant has received at least 4 weeks of appropriate LTBI therapy as per WHO or US CDC guidelines, and - if there is no evidence of hepatotoxicity (ALT/AST must remain ≤ 2 times ULN) or other treatment intolerance. The participant must complete appropriate LTBI therapy to remain eligible to receive study intervention.
has a serious or opportunistic infection, as defined in Section 5.2 (for LTBI, see preceding row)	After resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment.
has HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification. In this situation, the sponsor's designated medical monitor should be contacted regarding the participant's status. HBV DNA testing is to be repeated as soon as is feasible	Negative for HBV DNA. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study intervention (see Section 7.1.1)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CDC = Centers for Disease Control and Prevention; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; LTBI = latent tuberculosis infection; ULN = upper limit of normal; US = United States; WHO = World Health Organization.

7.1.3. Liver Chemistry Stopping Criteria

See Section 8.2.9.3 for hepatic criteria for study intervention interruption or discontinuation.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request for any reason or without providing any reason
- at the request of the participant's designee, for example, parents or legal guardian
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if a participant transitioned to the Escape Arm from Week 16 (use of rescue treatment in the Induction Period or non-responder at Week 16) and does not achieve an EASI-50 response at 2 consecutive visits after Week 32
- if a participant is transitioned to the Escape Arm after Week 20 and does not achieve an EASI-50 response at 2 consecutive visits after 8 weeks of treatment
- if a participant requires long-term systemic treatment for symptoms of AD in the Maintenance Period (for example, non-responders), or
- if an investigator, site personnel performing assessments, or participant is unblinded.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA (Section 1.3). If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3).

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy and Health Outcome Assessments

8.1.1. Efficacy Assessments

Eczema Area and Severity Index (EASI)

The EASI assesses extent of disease at 4 body regions and measures 4 clinical signs:

(1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification each on a scale of 0 (clear) to 3 (severe). The EASI confers a maximum score of 72 (a higher score is more severe). The EASI evaluates 2 dimensions of AD: disease extent and clinical signs (Hanifin et al. 2001).

The EASI is assessed by the investigator and completed using a tablet device at the study visit.

BSA affected by AD will be derived from data collected as part of the EASI assessment.

Investigator's Global Assessment (IGA)

The IGA is a static assessment and rates the severity of the participant's AD. The IGA is composed 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. It is not necessary that all characteristics under Morphological Description be present. The IGA must be conducted prior to conducting the EASI. A single assessor should be assigned to each participant for as many visits as possible to avoid inter-assessor variability in scoring. The IGA is assessed by the investigator and completed using a tablet device at the study visit.

See [Table 7](#) below for the IGA.

Table 7. Investigator's Global Assessment

Score	Grade	Definition
0	Clear	Minor, residual discoloration; no erythema or induration/papulation; no oozing/crusting; no edema.
1	Almost Clear	Trace, faint pink erythema with barely perceptible induration/papulation and no oozing/crusting; no edema.
2	Mild	Faint-pink erythema with papulation and edema perceptible upon palpation and no oozing/crusting; minimal induration.
3	Moderate	Pink-red erythema with definite edema of skin papules and plaques; there may be some oozing/crusting; palpable induration.
4	Severe	Deep/bright red erythema with significant swelling and obvious raised borders of papules and plaques with oozing/crusting; significant induration.

SCORing Atopic Dermatitis (SCORAD)

The SCORAD index uses the rule of nines to assess disease extent and evaluates 6 clinical characteristics to determine disease severity: (1) erythema, (2) edema/papulation, (3) oozing/crusts, (4) excoriation, (5) lichenification, and (6) dryness. The SCORAD index also assesses subjective symptoms of itch and sleep loss. These 3 aspects, extent of disease, disease severity, and subjective symptoms, combine to give a maximum possible score of 103 (European Task Force on Atopic Dermatitis 1993; Kunz et al. 1997; Schram et al. 2012).

The SCORAD index is assessed by the investigator and participant and completed using a tablet device at each study visit.

8.1.2. Participant Reported Outcomes and Health-Related Quality of Life

The participant self-reported questionnaires will be administered via an electronic participant diary, electronic tablet, or will be paper-based and will be administered in countries where the questionnaires have been translated into the native language of the region and linguistically validated. Planned time points for these assessments are provided in the SoA (Section 1.3). Diaries and questionnaires that are missed by participants for less than 7 consecutive days at non-critical timepoints (i.e. visits other than Visit 2 and Visit 10) are not regarded as protocol deviations.

Itch Numeric Rating Scale (NRS)

The Itch NRS is a participant-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing “no itch” and 10 representing “worst itch imaginable”. Overall severity of a participant’s itching is indicated by selecting the number that best describes the worst level of itching in the past 24 hours (Naegeli et al. 2015; Kimball et al. 2016; Newton et al. 2019; Silverberg et al. 2021). The Itch NRS assessment will be completed daily by the participant using a handheld device.

Sleep-Loss Scale

The Sleep-Loss Scale is a participant-reported, single-item, daily scale that measures the extent of sleep-loss due to interference of itch over the last night. The Sleep-Loss Scale is rated based

on a 5-point Likert scale. Response options include “Not at all,” “A little,” “Moderately,” “Quite a bit,” and “Unable to sleep at all,” with corresponding scores of 0, 1, 2, 3 and 4, respectively. Assessment will be recorded daily by the participant. The minimal clinically important change is 3 points (Revolutionizing Atopic Dermatitis. 2022).

Skin Pain 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 (Newton et al. 2019; Silverberg et al. 2021). The Skin Pain NRS assessment will be completed daily by the participant using a handheld device.

Patient-Oriented Eczema Measure (POEM)

The POEM is a simple, 7-item, participant-administered scale that assesses disease severity in children and adults. Participants respond to questions about the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness) over the past week. Response categories include “No days,” “1-2 days,” “3-4 days,” “5-6 days,” and “Every day” with corresponding scores of 0, 1, 2, 3, and 4, respectively. Scores range from 0-28, with higher total scores indicating greater disease severity (Charman et al. 2004). The POEM assessment will be completed weekly by the participant and using a handheld device.

Dermatology Life Quality Index (DLQI)

The DLQI is a participant-reported, 10-item, quality-of-life questionnaire in those ≥ 16 years of age that covers 6 domains (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 include “not at all,” “a little,” “a lot,” and “very much,” with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered (or “not relevant”) responses scored as 0.

Scores range from 0 to 30 with higher scores indicating greater impairment of QoL. A DLQI total score of 0 to 1 is considered as having no effect on a participant’s health related quality-of-life (HRQoL) (Hongbo et al. 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Basra et al. 2015).

Participants ≥ 16 years of age will complete the DLQI questionnaire and should continue to complete the DLQI for the duration of the study.

Children’s Dermatology Life Quality Index (CDLQI)

The CDLQI is a simple, participant-reported, 10-item, QoL questionnaire in those ≥ 4 to <16 years of age that covers 6 domains (symptoms and feelings, leisure, school or holidays, personal relationships, sleep and treatment). The recall period of this scale is over the “last week.” Response categories include “not at all,” “a little,” “quite a lot,” and “very much,” with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered (or “not relevant”) responses scored as 0. Scores range from 0 to 30 with higher scores indicating greater impairment of QoL. A CDLQI total score of 0 to 1 is considered as having no effect on a participant’s HRQoL (Hongbo et al. 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Basra et al. 2015).

