Protocol J2T-MC-KGBO(a)

An Open-Label Study to Evaluate the Safety and Efficacy of Lebrikizumab in Adult and Adolescent Participants with Moderate-to-Severe Atopic Dermatitis Previously Treated with Dupilumab

NCT05369403

Approval Date: 27-Apr-2023

Title Page

Protocol Title:

An Open-Label Study to Evaluate the Safety and Efficacy of Lebrikizumab in Adult and Adolescent Participants with Moderate-to-Severe Atopic Dermatitis Previously Treated with Dupilumab

Protocol Number: J2T-MC-KGBO

Amendment Number: a

Compound: lebrikizumab (LY3650150)

Brief Title:

A Study to Evaluate the Safety and Efficacy of Lebrikizumab in Adult and Adolescent Participants with Moderate-to-Severe Atopic Dermatitis Previously Treated with Dupilumab

Study Phase: 3b

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number:

IND: 119866

Document ID: VV-CLIN-093432

Approval Date: Protocol Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*16-Aug-2022*

Amendment [a]

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the interpretation of the data generated in the clinical study.

Overall Rationale for the Amendment:

The main rationale for this amendment is provided below

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis and 3. Objectives, Endpoints, and Estimands	Revised the primary clinical research question and the attributes of the primary estimand.	To ensure that the primary clinical research question, primary estimand, and primary analysis are in alignment. The original treatment policy estimand is not aligned with the as-observed analysis
6.6. Continued Access to Study Intervention after the End of the Study	Updated to allow continued access to lebrikizumab for eligible participants who complete Visit 9 (Week 24)	Provide an uninterrupted supply of lebrikizumab to qualified participants, via the Continued Access addendum, until lebrikizumab is commercially available in the US
6.8.1 Permitted Treatments and Procedures	Added use of high-potency TCS up to 10 days	Permitting high-potency TCS for up to 10 days is similar to the real-world setting
6.8.2 Prohibited Treatments and Procedures	Updated use of high-potency TCS for >10 days	Alignment with rescue treatment for Atopic Dermatitis
6.8.3 Non-medicated moisturizers	Clarified permitted use by adding the word ‘may’	The intent is to convey that the use of emollients is not mandatory, but recommended
6.8.4 Topical treatment for Atopic Dermatitis	Added use of high-potency TCS >10 days	Permitting high-potency TCS > 10 days will be considered as rescue medication
6.8.5 Rescue treatment for Atopic Dermatitis	Added use of high-potency TCS >10 days	

Section # and Name	Description of Change	Brief Rationale
9.2. Analyses Sets	Added “population” to describe ITT and Safety analysis set	Clarification
9.3.2. Primary Endpoint(s)/Estimand(s) Analysis	Revised the primary clinical question of interest	To align primary estimand with primary analysis. The original treatment policy estimand is not aligned with the as-observed analysis
9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis	Removed reference to the treatment policy strategy for secondary endpoints	To clarify that secondary endpoints will be analyzed similarly to the primary endpoint of the primary estimand, that is, using all observed data. The original treatment policy estimand is not aligned with the as-observed analysis
9.3.4. Exploratory Endpoint(s) Analysis	Removed reference to the treatment policy strategy for exploratory endpoints	To clarify that exploratory endpoints will be analyzed similarly to the primary endpoint of the primary estimand, that is, using all observed data. The original treatment policy estimand is not aligned with the as-observed analysis
10.3.6. Regulatory Reporting Requirements SAE Regulatory Reporting	Added text for suspected unexpected serious adverse reactions	Alignment with latest guidance
Throughout	Minor editorial changes have been made throughout	These are minor, therefore they have not been individually summarized

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

An Open-Label Study to Evaluate the Safety and Efficacy of Lebrikizumab in Adult and Adolescent Participants with Moderate-to-Severe Atopic Dermatitis Previously Treated with Dupilumab

Brief Title:

A Study to Evaluate the Safety and Efficacy of Lebrikizumab in Adult and Adolescent Participants with Moderate-to-Severe Atopic Dermatitis Previously Treated with Dupilumab

Rationale:

Atopic dermatitis (AD) is a chronic heterogeneous inflammatory skin disorder caused by skin barrier dysfunction and dysregulation of the immune response. Due to the heterogeneous nature of the disease, patients have diverse treatment needs. Standard treatment modalities for the management of these patients are centered around the use of topical anti-inflammatory preparations and skin moisturizers, but patients with moderate-to-severe disease may require phototherapy or systemic treatment. Dupilumab, a monoclonal antibody which inhibits the signaling of interleukin (IL)-4 and IL-13, was approved for the treatment of patients with moderate-to-severe AD in 2017. Patients that undergo treatment with dupilumab may show a limited or partial response or even no response at all to treatment. Other patients may show an initial response to treatment but lose response over time. Still others are found to be intolerant or have adverse effects to dupilumab. Additionally, in real world practice other patients discontinue treatment due to issues such as cost or loss of access (for example, insurance) to the drug. Taken together, a significant number of patients do not continue dupilumab treatment over the course of their chronic disease. In the pivotal monotherapy dupilumab phase 3 trials, 36% to 38% of participants achieved the primary endpoint of an Investigator Global Assessment (IGA) (0,1) with a ≥2-point reduction in IGA and 44% to 51% achieved Eczema Area and Severity Index-75 (EASI-75) data from baseline to Week 16, indicating that a significant proportion of the patients did not achieve clinical response. (Simpson et al. 2016).

Therefore, there is an important gap in the clinical care of these patients for whom novel therapies are necessary to fulfill this unmet medical need.

In patients with AD, IL-13, a central pathogenic mediator in the disease, is overexpressed, driving multiple aspects of AD pathophysiology by promoting T-helper type 2 (Th2) cell inflammation and resulting in skin barrier dysfunction, itch, infection, and lichenification.

Dupilumab is a monoclonal antibody that binds to the shared α subunit of the IL-4 and IL-13 receptors, thereby inhibiting the signaling of IL-4 and IL-13. IL-4 is the driver of the differentiation of naïve CD4+ T cells into Th2 cells and a negative regulator of Th1 and Th17 pathways. Blockade of Th2 differentiation by dupilumab might cause a dysregulation in the T-helper balance, providing a mechanistic explanation for the development of Th1/Th17 diseases

in dupilumab-treated patients (Tracey et al. 2018; Safa and Paumier 2019; Varma and Levitt 2020; Heibel et al. 2021).

IL-13 is considered a key cytokine in AD (Tsoi et al. 2019 and reviewed in Bieber et al. 2020). Lebrikizumab specifically blocks IL-13 and therefore also IL-13 signaling via the IL-4 receptor alpha (IL-4Rα)/IL-13 receptor alpha 1 (IL-13Rα1) heterodimer complex. Important differences between dupilumab and lebrikizumab include receptor vs cytokine targets, respectively, and known strong binding affinity and lack of effect on IL-4 signaling with lebrikizumab. In addition, IL-13 endogenous regulation remains intact when bound to lebrikizumab, because lebrikizumab does not inhibit the binding of IL-13 to the decoy receptor, IL-13Rα2.

Lebrikizumab phase 2 and 3 data demonstrated its efficacy in AD. Leveraging data from both phase 2b monotherapy and phase 3 topical corticosteroids (TCS) combination therapy in which dupilumab experienced patients were included, lebrikizumab showed consistent treatment effects in both dupilumab naïve and dupilumab experienced participants. Nevertheless, those trials were not designed to evaluate this specific patient population.

This trial aims to specifically evaluate the safety and efficacy of lebrikizumab in patients previously treated with dupilumab.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To evaluate efficacy of lebrikizumab 250 mg Q2W on reducing signs and symptoms of AD at Week 16 in participants with moderate-to-severe AD previously treated with dupilumab	• Percentage of participants achieving EASI-75 at Week 16
Secondary	
• To evaluate the efficacy of lebrikizumab on reducing signs and symptoms of AD at Week 16 and Week 24 in participants with moderate-to-severe AD previously treated with dupilumab	• Percentage of participants achieving EASI-75 at Week 24 • Percentage of participants with an IGA score of 0 or 1 and a reduction ≥2 points from baseline to Weeks 16 and 24 • Percentage change in EASI from baseline to Weeks 16 and 24 • Change in EASI from baseline to Weeks 16 and 24 • Percentage of participants achieving EASI-90 from baseline to Weeks 16 and 24

	• Percentage of participants with a Pruritus NRS of ≥4 points at baseline who achieve at least 4-point reduction at Weeks 16 and 24 • Percentage of participants with a Pruritus NRS ≥3 points at baseline who achieve at least 3-point reduction at Weeks 16 and 24 • Percentage change in Pruritus NRS score from baseline to Weeks 16 and 24 • Percentage of participants with a Sleep-Loss Scale of ≥2 points at baseline who achieve at least 2-point reduction at Weeks 16 and 24 • Change in Sleep-Loss Scale from baseline at Weeks 16 and 24 • Percentage of participants with a Skin Pain NRS of ≥4 points at baseline who achieve a 4-point reduction from baseline at Weeks 16 and 24 • Change in Skin Pain NRS from baseline to Weeks 16 and 24 • Change in DLQI from baseline to Weeks 16 and Week 24 for participants ≥16 years of age at baseline • Percentage of participants with at least 4-point at baseline achieving ≥4-point improvement in DLQI from baseline at Weeks 16 and 24 for participants ≥16 years of age at baseline • Change in cDLQI from baseline to Weeks 16 and 24 for participants <16 years of age at baseline • Percentage change in SCORAD from baseline to Weeks 16 Week 24

Abbreviations: AD = atopic dermatitis; cDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-75 = ≥75% reduction from baseline in EASI; EASI-90 = ≥90% reduction from baseline in EASI; IGA = investigator's global assessment; NRS = numeric rating scale; Q2W = once every 2 weeks; SCORAD = SCORing atopic dermatitis.