Participants <16 years of age will complete the CDLQI questionnaire and should continue to complete the CDLQI for the duration of the study.

Work Productivity and Activity Impairment Questionnaire-Atopic Dermatitis (WPAI-AD)

The 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. Absenteeism, presenteeism, and work productivity will only be reported by those who are currently employed (working for pay) at the time of the scale completion. Scores are calculated as impairment percentages (Reilly et al. 1993), with higher scores indicating greater impairment and less productivity. The WPAI-AD assessment will be completed by the participant using a tablet device at the applicable study visit.

Hospital Anxiety Depression Scale (HADS)

The 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 uses a 4-point Likert scale (0 to 3) for each question and is intended for participants aged 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). The HADS assessment will be completed by the participant using a tablet device at the applicable study visit.

Asthma Control Questionnaire-5 (ACQ-5)

Participants who report comorbid asthma prior to enrollment will complete the ACQ-5 in addition to other participant-reported outcomes in this study. 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). The ACQ-5 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. The ACQ-5 assessment will be completed by the participant using a paper form at the applicable study visit.

EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status used to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of 2 components: a descriptive system of the respondent's health and a rating of his/her current health state using a 0- to 100-mm visual analog scale (VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box associated with the most appropriate statement in each of the 5 dimensions. It should be noted that the numerals 1 to 5 have no arithmetic properties and are not to be used as ordinal scores. The VAS records the respondent's self-rated health on a vertical VAS in which the endpoints are labeled "best imaginable health state" and "worst imaginable health state." This information can be used as a quantitative measure of health outcomes. The EQ-5D-5L health

states, defined by the EQ-5D-5L descriptive system, may be converted into a single summary index by applying a formula (China and Korea in this study) that essentially attaches values (also called weights) to each of the levels in each dimension (EuroQol Group 2019). The EQ-5D-5L assessment will be completed by the participant using a tablet device at the applicable study visit.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

Complete physical examinations and symptom-directed physical examinations will be conducted as specified in the SoA (Section 1.3).

Symptom-directed physical assessments may also be conducted at other visits as determined by the investigator, if a participant presents with complaints or as needed based on participant status and local standard of care.

TB assessments

At screening and approximately every 3 to 4 months thereafter, the specified physical evaluation, whether complete or symptom-directed, will include a documented assessment of TB risk factors and symptoms or signs of active TB, including an assessment of peripheral lymph nodes and body temperature (see Section 8.2.6).

Complete physical examination

The complete physical examination should include the following regions and body systems:

- general appearance
- skin
- head, ears, eyes, nose, and throat
- lymph nodes
- cardiovascular
- respiratory
- abdominal, and
- neurologic.

Genitourinary, pelvic, rectal, and breast examinations are not required unless clinically indicated.

Symptom-directed physical assessments

After screening, physical assessments should include

- a symptom-directed evaluation
- evaluation of eyes
- visual evaluation of the skin, other than area covered by clothing or other material, and

- examination for signs of active TB, including assessment of peripheral lymph nodes.

Height and weight

Height and weight will be measured and recorded as specified in the SoA (Section 1.3).

8.2.2. Vital Signs

For each participant, vital sign measurements should be conducted according to the SoA (Section 1.3). If warranted, additional vital signs may be measured.

Blood pressure and pulse rate should be measured after at least 5 minutes rest. When possible, measurements of blood pressure and pulse rate should be performed at approximately the same time of day at each scheduled time point.

8.2.3. Electrocardiograms

For each participant, a single 12-lead digital ECG will be collected according to the SoA (Section 1.3). All single ECGs recorded should be stored at the investigational site.

ECGs (single) may be obtained at additional times when deemed clinically necessary (for example, to assess participants' safety).

ECGs must be recorded before collecting any blood samples. It is recommended that participants should be in a supine for at least 5 to 10 minutes before ECG collection, and remain supine and awake, during ECG collection.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of study intervention should be reported to the sponsor, or its designee, as an AE via the eCRF.

ECGs will be interpreted by the investigator (a physician or qualified designee) at the site as soon after the time of ECG collection as practical, to determine whether the participant meets entry criteria.

8.2.4. Clinical Safety Laboratory Tests

See Section 10.2, Appendix 2, for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, Appendix 2, must be conducted in accordance with the SoA (Section 1.3), standard collection requirements and laboratory manual.

If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator, for example, SAE or AE or dose modification, then report the information as an AE.

8.2.5. Chest Radiography

A high-quality chest x-ray (CXR) (posterior-anterior view and, if needed, a lateral view), interpreted and reported by a radiologist or pulmonologist, will be obtained as specified in the SoA (Section 1.3).

Note: Participants do not need to have a CXR at screening if, in the opinion of the investigator, both of these 2 conditions are met:

- the CXR was performed within 3 months before initial screening, and
- documentation of the CXR, read by a qualified radiologist or pulmonologist, is sufficient for TB evaluation according to local standard of care.

For each participant, the CXR films, images, or a radiology report must be available to the investigator for review before the participant is randomized.

Note: Results of a chest CT scan or other imaging study similar to a CXR may be used instead of the CXR for TB evaluation, in consultation with the sponsor's medical monitor.

8.2.6. Tuberculosis Testing and Monitoring

Screening

During screening, all participants are to be assessed for risk factors, symptoms, and signs of TB with all of the following:

- Thorough history to determine the lifetime risk factors for TB infection, for TB progression, and for symptoms and/or signs of active TB, and
- Signs of previous or active TB by means of
 - Thorough physical examination for signs of active TB, including measurement of body temperature (Section 8.2.2) and assessment of peripheral lymph nodes (Section 8.2.1), and
 - A high-quality CXR (posterior-anterior, including a lateral view if needed) interpreted and reported by a radiologist or pulmonologist (Section 8.2.5).

All participants with no history of LTBI or active TB, and no history of positive Mantoux tuberculin skin test (TST) using purified protein derivative (PPD) or positive *M tuberculosis* interferon gamma release assay (IGRA) must have one of the following tests:

- PPD TST, or
- IGRA for *M tuberculosis* (T-SPOT® or QuantiFERON®-TB Gold).

For details about these tests, see Sections 10.2.1 and 10.6

Diagnosed LTBI

Participants diagnosed with LTBI are excluded (Section 5.2) unless they are candidates for LTBI treatment, are treated for LTBI, and the following criteria are met:

- After receiving at least 4 weeks of appropriate LTBI therapy (as per WHO or the United States CDC guidelines, or the local country guidelines), there is no evidence of hepatotoxicity (ALT/AST must remain ≤ 2 times ULN) or other treatment intolerance. In this case, the participant may be rescreened (Section 5.4) and is not excluded due to LTBI.
- The participant must continue and complete appropriate LTBI therapy in order to remain eligible to continue to receive study intervention (Section 7.1).

Monitoring during the study

For all participants, monitoring for TB is to be continuous throughout the study. At a minimum, each participant is to have the following documented at least every 3 to 4 months:

- Thorough history to determine any risk factors for TB infection and for TB progression, and symptoms or signs of active TB, and
- Physical examination for signs of active TB, including measurement of body temperature and assessment of peripheral lymph nodes (Sections 8.2.1 and 8.2.2).

8.2.7. Hepatitis B Testing and Monitoring

As specified in the SoA (Section 1.3), initial testing for HBV infection includes HBsAg and anti-HBc.

- If HBsAg is positive, the participant is excluded.
- If HBsAg is negative and anti-HBc is negative, the participant is not excluded.
- If HBsAg is negative and anti-HBc is positive, further testing for HBV DNA is required.
 - If the screening HBV DNA is positive, the participant is excluded.
 - If the screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least every 3 to 4 months during the study.

Management of enrolled participants with detectable HBV DNA during the study

If HBV DNA is detected, study intervention will be temporarily withheld or permanently discontinued, as described in Sections 7.1.1 and 7.1.2, and the participant should receive appropriate follow-up medical care.

8.2.8. Hepatitis C Testing

As specified in the SoA (Section 1.3), initial testing for HCV infection includes testing for anti-HCV. If anti-HCV is positive, a test for circulating HCV RNA is required.

- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the participant is excluded (see Section 5.2).

Participants who have had HCV infection and have been successfully treated, defined as a sustained virologic response (HCV RNA by PCR negative for at least 24 weeks following treatment completion) are not excluded on the basis of HCV as long as HCV RNA test is negative at screening.

If HCV RNA is detected during the study, the study intervention will be permanently discontinued (Section 7.1.1), and the participant should receive appropriate follow-up medical care.

8.2.9. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Intervention Interruption or Discontinuation

The following tables summarize actions to take based on abnormal hepatic laboratory or clinical changes.

Participants with normal or near normal baseline (ALT, AST, or ALP < 1.5 × ULN)

If this laboratory value is observed...	Then...		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study intervention
ALT or AST $\geq 3 \times$ ULN	X		
ALP $\geq 2 \times$ ULN	X		
TBL $\geq 2 \times$ ULN ^b	X		
ALT or AST $\geq 5 \times$ ULN	X	X	
ALP $\geq 2.5 \times$ ULN	X	X	
ALT or AST $\geq 3 \times$ ULN with hepatic signs or symptoms ^a	X	X	X
ALT or AST $\geq 5 \times$ ULN for more than 2 weeks	X	X	X
ALT or AST $\geq 8 \times$ ULN	X	X	X
ALT or AST $\geq 3 \times$ ULN and TBL $\geq 2 \times$ ULN ^b or INR ≥ 1.5	X	X	X
ALP $\geq 3 \times$ ULN	X	X	X
ALP $\geq 2.5 \times$ ULN and TBL $\geq 2 \times$ ULN ^b	X	X	X
ALP $\geq 2.5 \times$ ULN with hepatic signs or symptoms ^a	X	X	X

Abbreviations: ALP = Alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

^a Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

^b In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Participants with elevated baseline (ALT, AST, or ALP $\geq 1.5 \times$ ULN)

If this laboratory value is observed...	Then...		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study intervention
ALT or AST $\geq 2 \times$ baseline	X		
ALP $\geq 2 \times$ baseline	X		
TBL $\geq 2 \times$ ULN ^b	X		
ALT or AST $\geq 3 \times$ baseline or ≥ 250 U/L (whichever occurs first)	X	X	
ALP $\geq 2.5 \times$ baseline	X	X	
ALT or AST $\geq 2 \times$ baseline or ≥ 250 U/L (whichever occurs first) with hepatic signs or symptoms ^a	X	X	X
ALT or AST $\geq 3 \times$ baseline or ≥ 250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST $\geq 4 \times$ baseline or ≥ 400 U/L (whichever occurs first)	X	X	X
ALT or AST $\geq 2 \times$ baseline or ≥ 250 U/L (whichever occurs first) and TBL $\geq 2 \times$ ULN ^b or INR ≥ 1.5	X	X	X
ALP $\geq 3 \times$ baseline	X	X	X
ALP $\geq 2.5 \times$ baseline and TBL $\geq 2 \times$ ULN ^b	X	X	X
ALP $\geq 2.5 \times$ baseline with hepatic signs or symptoms ^a	X	X	X

Abbreviations: ALP = Alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

^a Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

^b In participants with Gilbert's syndrome, the threshold for TBL may be higher.

8.2.9.1. Close Hepatic Monitoring

If a participant develops any one of these changes, initiate close hepatic monitoring:

Participants with normal or near normal baseline (ALT, AST, or ALP $< 1.5 \times$ ULN)	Participants with elevated baseline (ALT, AST, or ALP $\geq 1.5 \times$ ULN)
ALT or AST $\geq 3 \times$ ULN or	ALT or AST $\geq 2 \times$ baseline
ALP $\geq 2 \times$ ULN or	ALP $\geq 2 \times$ baseline
TBL $\geq 2 \times$ ULN ^a	TBL $\geq 2 \times$ ULN ^a

Abbreviations: ALP = Alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

^a In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Close hepatic monitoring should include these actions:

- Laboratory tests (Section 10.5), including ALT, AST, ALP, TBL, direct bilirubin (D. Bil), gamma-glutamyltransferase (GGT), creatine kinase (CK), and complete blood count (CBC) with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.
- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels normalize or return to approximate baseline values. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize.
- In addition to lab tests, basic evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the sponsor's designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including current symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

8.2.9.2. Comprehensive Hepatic Evaluation

If a participant develops any one of the following laboratory or clinical changes, initiate a comprehensive hepatic evaluation:

Participants with normal or near normal baseline (ALT, AST, or ALP < 1.5 × ULN)	Participants with elevated baseline (ALT, AST, or ALP ≥ 1.5 × ULN)
ALT or AST ≥ 5 × ULN or	ALT or AST ≥ 3 × baseline or ≥ 250 U/L (whichever occurs first) or
ALP ≥ 2.5 × ULN or	ALP ≥ 2.5 × baseline or
ALT or AST ≥ 3 × ULN with hepatic signs or symptoms ^a or	ALT or AST ≥ 2 × baseline or ≥ 250 U/L (whichever occurs first) with hepatic signs or symptoms ^a or
ALT or AST ≥ 5 × ULN for more than 2 weeks or	ALT or AST ≥ 3 × baseline or ≥ 250 U/L (whichever occurs first) for more than 2 weeks or
ALT or AST ≥ 8 × ULN or	ALT or AST ≥ 4 × baseline or ≥ 400 U/L (whichever occurs first) or
ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN ^b or INR ≥ 1.5	ALT or AST ≥ 2 × baseline or ≥ 250 U/L (whichever occurs first) and TBL ≥ 2 × ULN ^b or INR ≥ 1.5

Abbreviations: ALP = Alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

^a Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

^b In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio (PT-INR); tests for viral hepatitis A, B, C, and E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

- Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol.
- Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, and additional tests including magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.
- For participants with isolated ALP elevation $\geq 2.5 \times \text{ULN}$ without GGT elevation, consider testing for ALP isoenzymes and evaluating for extrahepatic sources such as bone disease (e.g., fractures, bone metastases, osteomalacia, Paget's disease), or pregnancy.
- Clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels normalize or return to approximate baseline values. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize.
- All the medical information and tests results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.9.3. Study Intervention Interruption or Discontinuation

If a participant develops any one of the following laboratory or clinical changes, interrupt the study intervention and continue close monitoring and comprehensive hepatic evaluation as described in Sections 8.2.9.1 and 8.2.9.2.