NOTE: Endpoints in the table above collected by visit references data collection visits.

Primary estimand

The primary clinical question of interest is: What is the intervention effect in percentage of participants achieving EASI-75 after 16 weeks of lebrikizumab 250 mg once every 2 weeks (Q2W) intervention in participants with moderate-to-severe AD, who have been previously treated with dupilumab and who remain on study treatment until Week 16.

The estimand is described by the following attributes:

Population: participants with moderate-to-severe AD who have been previously treated with dupilumab and who remain on study treatment until Week 16.

Further details can be found in Section 5.

Endpoint: Do participants achieve at least 75% improvement from baseline to Week 16 in EASI.

Intercurrent events: There are no intercurrent events for this population since participants who initiate rescue medication are discontinued from the study and hence study treatment. Therefore, participants who stay on study treatment through Week 16 will not have an intercurrent event such as initiating rescue medication or permanently discontinuing treatment.

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

Secondary estimand(s)

There is no secondary estimand planned at this stage, however, additional estimand(s) might be specified in the statistical analysis plan (SAP).

Overall Design

Study J2T-MC-KGBO (KGBO) is an open-label, Phase 3b study, which is 24 weeks in treatment duration. The study is designed to evaluate the safety and efficacy of lebrikizumab in adults and adolescents (≥12 years to <18 and weighing ≥40 kg) with moderate-to-severe AD and previously treated with dupilumab.

During the 24-week Treatment Period, approximately 120 participants will receive treatment:

- 500 mg subcutaneous (SC) once every 2 weeks (Q2W) loading dose at baseline and Week 2, followed by 250 mg SC Q2W until Week 16.
- Responders, defined as achieving IGA (0,1) or EASI-75 at Week 16, will receive 250 mg SC once every 4 weeks (Q4W).
- Inadequate responders at Week 16 will continue to receive 250 mg SC Q2W.

Brief Summary:

The purpose of this study is to determine the proportion of participants achieving EASI-75 at Week 16 with lebrikizumab in participants with moderate-to-severe AD previously treated with dupilumab.

Study details include:

- The planned study duration will be up to 38 weeks.
- The treatment duration will be up to 24 weeks.

- The visit frequency will be every 2 weeks for the first 2 visits, then every 4 weeks thereafter.

Number of Participants:

Approximately 120 participants previously treated with dupilumab will be enrolled to study intervention. Among those, approximately 80 participants will be enrolled who discontinued dupilumab due to: a) no response to treatment, b) a partial response to treatment, or c) who lost response to treatment. Additionally, approximately 15 participants will be enrolled who discontinued dupilumab treatment due to intolerance or adverse events (AEs). Finally, approximately 25 participants will be enrolled who stopped dupilumab treatment for other reasons (for example, cost, insurance coverage, access to medication, previous trial participants). Approximately 10% (n=12) of participants will be adolescents (12 to less than 18 who weigh at least 40 kg).

Intervention Groups and Duration:

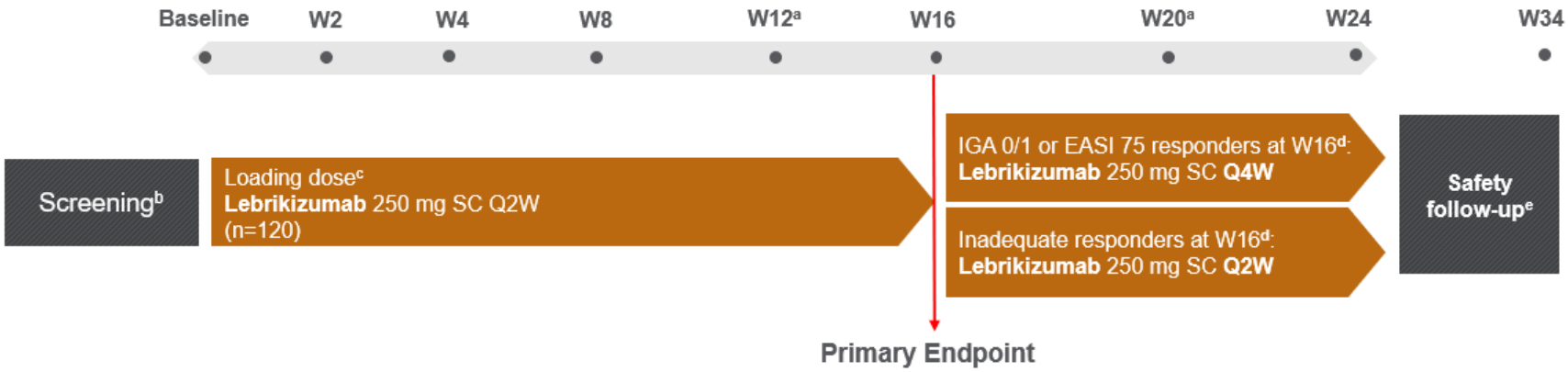
Lebrikizumab drug product is provided as sterile liquids and contain no preservatives.

Intervention Name	**Lebrikizumab**
Dose Formulation	**250 mg (125 mg/mL), 2 mL Solution**
Dosage Level	**Loading Dose:** **Week 0**: 500 mg (2 injections of 250 mg) **Week 2**: 500 mg (2 injections of 250 mg) **Post-loading dose:** **Weeks 4-16:** 250 mg SC Q2W (1 injection of 250 mg) **Responders at Week 16:** 250 mg SC Q4W (1 injection of 250 mg) at W20 **Inadequate responders at Week 16**: 250 mg SC Q2W (1 injection of 250 mg) at W18, W20, and W22
Route of Administration	**SC**

Abbreviations: mg = milligram; mL = milliliter; SC = subcutaneously; Q2W = once every 2 weeks; Q4W = once every 4 weeks; W = week.

Data Monitoring Committee: No

1.2. Schema



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

[a] Weeks 12 and 20 are phone visits.

[b] 30-day screening window.

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

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

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

1.3. Schedule of Activities (SoA)

	Period I	Period II									Period III	Comments
	Screening	Baseline	Treatment Period								Post-Treatment Follow-up	
Visit Number	1	2	3	4	5	6	7	8	9	ED	801	
Week Relative to Study Drug Start	≤30 (days)	0	2	4	8	12	16	20	24	-	Approximately 12 weeks post last dose	
Visit Interval Tolerance (Days)		–	±3	±3	±5	±5	±5	±5	±5	-	±7	
Visit Detail						T		T				
Informed consent and assent	X											The informed consent must be signed before any protocol-specific tests or procedures are performed. Parent or legally authorized representative signs ICF as appropriate per local requirements. Assent will be collected as specified by ethics board. See Section 10.1.3 for additional details.
Inclusion and exclusion criteria, review and confirm	X	X										Inclusion or exclusion criteria should be confirmed-prior to drug assignment and administration of first dose of study intervention.
Demographics	X											Includes: • ethnicity, sex, and race • full date of birth for participants 12-17 years of age, and • year of birth for participants ≥18 years of age.
Preexisting conditions and medical history, including relevant surgical history	X											All conditions ongoing and relevant past surgical and medical history should be collected.

	Period I	Period II									Period III	Comments
	Screening	Baseline	Treatment Period								Post-Treatment Follow-up	
Visit Number	1	2	3	4	5	6	7	8	9	ED	801	
Week Relative to Study Drug Start	≤30 (days)	0	2	4	8	12	16	20	24	-	Approximately 12 weeks post last dose	
Visit Interval Tolerance (Days)		–	±3	±3	±5	±5	±5	±5	±5	-	±7	
Visit Detail						T		T				
Prespecified medical history (indication and history of interest)	X											Additional data for the indication and comorbidities of interest are collected, (including conjunctivitis and facial dermatitis).
Record prior treatments for indication	X											Includes medications and therapies for AD.
Review immunization record	X											The investigator should review the vaccination status of each pediatric participant <18 years of age to assess if the participant is up to date with immunizations following the local guidelines for vaccination with vaccines intended to prevent infectious disease prior to enrolling participants into the study. For participants who are under-vaccinated, the investigator should document the benefit or risk rationale for enrolling the participants in the study.
Review menarche status with date of menarche (if applicable)	X	X	X	X	X		X		X	X		For participants <18 years of age. If the participant reaches menarche at any time during the trial and is sexually active, pregnancy testing and contraception requirements will apply. See Section 10.4, Appendix 4.

	Period I	Period II									Period III	Comments
	Screening	Baseline	Treatment Period								Post-Treatment Follow-up	
Visit Number	1	2	3	4	5	6	7	8	9	ED	801	
Week Relative to Study Drug Start	≤30 (days)	0	2	4	8	12	16	20	24	-	Approximately 12 weeks post last dose	
Visit Interval Tolerance (Days)		–	±3	±3	±5	±5	±5	±5	±5	-	±7	
Visit Detail						T		T				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the ICF or assent are considered AEs as defined in Section 10.3, Appendix 3**.** For AESIs, additional data could be collected. See Section 8.3.3.
Physical Evaluation												
Height	X								X			
Weight	X	X					X		X	X		
Vital signs	X	X					X		X	X		Includes pulse rate, blood pressure, respiratory rate, and temperature. Measured after participant has been sitting at least 5 minutes. Use size appropriate blood pressure cuffs.
Physical examination	X								X	X		The physical examination is performed (excludes pelvic and rectal, unless clinically indicated). Full skin examination is required for BSA calculation.
Symptom-directed physical assessment		X	X	X	X		X				X	As indicated based on participant status and standard of care. May be performed by qualified personnel per local regulations.