Participants with normal or near normal baseline (ALT, AST, or ALP $< 1.5 \times \text{ULN}$)	Participants with elevated baseline (ALT, AST, or ALP $\geq 1.5 \times \text{ULN}$)
ALT or AST $\geq 3 \times \text{ULN}$ with hepatic signs or symptoms ^a or	ALT or AST $\geq 2 \times \text{baseline}$ or $\geq 250 \text{ U/L}$ (whichever occurs first) with hepatic signs or symptoms ^a or
ALT or AST $\geq 5 \times \text{ULN}$ for more than 2 weeks or	ALT or AST $\geq 3 \times \text{baseline}$ or $\geq 250 \text{ U/L}$ (whichever occurs first) for more than 2 weeks or
ALT or AST $\geq 8 \times \text{ULN}$ or	ALT or AST $\geq 4 \times \text{baseline}$ or $\geq 400 \text{ U/L}$ (whichever occurs first) or
ALT or AST $\geq 3 \times \text{ULN}$ and TBL $\geq 2 \times \text{ULN}^b$ or INR ≥ 1.5 or	ALT or AST $\geq 2 \times \text{baseline}$ or $\geq 250 \text{ U/L}$ (whichever occurs first) and TBL $\geq 2 \times \text{ULN}^b$ or
ALP $\geq 3 \times \text{ULN}$ or	ALP $\geq 3 \times \text{baseline}$ or
ALP $\geq 2.5 \times \text{ULN}$ and TBL $\geq 2 \times \text{ULN}^b$ or	ALP $\geq 2.5 \times \text{baseline}$ and TBL $\geq 2 \times \text{ULN}^b$ or
ALP $\geq 2.5 \times \text{ULN}$ with hepatic signs or symptoms ^a	ALP $\geq 2.5 \times \text{baseline}$ with hepatic signs or symptoms ^a

Abbreviations: ALP = Alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

^a Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia $> 5\%$.

^b In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Interruption or discontinuation of study intervention should include these actions:

- While the participant is not receiving the study, clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until liver tests normalize or return to approximate baseline values.
- If the hepatic event continues past the anticipated end of the study (that is, data lock) the investigator should consult with the Lilly-designated medical monitor to determine the need for further data collection beyond the end date of the study (that is, data lock date).
- All the medical information and tests results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.
- Resumption of the study intervention after interruption for a hepatic reason can be considered only in consultation with the Lilly designated medical monitor and only if the liver test results returned to near baseline and if a self-limited non-study-drug etiology is identified. Otherwise, the study intervention should be permanently discontinued.

8.2.10. Injection Site Reactions

Symptoms and signs of a local injection site reaction may include erythema, induration, pain, pruritus, and edema.

If an ISR is reported by a participant or site staff, it will be recorded as an AE of a local ISR, and the ISR CRF will be used to capture additional information about this reaction, for example, injection-site pain, degree and area of erythema, induration, pruritus, and edema.

8.2.11. Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

8.2.12. Growth Monitoring

Height and weight will be measured according to the SoA (Section 1.3) to allow for identification of potential effects on growth and development of adolescents.

8.2.13. Pregnancy Testing

Pregnancy testing will be conducted for women of childbearing potential (WOCBP) at visits specified in the SoA (Section 1.3).

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Section 10.3, Appendix 3:

- AEs
- SAEs, and
- product complaints (PCs).

These events will be reported by the participant, or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature or causality. Further information on follow-up procedures is provided in Section 10.3, Appendix 3.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention and deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE# and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE* – after participant's study participation has ended and the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	Participation in the study has ended	Within 24 hours (see Section 8.3.2)	Pregnancy CRF	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

Abbreviations: AE = adverse event; CRF = case report form; IB = investigator's brochure; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

* SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

After learning of a pregnancy in the female partner of a study participant, the investigator

- will obtain a consent to release information from the pregnant female partner directly, and
- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Events of Special Interest

The following TEAEs will be designated adverse events of special interest (AESI):

- conjunctivitis
- herpes infection or zoster, and
- parasitic infection or an infection related to an intracellular pathogen.

If these AESIs are reported, sites will be prompted to collect additional details and data.

8.3.3.1. Infections, Including Serious Infections and Opportunistic Infections

Completion of the Infection CRF page is required for each infection reported as an AE or SAE. The sponsor will identify infections considered to be opportunistic based on the article by Winthrop et al. (2015) (Section 10.7).

8.4. Pharmacokinetics

Venous blood samples of approximately 3 mL will be collected for measurement of serum concentrations of lebrikizumab as specified in the SoA (Section 1.3).

A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (for example, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.4.1. Bioanalysis

Serum samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of lebrikizumab will be assayed using a validated enzyme-linked immunosorbent assay. Bioanalytical samples collected to measure lebrikizumab concentrations will be retained for a maximum of 1 year following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory metabolism studies or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine antibody production against lebrikizumab. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of lebrikizumab. All samples for immunogenicity collected on a dosing day should be taken predose when applicable and possible.

Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies (ADA) in the presence of lebrikizumab at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of lebrikizumab.

Treatment-emergent (TE) ADA are defined in Section 9.3.6.

ADA samples retention are detailed in Section 10.1.12.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health economics and medical resource utilization are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan will be finalized prior to unblinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and major secondary endpoints.

9.1. Statistical Hypothesis

No formal statistical hypotheses are planned to be tested in this study.

9.1.1. Multiplicity Adjustment

Not applicable.

9.2. Analyses Sets

The following populations are defined for combo cohort and mono cohort separately:

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	All participants who were randomized to lebrikizumab 250 mg Q2W at baseline visit and re-randomized 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 without using rescue medication 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	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 Maintenance Period Secondary Population.
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.

Participant Analysis Set	Description
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 W20-52 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.
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.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of the sponsor or its designee.

Analysis will be conducted for combo cohort and mono cohort separately.

Unless otherwise stated, all confidence intervals (CIs) will be given at a 2-sided 95% level. P value will be provided for descriptive purpose.

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

For safety analyses during the Induction Period, the Baseline Period is defined as the time from the screening visit (Visit 1) to the date/time of the first injection in the Induction Period. Baseline will be the last scheduled non-missing assessment recorded during the baseline 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.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of participants in each category will be presented. For continuous parameters, descriptive statistics will include number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Appropriate inferential statistics will be used for the primary and secondary efficacy variables.

Any change to the data analysis methods described in the protocol will require an 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 statistical analysis plan (SAP) and the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to unblinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the

planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Primary estimand will be applied to the co-primary endpoints on intent to treat (ITT) population in combo and mono cohort separately.

The primary estimand addresses the treatment response as directed. The analysis assumes that treatment failures for participants who take rescue medication (refer to Section 6.9.3 for rescue medication definition) or withdraw from the study due to lack of efficacy, therefore setting to a non-responder. Other missing values will be imputed using Markov chain Monte Carlo Multiple Imputation (MCMC-MI) based on missing at random assumption. The binary endpoint will be derived from the imputed continuous variables.

For combo cohort primary analysis, a Bayesian decision criterion will be used to assess the treatment effect by determining whether the CCI

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 model will be provided in the SAP.

For mono cohort primary analysis, 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) along with corresponding 95% CIs.

9.3.3. Secondary Endpoint Analysis

For binary secondary endpoints during the Induction Period, the intercurrent events handling strategies and the analysis method will follow the primary estimand excluding the Bayesian approach. 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 [the mono cohort only]).

For continuous secondary endpoints, the analysis assumes that treatment response disappears for participants who take rescue medication (refer to Section 6.9.3 for rescue medication definition) or withdraw 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. Treatment comparisons of continuous secondary efficacy endpoints during the Induction Period will be made using an analysis of covariance with the following in the model: treatment group, baseline value, and stratification factors.

Efficacy, health outcome, and safety measures during the Maintenance Period will be summarized using descriptive statistics by treatment group.

More details will be specified in the SAP.

9.3.4. Safety Analyses

Safety analyses will include AEs, SAEs, AESI, vital signs, and laboratory analytes. The safety data will be summarized descriptively by treatment group. Categorical safety measures will be summarized with the number and percentage of participants. Continuous safety measures will be summarized as mean change by visit. Exposure to study intervention will be calculated for each participant and summarized by treatment group.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC), preferred term (PT), severity, and relationship to the study intervention. A TEAE is defined as an event that first occurred or worsened in severity after the baseline period. The baseline period for the Induction Period is defined as the time from the screening visit (Visit 1) to the date/time of the first injection in the Induction Period. Baseline for the Maintenance Period is the events ongoing just prior to the first injection of study intervention at Week 16. The Treatment Period will be used as the postbaseline period for the analysis. For events that are gender specific, the denominator and computation of the percentage will include only participants from the given gender.

The number and percentage of participants who experienced TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study intervention, discontinuations from study intervention due to an AE, and AESI will be summarized. TEAEs (all, by maximum severity), SAEs including deaths, and AEs that lead to study intervention discontinuation will be summarized and analyzed by MedDRA SOC and PT.

Treatment-related TEAEs (TEAEs considered related to study intervention) are defined as events that are indicated by the investigator on the eCRF to be related to treatment.

AESIs will be identified by a Standardised MedDRA Query (SMQ) or a Lilly-defined MedDRA PT listing.

Follow-up emergent AEs, SAEs including deaths, and AEs that lead to study discontinuation will be listed. All AEs, including preexisting conditions, will be listed by participant, visit, PT, treatment group, severity, and relationship to the treatment.

Growth monitoring of adolescent participants will be summarized. More details will be provided in the SAP.

9.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Serum concentration data will be tabulated and summarized (for example, by geometric mean and % coefficient of variation) by treatment group for each visit at which samples were taken.

The data from this study may be combined with data from other studies to better characterize the PK of lebrikizumab and to make ethnic comparisons using graphical analyses and population PK methodology as needed. Further details on PK and PK/pharmacodynamic (PD) analyses will be provided in the PK/PD analysis plan. The results of these analyses may be described in a separate PK/PD report.

9.3.6. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with TE ADA to lebrikizumab may be tabulated. Participants who are TE ADA positive 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). The frequency of neutralizing antibodies and distribution of maximum titers may also be tabulated in TE ADA positive participants. The relationship between the presence of antibodies and the PK parameters and PD response, including efficacy and safety to lebrikizumab, may be assessed.

9.3.7. Other Analyses

Subgroup analyses will be made to assess consistency of the study intervention effect across the following subgroups:

- Age group: ≥ 12 to < 18 years vs ≥ 18 years
- Sex: female vs male
- Baseline IGA score: 3 vs 4.
- Country: China vs Korea (the mono cohort only)

The analysis will be conducted for ITT population on primary and major secondary endpoints at Week 16. Further details on the statistical analysis will be provided in the SAP.

Other exploratory analysis will be specified in SAP.

9.4. Interim Analysis

An interim database lock and unblinding for the induction period will occur, and the interim analysis will be performed at the time (that is, a cut-off date) the last participant completes Week 16 or the early termination visit from study. This database lock will be considered as the primary database lock of this study, and include all data collected by the cut-off date. The study will not be terminated early on the basis of efficacy following this analysis. Refer to Section 6.4 for the details of blinding.

Another interim database lock and unblinding will occur, and the interim analysis will be performed at the time (that is, a cut-off date) the last participant completes Week 52 or the early termination visit from study. This database lock will include all data collected by the cut-off date.

A final database lock will be conducted after all participants have completed the follow-up period or discontinued the study early.

Depending on the regulatory submission timeline, the interim database lock at Week 52 and the final database lock may be combined, that is, one final database lock will occur after all participants have either completed the follow-up period or discontinued the study early.

Additional database lock/snapshot may be conducted for regulatory interaction purpose.

The SAP will describe the planned interim analyses in greater detail.

The timing of dissemination of data summaries based on interim analyses is addressed in Section 10.1.6.

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

9.5. 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 (i.e. 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),
- 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%, i.e. $\Pr(\text{lebrikizumab-placebo} > 0) > 90\%$ for both co-primary endpoints. Details of this method will be provided in the SAP.

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 at least 50% effect size of global studies (Studies KGAB and KGAC) with > 90% probability for both co-primary endpoint EASI-75 (i.e. 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 0 or 1 (i.e. to observe a treatment difference in IGA score 0 or 1 response to be greater than 12.9%, assuming true response rates of IGA score 0 or 1 at Week 16 between lebrikizumab Q2W and placebo are 38.8% and 13.0%).

9.6. Data Monitoring Committee

An independent data monitoring committee (DMC) composed of members who are independent of the study sponsor and study investigators will monitor patient safety by conducting formal reviews of accumulated safety data that is unblinded by treatment group; if requested, the DMC may request any other data for the purposes of a risk-benefit assessment.

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.

Activities and responsibilities of the DMC are described in Section [10.1.5](#) and the DMC charter.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (for example, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following

- providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant or the potential participant's legally authorized representative and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

For adult participants, the medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

For adolescent participants, the medical record must include a statement that legally acceptable representative consent and child/adolescent assent (if deemed appropriate by local ethics review) was obtained before the participant was enrolled in the study and the date the written consent was obtained. The medical record should also describe how the clinical investigator determined that the person signing the ICF was the participant's legally acceptable representative or parent(s). The acceptable person obtaining the informed consent must also sign the ICF. Adolescent participants who become 18 years of age (or the acceptable age according to local regulations, whichever is older) while on study, will need to re-consent.

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and ERB consenting guidance.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.1.5. Committees Structure

A DMC consisting of members external to Lilly will be established. The purpose of the DMC is to conduct periodic safety monitoring of clinical trial data for this study. The DMC will consist of a minimum of 3 members, including, at minimum, a physician with expertise in dermatology and a statistician.

No member of the DMC will have contact with study sites. A statistical analysis center (SAC) will prepare and provide unblinded data to the DMC. The SAC members may be Lilly employees or from third-party organizations designated by Lilly. The SAC members will be external to the study team and will have no contact with sites and no privileges to influence changes to the ongoing studies. The timing and frequency of the periodic clinical trial data review by the DMC will be detailed in a DMC charter.

The DMC is authorized to evaluate unblinded interim safety analyses. In addition, the DMC may request key efficacy data to put safety observations into context and to assess a reasonable benefit/risk profile for ongoing participants in the study. The DMC will make recommendation to the Lilly Research Laboratories Senior Management Designee, who may order the immediate implementation of the DMC recommendation, or may convene an internal review committee (IRC), which is independent from the study team, to review the recommendation according to standard Lilly policy. Study sites will receive information about interim results ONLY if it is required for the safety of their patients.