	Period I	Period II									Period III	Comments
	Screening	Baseline	Treatment Period								Post-Treatment Follow-up	
Visit Number	1	2	3	4	5	6	7	8	9	ED	801	
Week Relative to Study Drug Start	≤30 (days)	0	2	4	8	12	16	20	24	-	Approximately 12 weeks post last dose	
Visit Interval Tolerance (Days)		–	±3	±3	±5	±5	±5	±5	±5	-	±7	
Visit Detail						T		T				
Participant Diary (Electronic)												
Diary dispensed	X											Diary includes daily collection of PRO assessments (Pruritus NRS, Sleep-Loss Scale, and Skin Pain NRS); bi-weekly collection of study drug administration information (as applicable). TCS usage will be collected daily beginning at V2. Pruritus NRS and Sleep-Loss Scale should be completed a minimum of 4 of 7 days before baseline.
Review diary for completion of PRO and TCS assessments		X	X	X	X	X	X	X	X	X		For details of these assessments see Section 8.1.
Drug administration diary compliance check					X	X	X	X	X	X		
Diary return									X	X		
PROs (Electronic) ***Complete prior to any clinical administered assessments***												
DLQI		X					X		X	X		Only for participants ≥16 years of age at baseline.

	Period I	Period II									Period III	Comments
	Screening	Baseline	Treatment Period								Post-Treatment Follow-up	
Visit Number	1	2	3	4	5	6	7	8	9	ED	801	
Week Relative to Study Drug Start	≤30 (days)	0	2	4	8	12	16	20	24	-	Approximately 12 weeks post last dose	
Visit Interval Tolerance (Days)		–	±3	±3	±5	±5	±5	±5	±5	-	±7	
Visit Detail						T		T				
cDLQI		X					X		X	X		Only for participants <16 years of age at baseline.
WPAI-AD		X					X		X	X		
ADCT		X		X			X		X	X		
Participant-Reported Satisfaction Question							X		X	X		
Clinical-Administered Assessments (Electronic)												
IGA	X	X	X	X	X		X		X	X		
F-IGA		X	X	X	X		X		X	X		
EASI	X	X	X	X	X		X		X	X		
BSA	X	X	X	X	X		X		X	X		
mTLSS		X		X			X		X	X		
SCORAD		X					X		X	X		
Clinical-Administered Assessments (Paper)												
Fitzpatrick Skin Type Assessment		X										

	Period I	Period II									Period III	Comments
	Screening	Baseline	Treatment Period								Post-Treatment Follow-up	
Visit Number	1	2	3	4	5	6	7	8	9	ED	801	
Week Relative to Study Drug Start	≤30 (days)	0	2	4	8	12	16	20	24	-	Approximately 12 weeks post last dose	
Visit Interval Tolerance (Days)		–	±3	±3	±5	±5	±5	±5	±5	-	±7	
Visit Detail						T		T				
Participant Education and Supplies												
Participant or caregiver instructions on diary completion	X											Education can also be performed, as needed.
Remind participant of TCS usage restrictions and expectations	X											Required 2 week wash out of TCS prior to Visit 2. See Section 6.8.1 for TCS usage during the study.
Train participant and/or caregiver on study intervention administration			X	X								Participants and/or caregivers need to be adequately trained on injection technique prior to administering injections. Training can be done at Week 2 and/or Week 4 prior to self-administration.
Dispense ancillary supplies for at home dosing				X	X		X					
Laboratory Tests and Sample Collections												
Hematology	X	X		X			X		X	X	X	
Clinical chemistry	X	X					X		X	X	X	

	Period I	Period II									Period III	Comments
	Screening	Baseline	Treatment Period								Post-Treatment Follow-up	
Visit Number	1	2	3	4	5	6	7	8	9	ED	801	
Week Relative to Study Drug Start	≤30 (days)	0	2	4	8	12	16	20	24	-	Approximately 12 weeks post last dose	
Visit Interval Tolerance (Days)		–	±3	±3	±5	±5	±5	±5	±5	-	±7	
Visit Detail						T		T				
Serum pregnancy	X											Only for WOCBP. Pregnancy tests prior to first dose of study intervention for females ≥12 years of age if menarche reached or if there is reason to believe the participant is sexually active. Pregnancy test results from baseline must be known prior to first dose of study intervention. See Section 10.4, Appendix 4.
Urine pregnancy (local)		X		X	X		X		X	X		Collect for WOCBP only. Done locally and prior to administering study intervention. Additional pregnancy tests (beyond those required per the SoA) should be performed at any time during the trial if a menstrual period is missed, there is clinical suspicion of pregnancy. See Section 10.4, Appendix 4. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.
HIV screening tests	X											
HCV screening tests	X											If anti-HCV is positive, it must be followed by a HCV RNA test. See Section 8.2.4.
HBV screening tests	X											Includes testing for HBsAg, HBcAb and HBsAb.

	Period I	Period II									Period III	Comments
	Screening	Baseline	Treatment Period								Post-Treatment Follow-up	
Visit Number	1	2	3	4	5	6	7	8	9	ED	801	
Week Relative to Study Drug Start	≤30 (days)	0	2	4	8	12	16	20	24	-	Approximately 12 weeks post last dose	
Visit Interval Tolerance (Days)		–	±3	±3	±5	±5	±5	±5	±5	-	±7	
Visit Detail						T		T				
HBV DNA	X						X			X	X	If HBsAg is negative and HBcAb is positive at screening, further testing for HBV DNA is required. See Section 8.2.3.
IgE		X		X			X		X	X		Collect prior to dosing.
Exploratory Biomarkers		X		X			X		X	X		Collect prior to dosing.
PK samples		X		X					X	X		Samples to be collected predose. If an immediate or nonimmediate systemic drug hypersensitivity reaction occurs in any participant, then also collect an additional unscheduled sample as detailed in Section 8.4.
Immunogenicity (ADA) samples		X		X					X	X		Samples to be collected predose. If an immediate or nonimmediate systemic drug hypersensitivity reaction occurs in any participant then also collect an additional unscheduled sample as detailed in Section 10.2.1.
Stored Samples												
Genetics sample		X										Sample can be obtained at or after the specified visit.
Exploratory biomarker samples		X		X			X		X	X		Collect predose.

	Period I	Period II									Period III	Comments
	Screening	Baseline	Treatment Period								Post-Treatment Follow-up	
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Visit Interval Tolerance (Days)		–	±3	±3	±5	±5	±5	±5	±5	-	±7	
Visit Detail						T		T				
Registration and Dosing												
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	
Dispense study intervention via IWRS		X	X	X	X		X					
Administer study intervention in clinic		X	X	X	X		X					Week 0 (Visit 2) and Week 2, dose to be administered in the clinic by site. Weeks 4, 8, and 16 dosing to be performed in clinic administered by site or participant or caregiver.
Dispense study intervention to participant for at home dosing				X	X		X					Injections will be administered by participant or caregiver at home on Weeks 6, 10, 12, and 14. Responders at Week 16 who will receive Q4W dose will administer study intervention at Week 20. Inadequate responders at Week 16 who will receive Q2W dosing will administer study intervention at Weeks 18, 20, and 22.
Observe participant or caregiver administer study intervention				X								

	Period I	Period II									Period III	Comments
	Screening	Baseline	Treatment Period								Post-Treatment Follow-up	
Visit Number	1	2	3	4	5	6	7	8	9	ED	801	
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Visit Interval Tolerance (Days)		–	±3	±3	±5	±5	±5	±5	±5	-	±7	
Visit Detail						T		T				
Participant returns study intervention					X		X		X	X		If study intervention was administered at home by participant or caregiver, the injection supplies should be saved and returned at the next on-site visit.
Assess study intervention compliance					X		X		X			

Abbreviations: AD = atopic dermatitis; ADA = anti-drug antibody; ADCT = atopic dermatitis control tool; AE = adverse event; AESI = adverse event of special interest; BSA = body surface area; cDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; EASI = Eczema Area and Severity Index; ED = early discontinuation; F-IGA = face-IGA; 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; ICF = informed consent form; IgE = immunoglobulin E; IGA = investigator's global assessment; IWRS = interactive web-response system; mTLSS = Modified Total Lesion Symptom Scale; NRS = numeric rating scale; PK = pharmacokinetics; PRO = patient-reported outcome; Q2W = once every 2 weeks; Q4W = once every 4 weeks; RNA = ribonucleic acid; SCORAD = SCORing atopic dermatitis; T = Telephone; TCS = topical corticosteroids; WOCBP = women of child-bearing potential; WPAI-AD = Work Productivity and Activity Impairment Questionnaire - Atopic Dermatitis.

2. Introduction

Lebrikizumab (LY3650150) is a monoclonal antibody based on the immunoglobulin G4 antibody stabilized by a mutated Fc region. Lebrikizumab binds with high affinity specifically to soluble interleukin (IL)-13 and blocks IL-13 signaling through the IL-4 receptor alpha (IL-4Rα) or IL-13 receptor alpha 1 (IL-13Rα1) pathway, thereby preventing the downstream effects of human IL-13 with high potency. Blockade of IL-13 signaling is expected to be of benefit in diseases in which IL-13 is a key contributor to the disease pathogenesis.