10.1.6. Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data.

Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement.

Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This includes laboratory tests, medical records, and clinical notes.

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.

Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the clinical study report.

Monitoring details describing strategy, for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals, for example, contract research organizations.

The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that

the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the authorized study personnel into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, ACQ-5 assessment will be collected by the participant/authorized study personnel via a paper source document and will be transcribed by the authorized study personnel into the EDC system.

Additionally, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant/investigator site personnel into an instrument (for example, hand held smart phone or tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate written or electronic record of these data.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global product complaint management system.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the site confirmation of source data.

10.1.9. Study and Site Start and Closure**First Act of Recruitment**

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study or Site Termination

The sponsor or sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to

- for study termination due to discontinuation of further study intervention development
- for site termination due to
 - failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
 - inadequate recruitment, evaluated after a reasonable amount of time of participants by the investigator, or
 - total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

10.1.12. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of lebrikizumab or after lebrikizumab become(s) commercially available for AD.

Sample Type	Custodian	Retention Period After Last Participant Visit
Pharmacokinetics	Sponsor or designee	1 year
Immunogenicity	Sponsor or designee	Samples will be stored as per local regulation/EC requirements. Samples will be immediately destroyed once lebrikizumab is launched or there is no further request on testing samples from local authority

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central or local laboratory.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of the laboratory safety results.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Clinical Laboratory Tests

Hematology^{a,b}	Clinical Chemistry^{a,b}
Hemoglobin	Serum Concentrations of:
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Chloride
Mean cell hemoglobin	Phosphorus/phosphate
Mean cell hemoglobin concentration	Bicarbonate
Leukocytes (WBC)	Total protein
Platelets	Albumin
	Total bilirubin
Differential WBC [Absolute counts and/or %] of:	Direct bilirubin
Neutrophils	Alkaline phosphatase (ALP)
Lymphocytes	Lactic dehydrogenase (LDH)
Monocytes	Gamma-glutamyltransferase (GGT)
Eosinophils	Alanine aminotransferase (ALT)
Basophils	Aspartate aminotransferase (AST)
	Blood urea nitrogen (BUN)
	Creatinine
Urinalysis^a	Uric acid
Specific gravity	Calcium
pH	Glucose (random)
Protein	Creatine kinase (CK)
Glucose	
Ketones	
Blood	Serology
Urine leukocyte esterase	HIV Antibody (HIV Ab) ^a
Bilirubin	Hepatitis B Core Antibody (HBcAb) ^a
Nitrite	Hepatitis B Surface Antigen (HBsAg) ^a
Urobilinogen	Hepatitis B Surface Antibody (HBsAb) ^a
Microscopic examination of sediment ^c	Hepatitis B DNA (HBV DNA) ^a
	Hepatitis C Antibody (HCV Ab) ^a
	HCV RNA (participants who test positive for hepatitis C antibody only)
Hormones^a	TB Serology ^h (The QuantiFERON®-TB Gold test T-SPOT®.TB test or PPD TST)
Follicle-stimulating hormone(FSH) ^f	
	Other tests
Pregnancy Test (females of childbearing potential only) ^d	Pharmacokinetic ^{a,g}
(serum ^a /urine ^e)	Immunogenicity (anti-lebrikizumab Ab) ^{a,g}

Abbreviations: FSH = follicle-stimulating hormone; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PPD = purified protein derivative; RBC = red blood cells; TB = tuberculosis; TST = tuberculin skin test; WBC = white blood cells.

a Assayed by Lilly-designated laboratory.

- b Participants should not eat or drink anything except water for 12 hours prior to test. If a participant attends these visits in a nonfasting state, this will not be considered a protocol violation.
- c Test only if dipstick result is abnormal.
- d Local- or investigator-designated laboratory.
- e Urine pregnancy test to be performed only on women of childbearing potential and women with history of tubal ligation. Local testing. Result must be negative before dosing at each dosing visit.
- f For female participants who are ≥ 40 to ≤ 55 years of age.
- g Results will not be provided to the investigative sites.
- h The QuantiFERON-TB Gold test may be performed centrally; the PPD TST and T-SPOT must be performed locally.

10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up pre-dose samples at the next regularly scheduled laboratory sample collection, ideally prior to the next dose after the event, to assess post-event return-to-baseline values.

Timing	Laboratory Test ^a
Collect from 30 minutes to 4 hours after the start of the event. Note: The optimal collection time is from 1 to 2 hours after the start of event.	total tryptase
	complements (C3, C3a, and C5a)
	cytokine panel (IL-6, IL-1 β , IL-10 or any cytokine panel that includes these 3 cytokines)
Collect only if not already collected on the same day as the event. Note: If collecting, collect up to 12 hours after the start of the event.	Lebrikizumab ADA
	Lebrikizumab concentration

Abbreviations: ADA = anti-drug antibodies; IL = interleukin.

^a All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, or investigational combination product, whether or not related to the medicinal (investigational) product or investigational combination product.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, ECG, radiological scans, and vital signs measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure, for example, endoscopy, appendectomy. The condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- Results in death
- Is life-threatening
 - The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
 - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
 - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity
 - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
 - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
 - Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.
- Other situations:
 - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product complaint

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:

- deficiencies in labeling information, and
- use errors for device or drug-device combination products due to ergonomic design elements of the product.

Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.

An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and product complaint recording

When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.

Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as “serious” when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the Investigator’s Brochure (IB) in their assessment.

The investigator **must** review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via an electronic data collection tool

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the SAE paper form (see next section) in order to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a SAE paper form (see next section).

Contacts for SAE reporting can be found in Global Patient Safety Serious Adverse Event Reporting Form and Transmission Cover Sheet.

SAE reporting via paper form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor or designee.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in Global Patient Safety Serious Adverse Event Reporting Form and Transmission Cover Sheet.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and

expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP. Females less than 18 years of age are considered WOCBP if they have • had at least 1 cycle of menses, or • Tanner stage 4 breast development (if Tanner staging assessments are required as part of the specific study protocol) Any amount of spotting should be considered menarche. Menarche status and date of menarche should be monitored for every pediatric female study participant starting at 8 years of age until the onset of menses, and therefore, childbearing potential. It is recommended that such monitoring be conducted every 3 to 6 months at a site visit following evaluation from the provider/investigator.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy^a, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL; or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. ^a Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

10.4.2.1. Female Participants

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must...	Must not...
agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males, and not plan a pregnancy during the study	• use periodic abstinence methods ○ calendar ○ ovulation ○ symptothermal, or ○ post-ovulation • declare abstinence just for the duration of a trial, or • use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Contraception	Agree to use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception. These methods of contraception must be used for the duration of the study.

Examples of different methods of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization^a (including fallopian tube ligation, hysteroscopic sterilization) • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (for men in clinical trials and for female partner if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide ○ condom with spermicide ○ diaphragm with spermicide, or ○ female condom with spermicide Note: Male and female condoms should not be used in combination.
Ineffective methods of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

^a Hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy are the only types of permanent female sterilization that allow a participant to be a WNOCBP.