2.1. Study Rationale

Atopic dermatitis (AD) is a chronic heterogeneous inflammatory skin disorder caused by skin barrier dysfunction and dysregulation of the immune response. Due to the heterogeneous nature of the disease, patients have diverse treatment needs. Standard treatment modalities for the management of these patients are centered around the use of topical anti-inflammatory preparations and skin moisturizers, but patients with moderate-to-severe disease may require phototherapy or systemic treatment. Dupilumab, a monoclonal antibody which inhibits the signaling of IL-4 and IL-13, was approved for the treatment of patients with moderate-to-severe AD. Dupilumab was the first available biologic for patients with chronic moderate-to-severe AD for which topical treatment provided inadequate control or was medically inadvisable. A proportion of patients that undergo treatment with dupilumab may show a limited or partial response or even no response at all to treatment. Other patients may show an initial response to treatment but lose response over time. Still others are found to be intolerant or have adverse effects to dupilumab. Additionally, in real world practice other patients discontinue treatment due to issues such as cost or loss of access (for example, insurance) to the drug. Taken together, a significant number of patients do not continue dupilumab treatment over the course of their chronic disease. In the pivotal monotherapy dupilumab Phase 3 trials, 36% to 38% of participants achieved the primary endpoint of an Investigator's Global Assessment (IGA) (0,1) with a ≥2-point reduction in IGA and 44% to 51% achieved Eczema Area and Severity Index-75 (EASI-75) data from baseline to Week 16, indicating that a significant proportion of the patients did not achieve clinical response. (Simpson et al. 2016).

Therefore, there is an important gap in the clinical care of these patients for whom novel therapies are necessary to fulfill this unmet medical need.

In patients with AD, IL-13, a central pathogenic mediator in the disease, is overexpressed, driving multiple aspects of AD pathophysiology by promoting T-helper type 2 (Th2) cell inflammation and resulting in skin barrier dysfunction, itch, infection, and lichenification.

Dupilumab is a monoclonal antibody that binds to the shared α chain subunit of the IL-4 and IL-13 receptors, thereby inhibiting the signaling of IL-4 and IL-13. IL-4 is the driver of the differentiation of naïve CD4+ T cells into T-helper Type 2 (Th2) cells and a negative regulator of T-helper Type 1 (Th1) and T-helper Type 17 (Th17) pathways. Blockade of Th2 differentiation by dupilumab might cause a dysregulation in the T-helper balance, providing a mechanistic explanation for the development of Th1 or Th17 diseases in dupilumab-treated patients (Tracey et al. 2018; Safa and Paumier 2019; Varma and Levitt 2020; Heibel et al. 2021).

IL-13 is considered a key cytokine in AD (Tsoi 2019 and reviewed in Bieber et al. 2020). Lebrikizumab specifically blocks IL-13 and therefore also IL-13 signaling via the IL-4Rα - IL-13Rα1 heterodimer complex. Important differences between dupilumab and lebrikizumab include receptor vs cytokine targets, respectively, and known strong binding affinity and lack of effect on IL-4 signaling with lebrikizumab. In addition, IL-13 endogenous regulation remains intact when bound to lebrikizumab, because lebrikizumab does not inhibit the binding of IL-13 to the decoy receptor, IL-13Rα2.

Lebrikizumab Phase 2 and 3 data demonstrated its efficacy in AD. Leveraging data from both Phase 2b monotherapy and Phase 3 TCS combination therapy in which dupilumab experienced patients were included, lebrikizumab showed consistent treatment effects in both dupilumab naïve and dupilumab experienced participants. Nevertheless, those trials were not designed to evaluate this specific patient population.

This trial aims to specifically evaluate the safety and efficacy of lebrikizumab in patients previously treated with dupilumab. Biologics experienced patients requiring a second biological therapy constitute an important and constantly expanding clinical conundrum in immune mediated diseases. The results from this trial will provide insights into the clinical response in this difficult to treat population and its comparison with the response in dupilumab naïve population studied in the pivotal Phase 3 programs.

2.2. Background

Atopic dermatitis is a complex heterogeneous 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 immunoglobulin E (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, pruritus and decrease the expression of antimicrobial peptides and the barrier proteins FLG, LOR, and involucrin (Caretti et al. 2015). 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). Itch is one of the predominant symptoms in AD and studies have shown IL-13 acts as a potent neuronal enhancer to itch signals, resulting in amplification of histaminergic and non-histaminergic itch in human sensory neurons and driving the persistence of heightened chronic itch, as seen in AD. Miron et al. recently published results from human cadaveric neurons stimulated with IL-13, in the absence or presence of lebrikizumab. Lebrikizumab blocked the neuronal response to multiple itch stimuli and may be an effective treatment for chronic itch (Miron et al. 2022).

Epidemiology of Atopic Dermatitis

The one-year prevalence of AD among adults is estimated between 2% to 7% in the US, Europe, and Japan (Saeki et al. 2006; Harrop et al. 2007; Diepgen et al. 2016; Sacotte and Silverberg 2018). Approximately 30% of adult patients with AD have moderate-to-severe disease (Bieber and Straeter 2015).

Clinical Manifestations

Clinically, AD is characterized by erythematous and sometimes violaceous to brown macules, papules and/or plaques with scale, 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 and skin types, have been noted (Weidinger and Novak 2016; Weidinger et al. 2018).

Classic AD lesions, which are most common in adolescents and adults, present on the antecubital and popliteal fossae. Lesions frequently localize to the face and neck, and a considerable portion of patients (around 30%) develop atopic hand dermatitis, which may interfere with workplace activities. Lesions may have associated lichenification and crusting, and patients with AD may be at increased risk for bacterial cutaneous superinfection.

Quality of Life (QoL)

Patients with AD have a high disease burden, and their quality of life (QoL) 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). Adolescent 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 adolescent patients with AD but also affect their caregivers (Zuberbier et al. 2006). Compared with patients with psoriasis, another common and debilitating skin disease, adult and adolescent patients with AD have lower physical vitality, social functioning, role-emotional, and mental health scores (Kiebert et al. 2002; Langan et al. 2020; Eckert et al. 2018, 2019; Vakharia et al. 2017; Silverberg et al. 2018, 2019).

Treatment for Atopic Dermatitis

The therapeutic approach to AD consists primarily of trigger avoidance, skin hydration, and use of moisturizers and anti-inflammatory therapies consisting predominantly of topical

corticosteroids (TCS). In many patients, treatment with TCS provides some measure of symptomatic relief but does not always adequately control the disease. In patients not responding adequately to TCS, the topical TCI step-up options include phototherapy and systemic immunosuppressive agents such as oral or injected corticosteroids, cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. In 2017, dupilumab, a monoclonal antibody that binds specifically to the shared α chain subunit of the IL-4 and IL-13 receptors, thereby inhibiting the signaling of IL-4 and IL-13, was approved for the treatment of adult patients with moderate-to-severe AD (Seegräber et al. 2018; Gooderham et al. 2018). In 2 randomized clinical trials, SOLO 1 and SOLO 2, dupilumab demonstrated better results than placebo over 16 weeks of treatment across multiple outcome measures that reflected objective signs of AD, subjective symptoms (for example, pruritus), important aspects of mental health (that is, anxiety and depression), and QoL. In these trials, 36% to 38% of participants achieved the primary endpoint of an IGA (0,1) with a ≥2-point reduction in IGA and 44% to 51% achieved EASI-75 data from baseline to Week 16, indicating that a significant proportion of the patients did not achieve clinical response. (Simpson et al. 2016).

In 2021 an IL-13 antagonist, tralokinumab, was approved for adults with moderate-to-severe AD. Also in 2021, the topical Janus kinase (JAK) inhibitor ruxolitinib was approved for the treatment of mild to moderate AD in adults and children age 12 and older, and in 2022 the oral JAK inhibitors, upadacitinib, and abrocitinib, were approved for treatment of moderate-to-severe AD in adults and children age 12 and older and adults, respectively.

Despite this availability of new medications for the treatment of moderate-to-severe AD, dupilumab was the first available biologic for the treatment of moderate-to-severe AD, and may continue to be widely used. However, dupilumab is not effective or acceptable for every patient and discontinuation of dupilumab therapy is known to occur; there is a need to fill this clinical care gap to improve the lives of patients. (Marniquet et al. 2022 and Faiz et al. 2019). There are limited data on the reasons for dupilumab discontinuation. A multicenter study confirmed that 15.5% (150/968) of patients discontinued dupilumab over a 3.5-year period. (Marniquet et al. 2022) Reasons for discontinuation included side effects (40.7%), lack of efficacy (14.7%), both side effects and lack of efficacy (15.3%), planned pregnancy (8%), disease remission (4%) and “other” (17.3%). Side effects included ophthalmological (24%), facial erythema (8%), diffuse AD exacerbation (6.7%), eosinophilia (4%), alopecia areata (2.7%), psoriasis (2.7%), headache (0.7%), injection site reaction (0.7%) and “other” (5.3%). Another French study confirmed that of 241 patients taking dupilumab for moderate-to-severe AD from 29 centers, 79.7% remained on the medication at 6 months. (Faiz et al. 2019). Of the 42 patients for which data were available, reasons for discontinuation included adverse event (AE) (11.3%), inefficiency (3.8%), patient wish (3.4%), pregnancy (<1%), surgery (1.7%) and improvement of AD (<1%). AEs included ophthalmologic (4.2%), eosinophilia (2.1%) and “other” (5%).

Lebrikizumab is an IL-13 inhibitor which has been shown to be highly effective and safe for the treatment of adults and adolescents with moderate-to-severe AD in Phase 2 and 3 clinical trials. Lebrikizumab is a potential treatment candidate to fill the clinical care gap for patients with moderate-to-severe AD who discontinued dupilumab because of lack of efficacy, loss of effect, intolerance or AEs, or for other reasons.

A detailed description of the chemistry, pharmacology, efficacy, and safety of lebrikizumab is provided in the Investigator’s Brochure (IB).

2.3. Benefit/Risk Assessment

As of 22 September 2021, cumulatively, approximately 7795 participants have been enrolled into the lebrikizumab clinical program, of which approximately 6374 participants have received lebrikizumab. Lebrikizumab has been given to 525 healthy people and 5849 study participants with AD, asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and Hodgkin's lymphoma. Approximately 2051 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/TREBLE, J2T-DM-KGAH/ARBAN and J2T-DM-KGAF/DRM06-AD01) demonstrated significant clinical benefit in participants with AD. The top-line results from the 2 monotherapy Phase 3 studies of lebrikizumab (ADvocate 1 and ADvocate 2) 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 (ADhere) 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 8.3.4), and other infections (Section 8.3.3.1).

In the initial 16-week placebo-controlled period of ADvocate 1 and ADvocate 2, the incidence of treatment-emergent AEs and serious AEs among patients treated with lebrikizumab was consistent with that of the previous Phase 2 lebrikizumab studies in AD. The most common AEs included conjunctivitis, nasopharyngitis, and headache for lebrikizumab-treated patients. 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 immediate systemic hypersensitivity or anaphylaxis events were reported in the Phase 3 trials ADvocate 1, ADvocate 2, and ADhere. 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, 8.3.4, and 8.3.5.

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 3b study.

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

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To evaluate efficacy of lebrikizumab 250 mg Q2W on reducing signs and symptoms of AD at Week 16 in participants with moderate-to-severe AD previously treated with dupilumab	• Percentage of participants achieving EASI-75 at Week 16
Secondary	
• To evaluate the efficacy of lebrikizumab on reducing signs and symptoms of AD at Week 16 and Week 24 in participants with moderate-to-severe AD previously treated with dupilumab	• Percentage of participants achieving EASI-75 at Week 24 • Percentage of participants with an IGA score of 0 or 1 and a reduction ≥2 points from baseline to Weeks 16 and 24 • Percentage change EASI from baseline to Weeks 16 and 24 • Change in EASI from baseline to Weeks 16 and 24 • Percentage of participant achieving EASI-90 from baseline to Weeks 16 and 24 • Percentage of participants with a Pruritus NRS of ≥4 points at baseline who achieve at least 4-point reduction at Weeks 16 and 24 • Percentage of participants with a Pruritus NRS of ≥3 points at baseline who achieve at least 3-point reduction at Weeks 16 and 24 • Percentage change in Pruritus NRS score from baseline to Weeks 16 and 24 • Percentage of participants with a Sleep-Loss Scale of ≥2 points at baseline who achieve at least 2-point reduction at Weeks 16 and 24 • Change in Sleep-Loss Scale from baseline at Weeks 16 and 24 • Percentage of participants with a Skin Pain NRS of ≥4 points at baseline who achieve a

	4-point reduction from baseline at Weeks 16 and 24 • Change in Skin Pain NRS from baseline to Weeks 16 and 24 • Change in DLQI from baseline to Weeks 16 and 24 for participants ≥16 years of age at baseline • Percentage of participants with at least 4 point at baseline achieving ≥4-point improvement in DLQI from baseline at Weeks 16 and 24 for participants ≥16 years of age at baseline • Change in cDLQI from baseline to Weeks 16 and 24 for participants <16 years of age at baseline • Percentage change in SCORAD from baseline to Weeks 16 and 24
Exploratory	

To evaluate the efficacy of lebrikizumab in participants with moderate-to-severe AD previously treated with dupilumab	• Percentage change from baseline in mTLSS (hands) at Weeks 16 and 24
	• Percentage change in ADCT from baseline by visit
	• Proportion of TCS/TCI-free days from baseline to Weeks 16 and 24
	• Using WPAI-AD by visit, change in baseline in:
	  • absenteeism, in those who are currently employed (working for pay)
	  • presenteeism, in those who are currently employed (working for pay),
	  • overall work impairment, in those who are currently employed (working for pay),
	  • impairment in activities (all participants)
	• Percentage of participants with an F-IGA score of 0 or 1 and a reduction ≥2 points from baseline by visit in those who have baseline at least 2 points

	• Percentage of participants achieving EASI-75 by visit • Percentage of participants with an IGA score of 0 or 1 and a reduction ≥2 points from baseline by visit • Percentage change in EASI by visit • Change in EASI by visit • Percentage of participants achieving EASI-90 by visit • Percentage of participants with a Pruritus NRS of ≥4 points at baseline who achieve a 4-point reduction by visit • Percentage of participants with a Pruritus NRS of ≥3 points at baseline who achieve a 3-point reduction by visit • Percentage change in Pruritus NRS score from baseline to Weeks 16 and 24 • Percentage of participants with a Sleep-Loss Scale of ≥2 points at baseline who achieve a 2-point reduction by visit • Change in Sleep-Loss Scale from baseline by visit • Percentage of participants with a Skin Pain NRS of ≥4 points at baseline who achieve a 4-point reduction from baseline by visit • Distribution of responses for participant satisfaction (1 question) at Weeks 16 and 24
To discern responder variability within the study and to track response variability to lebrikizumab	Changes from baseline in serum proteins related to AD pathogenesis; Refer to Section 10.2, Appendix 2

Abbreviations: AD = atopic dermatitis; ADCT = atopic dermatitis control tool; cDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-75 = ≥75% reduction from baseline in EASI; EASI-90 = ≥90% reduction from baseline in EASI; F-IGA = face - investigator's global assessment; IGA = investigator's global assessment; mTLSS = Modified Total Lesion Symptom Scale; NRS = numeric rating scale; Q2W = once every 2 weeks; SCORAD = SCORing atopic dermatitis; TCI = topical calcineurin inhibitors, TCS = topical corticosteroid; WPAI-AD = work productivity and activity impairment questionnaire–atopic dermatitis.

NOTE: Endpoints in the table above collected by visit references data collection visits.

Primary estimand

The primary clinical question of interest is: What is the intervention effect in percentage of participants achieving EASI-75 after 16 weeks of lebrikizumab 250 mg once every 2 weeks

(Q2W) intervention in participants with moderate-to-severe AD, who have been previously treated with dupilumab and who remain on study treatment until Week 16.

The estimand is described by the following attributes:

Population: participants with moderate-to-severe AD who have been previously treated with dupilumab and who remain on study treatment until Week 16.

Further details can be found in Section 5.

Endpoint: Do participants achieve at least 75% improvement from baseline to Week 16 in EASI.

Intercurrent events: There are no intercurrent events for this population since participants who initiate rescue medication are discontinued from the study and hence study treatment. Therefore, participants who stay on study treatment through Week 16 will not have an intercurrent event such as initiating rescue medication or permanently discontinuing treatment. Further details on study interventions and concomitant medications, including rescue treatments, can be found in Section 6.8.1.

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

Secondary estimand(s)

There is no secondary estimand planned at this stage, however, additional estimand(s) might be specified in the SAP.

4. Study Design

4.1. Overall Design

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

Study Periods

This trial has 3 study periods:

- Screening (Visit 1: ≤30 days prior to baseline)
- Treatment (Visits 2-9: 24 weeks)
- Safety follow-up (Visit 801: approximately 12 weeks after last treatment)

Visit Types

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

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

Dosing

During the 24-week Treatment Period, approximately 120 participants will receive treatment:

- 500 mg subcutaneous (SC) once every 2 weeks (Q2W) loading dose at baseline and Week 2, followed by 250 mg SC Q2W until Week 16.
- Responders, defined as achieving IGA (0,1) or EASI-75 at Week 16, will receive 250 mg SC Q4W.
- Inadequate responders at Week 16 will continue to receive 250 mg SC Q2W.

The study population is described in Section 5.

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

4.2. Scientific Rationale for Study Design

The top-line results from 2 randomized controlled monotherapy phase 3 studies of lebrikizumab (ADvocate 1 and ADvocate 2) and a third completed phase 3 trial of lebrikizumab in combination with topical steroids (ADhere) demonstrated positive risk benefit in adult and adolescent patients with moderate-to-severe AD at Week 16. The safety profile of these 3 studies was consistent with prior AD lebrikizumab studies and demonstrated favorable benefit: risk profile in moderate-to-severe AD patients. Additional detailed discussion of the lebrikizumab studies (preclinical and clinical) is provided in the lebrikizumab IB.

Since randomized controlled data is already available, this study will be conducted as an open label study to mimic the real-world patient experience. Week 16 data will be used as the primary endpoint in this study and the safety and efficacy until Week 24 will also be evaluated to understand the durability of effect post Week 16.

The open-label trial design is appropriate as no direct comparison of therapeutic treatments will be made. Rather, this study will determine the efficacy and safety of lebrikizumab treatment in a patient population that previously discontinued use of dupilumab, the first targeted therapy available for treatment of AD. The participants recruited into this study have taken dupilumab for treatment of moderate-to-severe AD; it is possible that many of these patients may have more difficult to treat AD and they may therefore need adjunct topical therapy to control their symptoms. To make the study closer to a real world-setting and also to avoid participant discomfort, use of mild/moderate potency topical steroids/topical calcineurin inhibitors (TCI)/topical phosphodiesterase-4 (PDE4) inhibitors will be allowed during the study.

4.2.1. Participant Input into Design

Throughout this protocol, the term "participant" is used to indicate an individual who participates in a clinical trial, either as a recipient of an investigational drug or as a control. This usage reflects preferences indicated by patient advocates to more accurately reflect the role of people who take part in clinical trials.

No participant input was provided for this study design.

4.3. Justification for Dose

The lebrikizumab dosing regimen of 500 mg loading dose at baseline and Week 2, followed by 250 mg Q2W up to, and including Week 16, was selected based on an evaluation of safety, efficacy, and PK data from the Phase 2 and Phase 3 lebrikizumab trials.