10.4.2.2. Male Participants

Males may participate in this trial.

No male contraception is required except in compliance with specific local government study requirements.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic Evaluation Testing

See Section 8.2.9 for guidance on appropriate test selection.

The Lilly-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

In circumstances where required, in accordance with local regulations, local laboratory testing may be performed in lieu of Lilly-designated central laboratory testing (in the table below).

Local testing may be performed *in addition to central testing* when necessary for immediate participant management.

The local laboratory must be qualified in accordance with applicable local regulations. Note that availability of testing may vary based on local regulatory requirements or regional availability of test. If testing is not available based on local requirements, consult with Lilly designated medical monitor.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	Hepatitis A virus (HAV) testing:
Hemoglobin	HAV total antibody ^a
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	Hepatitis B virus (HBV) testing:
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA ^b
Basophils	Hepatitis C virus (HCV) testing:
Eosinophils	HCV total antibody ^a
Platelets	HCV RNA ^b
Cell morphology (RBC and WBC)	Hepatitis D virus (HDV) testing:
Hepatic Clinical Chemistry Panel	HDV total antibody ^a
Total bilirubin	HDV IgM antibody
Direct bilirubin	HDV RNA ^b
Alkaline phosphatase (ALP)	Hepatitis E virus (HEV) testing:
Alanine aminotransferase (ALT)	HEV IgG antibody
Aspartate aminotransferase (AST)	HEV IgM antibody
Gamma-glutamyltransferase (GGT)	HEV RNA ^b
Creatine kinase (CK)	Anti-nuclear antibody (ANA)
Hepatic Coagulation Panel	Anti-smooth muscle antibody (ASMA) or anti-actin antibody
Prothrombin time, INR (PT-INR)	Immunoglobulin IgA (quantitative)
Urine Chemistry	Immunoglobulin IgG (quantitative)
Drug screen	Immunoglobulin IgM (quantitative)
Haptoglobin	

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	Cytomegalovirus (CMV) testing:
Alkaline phosphatase isoenzymes	CMV antibody
Ceruloplasmin	CMV DNA ^b
Copper	Herpes simplex virus (HSV) testing:
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) antibody
Phosphatidylethanol (PEth)	HSV (Type 1 and 2) DNA ^b
Urine Chemistry	Liver kidney microsomal type 1 (LKM-1) antibody
Ethyl glucuronide (EtG)	Microbiology Culture:
Epstein-Barr virus (EBV) testing:	Blood
EBV DNA ^b	Urine
EBV antibody	

a. If lab does not offer total antibody testing, IgG and IgM are acceptable substitutes

b. Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.6. Appendix 6: Tuberculosis Testing

This table describes recommendations for performing and interpreting tuberculosis (TB) tests. It also provides recommendations on TB retesting.

TB test type	How to perform the test	How to interpret the test	When to retest
PPD TST	1. Inject 0.1 mL of tuberculin PPD into the inner surface of the forearm. Notes: - The injection should be made with a tuberculin syringe. - The TST is an intradermal injection. When placed correctly, the injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter. 2. Measure induration at the site of intradermal injection from 48 to 72 hours after intradermal injection. Notes: - Test must be read during this window of time. Test does not need to be read at the study site but must be read by a trained medical professional, and the result must be provided to the study site before randomization. - The reaction should be measured in millimeters of induration (palpable, raised, hardened area, or swelling). The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).	- An induration of 5 or more mm is considered positive in persons with: - HIV infection - a recent contact with a person with TB disease - fibrotic changes on chest radiograph consistent with prior TB - organ transplants, or - immunosuppression for other reasons (for example, taking the equivalent of >15 mg per day of prednisone for 1 month or longer, or taking TNF alpha antagonists) - An induration of 10 or more mm is considered positive in all other potential clinical trial participants.	- Two-step testing (that is, repeat TST from 1 to 3 weeks after the first TST) is recommended for certain participant groups, including those: - receiving immunosuppressant treatment - having a history of temporally remote increased risk of TB infection, or - for whom the first test is negative, and retesting is recommended per local public health and/or professional medical society recommendations.

TB test type	How to perform the test	How to interpret the test	When to retest
IGRA for <i>M tuberculosis</i>	Ensure that specimen handling, transport, timing, and laboratory procedures meet all requirements per package insert.	Results are provided by the laboratory assaying the test.	The investigator may discuss retesting with the sponsor's designated medical monitor if: - the investigator suspects a false positive IGRA result in a participant with no increased risk of TB infection during lifetime, and - there is no evidence of prior or current TB on physical examination and/or on CXR interpreted by radiologist and/or pulmonologist (investigator assessment by history and physical examination, and with documented CXR report).

Abbreviations: CXR = chest x-ray; IGRA = interferon gamma release assay; PPD = purified protein derivative; TB = tuberculosis; TNF = tumor necrosis factor; TST = tuberculin skin test.

10.7. Appendix 7: Examples of Infections that May Be Considered Opportunistic in the Setting of Biologic Therapy

This table lists examples of infections that may be considered opportunistic in the context of biologic therapy. This table is provided to aid the investigator in recognizing infections that may be considered opportunistic. This list is not exhaustive. For data analysis, infections will be categorized by Lilly as opportunistic according to the article by Winthrop et al. (2015).

Examples of Infections that May Be Considered Opportunistic in the Setting of Biologic Therapy

Bacterial	
	Bartonellosis (disseminated disease only)
	Campylobacteriosis (invasive disease only)
	Legionellosis
	Listeriosis (invasive disease only)
	Nocardiosis
	Tuberculosis
	Non-tuberculous mycobacterial disease
	Salmonellosis (invasive disease only)
	Shigellosis (invasive disease only)
	Vibriosis (invasive disease due to <i>Vibrio vulnificus</i>)
Viral	
	BK virus disease including polyomavirus-associated nephropathy
	Cytomegalovirus disease
	Hepatitis B virus reactivation
	Hepatitis C virus progression
	Herpes simplex (invasive disease only)
	Herpes zoster (any form)
	Post-transplant lymphoproliferative disorder (Epstein-Barr virus)
	Progressive multifocal leukoencephalopathy (PML), John Cunningham (JC) virus
Fungal	
	Aspergillosis (invasive disease only)
	Blastomycosis
	Candidiasis (invasive disease or oropharyngeal, esophageal. Not isolated lingual)
	Coccidioidomycosis
	Cryptococcosis
	Histoplasmosis
	Paracoccidioides infections
	Penicilliosis
	Pneumocystosis
	Sporotrichosis
	Other invasive molds: Mucormycosis (zygomycosis) (<i>Rhizopus</i> , <i>Mucor</i> , and <i>Lichtheimia</i>), <i>Scedosporium/Pseudallescheria boydii</i> , <i>Fusarium</i>
Parasitic	
	Leishmaniasis (visceral only)
	Strongyloidiasis (hyperinfection syndrome or disseminated disease)
	Microsporidiosis
	Toxoplasmosis
	Trypanosoma cruzi infection (Chagas' disease progression) (disseminated disease only)
	Cryptosporidiosis (chronic disease only)

Source: Based on Winthrop et al. (2015).