In the lebrikizumab Phase 3 programs, IGA 0/1 or EASI-75 responders at Week 16 were re-randomized to Q4W, Q2W, or withdrawal arms, and inadequate responders were assigned to Q2W dosing. These Phase 3 results have demonstrated that lebrikizumab Q4W and Q2W are similar in efficacy, and that inadequate responders benefited from continued Q2W dosing. The dose regimens in the present study post Week 16 are based on the results of these Phase 3 studies.

Adolescent Participants

In this phase 3b study, adolescent participants (≥12 to <18 years weighing ≥40 kg) will be included and will receive the same doses of lebrikizumab as adult participants. PK analyses of SC doses of lebrikizumab reveal similar kinetics for adults and adolescents ≥12 to <18 years. Although maximal exposures are slightly higher for any given dose in adolescent participants, due to their lower weight ranges, the safety profile observed in adolescent participants is comparable to the safety profile observed in adults. Therefore, a similar exposure-response relationship is expected in this age group compared to adults based on partial extrapolation and propose to include adolescent participants in this study. It is expected that the adolescent AD participants ≥40 kg will demonstrate a similar overall safety profile as adult participants.

4.4. End of Study Definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

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 Schedule of Activities (SoA) for the last participant in the study.

5. Study Population

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. All participants must have prior treatment with dupilumab meeting one of the following conditions:
    - Participants who stopped dupilumab treatment due to non-response, partial response, loss of efficacy must have been previously treated with dupilumab (at labeled dose level) for at least 4 months.
    - Participants who stopped dupilumab treatment due to intolerance or AEs to the drug may enter the study with no required prior length of dupilumab treatment.
    - Participants who stopped dupilumab treatment due to cost or loss of access to dupilumab (for example, insurance coverage) may enter the study with no required prior length of dupilumab treatment.
3. Participants who have chronic AD (according to American Academy of Dermatology Consensus Criteria; Eichenfield et al. 2014) that has been present for ≥1 year before screening visit.
4. Have EASI ≥16 at the baseline visit.
5. Have IGA score ≥3 (Scale of 0 to 4) at the baseline visit.
6. Have ≥10% body surface area (BSA) of AD involvement at the baseline visit
7. Have a history of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable.

Weight

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

Sex and Contraceptive/ Barrier Requirements

9. Male and/or female
    a. Male participants are not required to use any contraception except in compliance with specific local government study requirements.
    b. Female participants of child-bearing potential: must agree to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method during the treatment period and for at least 18 weeks after the last dose of study drug. Women of non-child-bearing potential (non-WOCBP) may participate

without any contraception requirements. For definitions of women of child-bearing potential (WOCBP) and non-WOCBP, see Section 10.4, Appendix 4.

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, Appendix 4.

Informed Consent

10. Informed consent/assent
    a. For adult participants: 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.
    b. For adolescent participants: a parent or legal guardian must be able to read, understand, and give documented informed consent for a child to participate in this study as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
    NOTE: Adolescents reaching the age of maturity while on study must provide consent to continue participation in the study.

Other Inclusions

11. Are willing and able to comply with all clinic visits and study-related procedures and questionnaires.

5.2. Exclusion Criteria

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

Medical Conditions

12. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
13. Have a current infection or chronic infection with hepatitis B virus (HBV) at screening (that is, positive for hepatitis B surface antigen and/or polymerase chain reaction positive for HBV DNA Section 8.2.3).
14. Have a current infection with hepatitis C virus (HCV) at screening (that is, positive for HCV RNA Section 8.2.4).
15. Have an uncontrolled chronic disease that might require multiple intermittent uses of oral corticosteroids at screening, as defined by the investigator.
16. Have uncontrolled asthma that
    a. might require bursts of oral or systemic corticosteroids, or
    b. required the following due to ≥1 exacerbations within 12 months before baseline
        i. systemic (oral and/or parenteral) corticosteroid treatment, or
        ii. hospitalization for >24 hours.
17. Have known liver cirrhosis and/or chronic hepatitis of any etiology.
18. History of malignancy, including mycosis fungoides or cutaneous T-cell lymphoma, within 5 years before the screening, except completely treated in situ carcinoma of the

cervix of completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin with no evidence of recurrence in the past 12 weeks.

19. Are diagnosed with active endoparasitic infections or at high risk of these infections.
20. Have a known or suspected history of immunosuppression, including history of invasive opportunistic infections (for example, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per the investigator's judgment.
21. Have presence of skin comorbidities that may interfere with study assessments.
22. Have a severe concomitant illness(es) that in the investigator's judgment would adversely affect the participant's participation in the study.
23. Have 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 their participation in this clinical trial, may make participant's participation unreliable, or may interfere with study assessments.
24. Have had any of the following types of infection within 3 months of screening or develop any of these infections during screening
    a. Serious (requiring hospitalization, and/or intravenous or equivalent oral antibiotic treatment)
    b. Opportunistic (as defined in Winthrop et al. 2015, see Section 10.9, Appendix 9) NOTE: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over
    c. Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
    d. Recurring (including, but not limited to recurring cellulitis, chronic osteomyelitis)

    NOTE: Participants with only recurrent, mild and uncomplicated orolabial and/or genital herpes may be discussed with the sponsor's medical monitor to determine whether the participants meet this exclusion criterion.
25. Have an active or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit (baseline; Visit 2), or superficial skin infections within 1 week before the baseline visit.

    NOTE:

    Participants may be rescreened after infections resolves.

    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.

Prior/Concomitant Therapy

26. Dupilumab treatment within 4 weeks prior to the baseline visit.
27. Prior treatment with tralokinumab.

28. Treatment with topical agents (corticosteroids, calcineurin inhibitors, JAK inhibitors, or phosphodiesterase-4 inhibitors) within 2 weeks prior to baseline visit.
29. Treatment with any of the following agents known to affect AD within 4 weeks prior to the baseline visit:
    a. systemic immunosuppressive/immunomodulating drugs (for example, systemic corticosteroids, cyclosporine, mycophenolate mofetil, IFN-gamma, azathioprine, methotrexate, and other immunosuppressants);
    b. small molecules (for example, JAK inhibitors);
    c. phototherapy and photochemotherapy for AD.
30. Have regularly used (more than 2 visits per week) a tanning booth or parlor within 4 weeks of the screening visit (Visit 1).
31. Are currently receiving build-up dosing of allergen immunotherapy (allergy shots).
32. Treatment with B cell-depleting biologics, including rituximab, within 6 months prior to the baseline visit.
33. Use of prescription moisturizers within 7 days of the baseline visit.
34. Have received a Bacillus Calmette-Guerin vaccination or treatment within less than 4 weeks before the baseline visit or intend to receive Bacillus Calmette-Guerin vaccination or treatment during the study.
35. Have received any live attenuated vaccine within less than 4 weeks of the baseline visit or intend to receive a live attenuated vaccine during the study, or within 4 weeks after receiving the last dose of study intervention.

    NOTE: The following are not considered live vaccines: RNA vaccines, vaccines with inactive viral elements, and/or non-replicating viral vector vaccines.

36. Use of cannabis or cannabinoids for the treatment of pruritus, pain and/or AD.

Diagnostic Assessments

37. In the opinion of the investigator, have clinically significant laboratory results from the chemistry or hematology tests obtained at the screening visit (Visit 1).

Prior/Concurrent Clinical Study Experience

38. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
39. Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer prior to the baseline visit.
40. Have received a dose of lebrikizumab in any prior lebrikizumab clinical study.

Other Exclusions

41. Are Lilly employees (or are employees of any third-party involved in study who require exclusion of their employees).
42. 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.

43. Are pregnant or breastfeeding or are planning to become pregnant or to breastfeed during the study.
44. Have a known hypersensitivity to any component of lebrikizumab.
45. Participant or caregiver who is unwilling to administer SC injections of study medication.

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 enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened as defined below. Rescreened participants should be assigned a new participant number for every screening or rescreening event.

5.4.1. Rescreening for Individuals Who Failed Screening

Informed consent for rescreenings

Individuals who are to be rescreened must first sign a new ICF/assent form as applicable (Section 10.1, Appendix 1, Section 10.1.3). Such individuals will be assigned a new participant number.

Rescreening after failure to meet study entry criteria

An individual who does not meet the criteria for participation in this study for any reason may be rescreened **one time**.

When rescreening, all of the screening tests and procedures should be repeated.

5.5. Criteria for Temporarily Delaying Enrollment/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 is provided as sterile liquids and contain no preservatives.

Intervention Name	**Lebrikizumab**
Dose Formulation	**250 mg (125 mg/mL), 2 mL Solution**
Dosage Level	**Loading Dose:** **Week 0**: 500 mg (2 injections of 250 mg) **Week 2**: 500 mg (2 injections of 250 mg) **Post-loading Dose:** **Weeks 4-16**: 250 mg SC Q2W (1 injection of 250 mg) **Responders at Week 16**: 250 mg SC Q4W (1 injection of 250 mg) at W20 **Inadequate responders at Week 16**: 250 mg SC Q2W (1 injection of 250 mg) at W18, W20, and W22
Route of Administration	**SC**

Abbreviations: mg = milligram; mL = milliliter; SC = subcutaneously; Q2W = every 2 weeks; Q4W = once every 4 weeks; W = week.

6.1.1. Medical Devices

1. Lebrikizumab will be administered using a sterile prefilled syringe with needle safety device. Each prefilled syringe is intended for a single 2 mL dose (250 mg) administered subcutaneously device.
2. Instructions on how to use the device will be provided.
3. All Product Complaints (PCs) (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

1. 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.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention, except for study intervention intended to be administered by the participant or caregiver. 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.

3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.
4. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

In this open-label study, potential bias will be reduced by specifying treatment response ascertained from all eligible participants and safety reporting. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

The site will contact the interactive web-response system (IWRS), prior to the start of study intervention administration and at the primary endpoint for each eligible participant, to provide demographic information and IGA/EASI results, respectively.

6.4. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee at the baseline (Week 0, Visit 2) and Week 2 (Visit 3) visits. The dose of study intervention and study participant identification will be confirmed prior to dispensing study drug. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

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

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

A record of the number of lebrikizumab injections supplies dispensed to and administered by each participant or caregiver must be maintained and reconciled with study intervention and compliance records.

6.5. Dose Modification

Dose modifications of lebrikizumab are not allowed in this study.

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

Lebrikizumab will be made available to eligible participants who complete Visit 9 (Week 24) via the Continued Access addendum, until lebrikizumab is commercially available in the US. Please refer to KGBO Protocol Addendum 2 for additional information. Otherwise, lebrikizumab will not be provided after participants exit this study.

6.7. 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 until lebrikizumab can no longer be detected systemically (at least 18 weeks).

6.8. Concomitant Therapy

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

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

The medical monitor should be contacted prior to entering the participant into the study if there are any questions regarding concomitant or prior therapy.

Participants should be instructed to consult with the investigator prior to initiating any new medication (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) while participating in the study. The investigator is expected to examine the acceptability of all concomitant medications, topical preparations, and dietary supplements taken by participants in the study.

The use of any concomitant medication must relate to an AE listed on the AE case report form (CRF) or the participant's medical history, unless the medication is a supplement or used as preventive care.

6.8.1. Permitted Treatments and Procedures

The following therapies will **be permitted** during the study:

Permitted Concomitant Medications and Vaccines	Comments
Medications	
Medications for medical conditions other than AD (for example, hypertension or diabetes)	
Low and /or mid potency TCS, TCIs (for example, tacrolimus and pimecrolimus), or topical PDE-4	Permitted as needed on AD lesions and must be documented in the diary

Permitted Concomitant Medications and Vaccines	Comments
inhibitors (for example, crisaborole) for treatment of AD (see Section 6.8.4)	
High-potency TCS for treatment of AD	Permitted up to 10 days
Non-medicated moisturizers	
Intranasal corticosteroids	
Inhaled corticosteroids and bronchodilators to control asthma	
Single intra-articular (bursa, tendons, and ligaments) corticosteroid injection	
Non-sedating antihistamines	
Ophthalmic drugs containing antihistamines, corticosteroids, or other immunosuppressants	
Allergen immunotherapies	If on maintenance dose
Leukotriene inhibitors	
Acute Systemic and topical anti-infectives/antibiotics	For treatment of acute infections
Sedating systemic antihistamines including, but not limited to, alimemazine, chlorphenamine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine, ketotifen, and promethazine	On an as needed basis
Systemic/oral sleep aid medications	On an as needed basis
Recreational use of cannabis and cannabinoid (if allowed per local regulations/law)	Not allowed for the treatment of pruritus, pain and/or AD
Vaccines	
Non-live vaccinations	Including non-live SARS-CoV-2 vaccines, RNA vaccines, vaccines with inactive viral elements, and/or non-replicating viral vectors that are clinically indicated

Abbreviations: AD = atopic dermatitis; RNA = Ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; PDE-4 = phosphodiesterase-4; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids.

NOTE: In the context of this table, "during the study" = from screening to post-treatment safety follow-up visit.

6.8.2. Prohibited Treatments and Procedures

The following therapies will be prohibited during the study:

Prohibited Concomitant Medications, Vaccinations, and Procedures	Comments
Medications or procedures	
Systemic corticosteroids (IM, PO, or IV)	NOTE: Any use of systemic corticosteroids will be considered as rescue medication (see Section 6.8.5)
Any investigational drug other than the study drug	
B cell-depleting biologics, including rituximab	
Other biologic agents (other than the study interventions)	
Topical JAK inhibitor for treatment of AD	Any use will be considered as rescue medication (see Section 6.8.5)

Prohibited Concomitant Medications, Vaccinations, and Procedures	Comments
TCS (high potency)	Use for >10 days is prohibited
Medications or therapies for other medical conditions known to affect AD (for example, immunosuppressive/immunomodulating drugs such as systemic corticosteroids, mycophenolate mofetil, IFN-gamma, topical, and systemic JAK inhibitors, cyclosporine, azathioprine, or methotrexate; phototherapy or PUVA; or systemic PDE-4 inhibitors)	
Chronic Systemic and topical anti-infectives	For chronic treatment during the study
Planned or anticipated major medical procedures or surgeries	
Tanning booth/parlor	
Bleach bath	
Use of cannabis or cannabinoids for the treatment of pruritus, pain and/or AD	
Vaccines	
Live or live attenuated vaccines, as well as BCG vaccine	

Abbreviations: AD = atopic dermatitis; AE = adverse event; BCG = Bacillus Calmette-Guerin; JAK = Janus kinase; IFN = interferon; IM = intramuscular; IV = intravenous; PDE-4 = phosphodiesterase-4; PUVA = photochemotherapy; TCS = topical corticosteroids; PO = by mouth.

NOTE: in the context of this table, "during the study" = from screening to post-treatment safety follow-up visit.

6.8.3. Non-Medicated Moisturizers

Participants may apply a stable dose of non-medicated topical moisturizer at least twice daily for ≥7 days prior to the baseline visit and throughout the study.

The participants may continue their current over-the-counter moisturizer regimen, if approved by the investigator.

All moisturizer use should be recorded in the CRF.

6.8.4. Topical Treatment for Atopic Dermatitis

The goal of this Phase 3b study is to demonstrate the safety and efficacy of lebrikizumab for moderate-to-severe AD in a population previously treated with dupilumab. Regular use of non-medicated, non-prescription moisturizers should be used by all participants. During this study, topical therapies may be needed if the participant experiences intolerable clinical worsening of symptoms. If needed, investigators are encouraged to recommend therapy in a staged fashion, beginning with a topical low-potency treatment first, then topical mid-potency treatment if needed. In sensitive skin areas (that is, face, neck, intertriginous, and genital areas), only low-potency topical treatments should be used.

If AD lesions recur or a participant experiences a flare, as needed use of low- and/or mid-potency TCS, TCI (tacrolimus or pimecrolimus), and/or topical PDE4 inhibitors (crisaborole) may be initiated at the participant's discretion but must be communicated to the investigator and documented in the patient diary or as concomitant medications.

Escalation to high-potency topical corticosteroid medications should only occur if participants do not respond adequately after at least 7 days of low/mid potency TCS, TCI and/or topical PDE4 inhibitors. Use of high-potency TCS for more than 10 days is considered rescue therapy (Section 6.8.5). Participants that receive Rescue therapy must be discontinued from the study. (see Section 7.1). All topical therapy usage must be recorded in the CRF or patient diary.

6.8.5. Rescue Medicine for Atopic Dermatitis

To be consistent with real world practice, defined topical medications are allowed in this study (see Section 6.8.4). However, rescue therapies may be needed if the participant experiences intolerable clinical worsening of symptoms. Escalation to high potency topical TCS, topical JAK inhibitors, phototherapy and/or systemic medications (including but not limited to corticosteroids, immunosuppressants, biologics, small molecules, etc.) for the treatment of AD should only occur if participants do not respond adequately after at least 7 days of low/mid potency TCS, TCI and/or topical PDE4 inhibitors. Any use of topical JAKs, phototherapy, and/or systemic medications will be considered rescue therapy. Use of high-potency TCS for more than 10 days is also considered rescue therapy. Participants that receive Rescue therapy must be discontinued from the study. (see Section 7.1).

All rescue medication must be recorded in the CRF.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study to complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA.

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons
- the participant develops a malignancy, except for successfully treated basal or squamous cell skin carcinoma
- the participant tests positive for HBV DNA (see Section 8.2.3)
- the participant tests positive for HCV RNA (Section 8.2.4)
- if the participant experiences a hepatic event or liver test abnormality as specified in the liver chemistry stopping criteria (see Section 7.1.1)
- the participant develops HIV infection
- the participant requires rescue medication treatment for symptoms of AD in the treatment period
- the participant develops any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status, and
- the participant has an AE or an SAE or a clinically significant change in a laboratory value that, in the opinion of the investigator, merits discontinuation of study intervention and appropriate measures being taken.

Hepatitis

- prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy due to hepatitis, 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.

Hypersensitivity

- if the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, 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.

7.1.1. Liver Chemistry Stopping Criteria

The study drug should be interrupted and close hepatic monitoring initiated (see Section 8.2.2) if 1 or more of these conditions occur:

Elevation[a]	Exception[a]
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and/or rash	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL > 2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and rash	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications.	

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

[a] All ULN values should be age adjusted (AAULN) for participants <18 years of age.

Resumption of the study intervention can be considered only in consultation with the Lilly-designated medical monitor and only if liver test results return to baseline and if a self-limiting non-drug etiology is identified. Otherwise, study intervention should be discontinued.

7.1.2. Temporary Discontinuation of Study Intervention

Temporary withholding of study intervention is required if the participant meets any of the following infection-related criteria during the study:

- Serious or opportunistic infections, as defined in Section 5.2. Study intervention is to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment.
- 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. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study intervention as described in Section 7.1.
- If a participant <18 years of age loses a clinically significant amount of weight (below 40 kg), the investigator should assess rationale for weight loss and use clinical judgment to determine if the participant should temporarily discontinue the treatment.