10.8. Appendix 8: American Academy of Dermatology: Criteria for the Diagnosis and Assessment of Atopic Dermatitis

Features to be considered in diagnosis of patients with AD:

Essential Features—Must be present:

- pruritus
- eczema (acute, subacute, chronic)
 - typical morphology and age-specific patterns*
 - chronic or relapsing history

*Patterns include:

- 1) facial, neck, and extensor involvement in infants and children
- 2) current or previous flexural lesions in any age group
- 3) sparing of the groin and axillary regions

Important Features—Seen in most cases, adding support to the diagnosis:

- early age of onset
- atopy
 - personal and/or family history
 - Immunoglobulin E reactivity
- xerosis

Associated Features—These clinical associations help to suggest the diagnosis of AD but are too nonspecific to be used for defining or AD for research and epidemiologic studies:

- atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
- keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- ocular/periorbital changes
- other regional findings (for example, perioral changes/periauricular lesions)
- perifollicular accentuation/lichenification/prurigo lesions

Exclusionary Features—It should be noted that a diagnosis of AD depends on excluding conditions, such as:

- scabies
- seborrheic dermatitis

- contact dermatitis (irritant or allergic)
- ichthyoses
- cutaneous T-cell lymphoma
- psoriasis
- photosensitivity dermatoses
- immune deficiency diseases
- erythroderma of other causes

Source: Eichenfield et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70(2):338-3351.

10.9. Appendix 9: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent/assent from the participant will be obtained, as required, and/or as required by ERB's and local regulations. Assent will also be obtained to the same parameters, with consent for participants reaching the legal age for consent during the study for continued participation, for:

- participation in remote visits, as defined in Section "Remote visits" below
- a change in the method of study intervention administration,
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Visit (V) 1, V2 and V10 are not allowed to be conducted remotely. And 2 consecutive remote visits are not allowed.

Types of remote visits

Telemedicine - Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to,

- concomitant medication,
- AE and SAE reports,
- participant diary education and compliance check,
- PROs via a tablet and/or a web-based collection system, and
- product complaints.

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Data capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of adverse events (AEs), serious adverse events (SAEs), and product complaints remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for samples listed below:

At...	Central laboratory testing must be retained for these samples...
Screen (V1); Week 0 (V2); Week 16 (V10)	All samples, unless local testing is specified in the SoA (Section 1.3) and Section 10.2.
All weeks/visits	PK, immunogenicity (ADA), and samples obtained because of a systemic hypersensitivity event (Section 10.2.1).

Central laboratory testing of PK and immunogenicity may be collected at the next visit.

The local laboratory must be qualified in accordance with applicable local regulations.

If a participant is unable to come to the site for central labs collections for routine safety monitoring, alternative methods to obtain pregnancy results are acceptable, e.g. home pregnancy test with results reviewed by the investigator.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include

- asking the participant to go to the site and receive study supplies (including study intervention injection) from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf (such as ediaary device, study intervention is not in the scope).

Screening period guidance

If the study screening window exceeds 30 days due to the exceptional circumstances, the participant would be considered a screen failure and may be rescreened. If rescreening is required more than once, it must first be approved by the sponsor.

The screening procedures per the Schedule of Activities (SoA) (Section 1.3) in the protocol should be followed (starting at Visit 1) to ensure participant eligibility by randomization visit (Visit 2). Before rescreening, the participant must sign a new ICF and receive a new identification number through IWRS.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA (Section 1.3). To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 3 through Visit 9	Within 7 days before the intended date, or up to 7 days after the intended date
Visit 10 through Visit 19	Within 14 days before the intended date, or up to 14 days after the intended date
Visit 20/early termination (ET) and Visit 801	Within 7 days before the intended date, or up to 14 days after the intended date.

Subsequent dosing should be a minimum of 7 days apart if the visit window is expanded due to extenuating circumstances.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.10. Appendix 10: Abbreviations and Definitions

Term	Definition
AAD	American Academy of Dermatology
ACQ-5	Asthma Control Questionnaire-5
AD	atopic dermatitis
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immune deficiency syndrome
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
blinding/masking	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
BMI	body mass index
BSA	body surface area
CBC	complete blood count
CDLQI	Children's Dermatology Life Quality Index
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatinine kinase
C_{avg,ss}	average concentration at steady state
CMV	Cytomegalovirus
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.

Term	Definition
CONSORT	consolidated standard of reporting trials
CRP	clinical research physician: individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CSR	clinical study report
C _{trough,ss}	concentration before the next dose at steady state
CXR	chest x-ray
D.Bil	direct bilirubin
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
EASI	Eczema Area and Severity Index
EASI-50	≥50% reduction from baseline in Eczema Area and Severity Index score
EASI-75	≥75% reduction from baseline in EASI score
EASI-90	≥90% reduction from baseline in EASI score
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
E-R	exposure-response
ERCP	endoscopic retrograde cholangiopancreatography
ET	early termination
FLG	Filaggrin
FSH	follicle stimulating hormone
GGT	gamma-glutamyltransferase
HADS	Hospital Anxiety Depression Scale
HBcAb	hepatitis B core antibody

Term	Definition
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HCV Ab	hepatitis C antibody
HIV	human immunodeficiency virus
HRQoL	health related quality-of-life
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN-γ	interferon γ
Ig	Immunoglobulin
IGA	Investigator's Global Assessment
IL	Interleukin
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IP	investigational product: a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
ISR	injection site reaction

Term	Definition
ITT	intent to treat: the principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participants allocated to a treatment group should be followed up, assessed, and analyzed as members of that group, irrespective of their compliance to the planned course of treatment.
IV	Intravenous
IWRS	interactive web-response system
JAK	Janus kinase
LDH	lactic dehydrogenase
LOR	Loricrin
LTBI	latent tuberculosis infection
MCMC-MI	Markov chain Monte Carlo Multiple Imputation
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MRCP	magnetic resonance cholangiopancreatography
MTX	Methotrexate
N/A	not applicable
NRS	numeric rating scale
NSD	needle safety device
participant	equivalent to Clinical Data Interchange Standards Consortium (CDISC) term “subject”: an individual who participates in a clinical study, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PCR	polymerase chain reaction
PD	pharmacodynamics
PFS	pre-filled syringe
PK	pharmacokinetics
POEM	Patient-Oriented Eczema Measure
PPD	purified protein derivative

Term	Definition
PT	preferred term
PT-INR	prothrombin time -international normalized ratio
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality-of-life
QTLs	quality tolerance limits
SAC	statistical analysis center
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
screen	The act of determining whether an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SoA	schedule of activities
SOC	system organ class
SMQ	Standardised MedDRA Query
Study KGAA	J2T-DM-KGAA, ADjoin
Study KGAB	J2T-DM-KGAB, ADvocate 1, DRM06-AD04 (AD04)
Study KGAC	J2T-DM-KGAC, ADvocate 2, DRM06-AD05 (AD05)
Study KGAD	J2T-DM-KGAD, ADhere, DRM06-AD06 (AD06)
Study KGAE	J2T-DM-KGAE, ADore
Study KGAF	J2T-DM-KGAF
TB	Tuberculosis
TBL	total bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid(s)

Term	Definition
TE ADA	treatment-emergent anti-drug antibodies
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TST	tuberculin skin test
ULN	upper limit of normal
VAS	visual analog scale
vs	Versus
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential
WPAI-AD	Work Productivity and Activity Impairment-Atopic Dermatitis

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