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
- 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
- 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, and
- if the participant, for any reason, requires rescue medication or treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, the participant will complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA. 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 he or she repeatedly fails to return for scheduled visits and is 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.
- 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, 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 Assessments

8.1.1. Eczema Area and Severity Index

The EASI is an investigator-reported, 20-item scale that evaluates 2 dimensions of AD: extent of disease at 4 body regions (head or neck, trunk, upper and lower extremities) and 4 clinical signs (erythema, induration or papulation, excoriation, and lichenification). The clinical signs are assessed for severity on a scale of 0 (absent) to 3 (severe).

The scores are added up for each of the 4 body regions. The assigned percentages of BSA for each section of the body are 10% for head or neck, 20% for upper extremities, 30% for trunk, and 40% for lower extremities, respectively. Each subtotal score is multiplied by the BSA represented by that region.

In addition, an area score of 0 to 6 is assigned for each body region, depending on the percentage of AD-affected skin in that area: 0 (none), 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). Each of the body area scores is multiplied by the area affected. The resulting EASI ranges from 0 to 72 points, with the highest score indicating worse severity of AD (Hanifin et al. 2001).

Assessors must be trained and certified by the sponsor prior to conducting this assessment. A single assessor should be assigned to each participant for as many visits as possible to avoid inter-assessor variability in scoring. The recall period of this assessment is present time.

8.1.2. Investigator's Global Assessment (IGA)

The IGA is an investigator-reported, single-item scale that 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.

Assessors must be trained and certified by the sponsor prior to conducting this assessment. A single assessor should be assigned to each participant for as many visits as possible to avoid inter-assessor variability in scoring. The recall period of this assessment is present time.

8.1.3. Body Surface Area (BSA)

BSA is an investigator-reported assessment, which estimates the extent of disease or skin involvement of a participant's AD. BSA is expressed as a percentage of total body surface and will be reported by body location. The recall period of this assessment is present time.

Assessors must be trained and certified by the sponsor prior to conducting this assessment. A single assessor should be assigned to each participant for as many visits as possible to avoid inter-assessor variability in scoring.

8.1.4. Face-Investigator's Global Assessment (F-IGA)

The F-IGA is an investigator-administered, single-item scale that rates the severity of the participant's AD on the face. The F-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 facial lesions at a given time point.

Assessors must be trained and certified by the sponsor prior to conducting this assessment. A single assessor should be assigned to each participant for as many visits as possible to avoid inter-assessor variability in scoring. The recall period of this assessment is present time.

8.1.5. SCORing Atopic Dermatitis (SCORAD)

The SCORAD index is an investigator- and participant-reported, 9-item assessment in both adults and adolescent participants that assesses 3 aspects as provided below.

- The **extent** (1-item) of AD is assessed by the investigator as a percentage of each defined body area and reported as the sum of all areas. The maximum score is 100%. The recall period of this scale is present time.
- The **severity** of 6 specific symptoms of AD is assessed by the investigator: erythema, edema or papulation, oozing or crusts, excoriation, lichenification, and dryness are assessed by the investigator using a 4-point scale (that is, none = 0, mild = 1, moderate = 2, severe = 3) with a maximum possible total of 18 points. The recall period of this scale is present time.
- The **subjective symptoms** of pruritus and sleep loss (2 items) are assessed by the participant via a 10-cm visual analog scale. The symptoms (itch and sleeplessness) are recorded by the participant or caregiver on a visual analogue scale, where 0 is no symptoms and 10 is the worst imaginable symptom, with a maximum possible score of 20. The recall period of this scale is over the last 3 days.

The maximum possible SCORAD score calculated based on the above 3 aspects is 103. The higher scores indicate poorer or more severe condition (Stalder and Taïeb 1993; Oranje et al. 2007; Schram et al. 2012). The recall period is present time for extent and intensity and average for the last 3 days or nights for subjective symptoms of AD.

8.1.6. Modified Total Lesion Symptom Scale

The Modified Total Lesion Symptom Scale is an investigator-reported scale that combines the evaluation of hand eczema (HE) lesion severity (erythema, edema, desquamation, fissures, hyperkeratosis or lichenification, and vesicles) with the intensity of pruritus or pain (Bissonnette

et al. 2010) to assess the severity of symptoms. This composite score assigns 0 (mild) to 3 (severe) to each component, giving a maximum disease severity of 21. The recall period for this scale is the present time. While no validation of this score has been published, it has been used as a secondary endpoint in studies investigating alitretinoin in HE (Ruzicka et al. 2008; Fowler et al. 2014), and as a primary outcome measure in recent Phase 2 studies of dupilumab and gusacitinib for HE (NCT03861455; NCT03728504).

8.1.7. Pruritus NRS

The Pruritus Numeric Rating Scale (NRS) is a participant-reported, single-item, daily, 11-point scale. The Pruritus NRS is used by participants to rate their worst itch severity over the past 24 hours with 0 indicating "No itch" and 10 indicating "Worst itch imaginable." Assessments will be recorded daily by the participant. The minimal clinically important change is 3 points. (Yosipovitch et al. 2019, 2021).

Participants will record the pruritus assessments daily using an electronic diary at home. As indicated in the SoA (Section 1.3), initial electronic diary entries for Pruritus NRS should be completed a minimum of 4 of 7 days before baseline.

8.1.8. 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 (0 [not at all] to 4 [unable to sleep at all]). Assessment will be recorded daily by the participant. The minimal clinically important change is 3 points. (Yosipovitch et al. 2021).

Participants will record the pruritus assessments daily using an electronic diary at home. As indicated in the SoA (Section 1.3), initial electronic diary entries for Sleep-Loss Scale should be completed a minimum of 4 of 7 days before baseline.

8.1.9. Skin Pain Numeric Rating Scale (Skin Pain NRS)

The Skin Pain NRS is a participant-reported, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." 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). Assessment will be recorded daily by the participant.

8.1.10. Dermatology Life Quality Index/Children's Dermatology Life Quality Index (DLQI/cDLQI)

The DLQI is a simple, participant-reported, 10-item, QoL questionnaire in adults 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 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 at baseline will complete the cDLQI and should continue to complete the cDLQI for the duration of the study.

8.1.11. Atopic Dermatitis Control Tool (ADCT)

The Atopic Dermatitis Control Tool is a patient-reported, simple, brief tool for adults and adolescents that evaluates 6 symptoms and effects associated with AD over the past week: overall severity of symptoms, days with intense episodes of itching, intensity of bother, problem with sleep, impact on daily activities, and impact on mood or emotions. Each of the 6 Atopic Dermatitis Control Tool items has a score range from 0 (no problem) to 4 (worst), rating the severity of each concept; the total score ranges from 0 to 24, which is the summation of the responses to all the items. A score of ≥7 points was derived as the threshold to identify participants "not in control." The threshold for meaningful within-person change was estimated to be 5 points (Simpson et al. 2019; Pariser et al. 2020).

8.1.12. Participant-Reported Satisfaction Question

The question on participant satisfaction asks "How satisfied are you with this treatment's ability to treat your skin condition?" The response options range from 1 (not satisfied) to 5 (completely satisfied).

8.1.13. Fitzpatrick Skin Phototype Assessment

The Fitzpatrick Scale is a clinician-rated scale and is based on a participant's cutaneous reaction to sun exposure and baseline skin pigmentation. Fitzpatrick skin phototypes range from I to VI, with a score of I indicating "always burns, does not tan, white skin tone" and a score of VI indicating "never burns, tans very easily, skin color black" (High et al. 2012). Investigators will follow the descriptive terms included in this protocol when recording the Fitzpatrick skin phototype. The sun sensitivity measure will represent the Fitzpatrick Scale score for each participant. The recall period for this scale is the present time.

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

The Work Productivity and Activity Impairment Questionnaire–Atopic Dermatitis is a participant-reported, 6-item questionnaire that records impairment due to AD over the past 7 days in adolescents and adults. The Work Productivity and Activity Impairment Questionnaire–Atopic Dermatitis consists of 6 items grouped into 4 domains: absenteeism (work time missed), presenteeism (impairment at work or reduced on the job effectiveness), work productivity loss (overall work impairment or absenteeism plus presenteeism), and activity impairment. Absenteeism, presentism, and work productivity will only be reported by those who are currently employed (working for pay) at the time of the scale completion. The recall period for the scale is over the past 7 days. Scores are calculated as impairment percentages (Reilly et al. 1993), with higher scores indicating greater impairment and less productivity.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

The routine safety assessments include physical examinations, clinical safety laboratory tests (including hematology and chemistry), and collection of vital signs and spontaneously reported AEs. The study design includes a Post-treatment Follow-Up Period with at least 1 study visit for safety assessments.

8.2.1. Clinical Safety Laboratory Tests

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- **Local anesthetics**
    - Use of local anesthetics, for example, Eutectic Mixture of Local Anesthetics (EMLA) cream, consistent with local prescribing information are permitted during the study visit to ease discomfort associated with venipunctures.
- The investigator must review the laboratory results, document this review, and consider whether or not any clinically relevant changes occurring during the study constitute 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 or within 28 days after the last dose of study intervention 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 or 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 Appendix 2, must be conducted in accordance with the SoA, 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.

8.2.2. Hepatic Safety

Close hepatic monitoring[a]

Laboratory tests (Appendix 6), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN, except for patients with Gilbert's syndrome
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline, except for patients with Gilbert's syndrome

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

[a] All ULN values should be age adjusted (AAULN) for participants <18 years of age.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, and history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. 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. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels. For participants <18 years of age, special care should be taken to minimize the volume of blood taken during hepatic monitoring.

Comprehensive hepatic evaluation[a]

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs or symptoms[b], or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs or symptoms[b], or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients with Gilbert's syndrome)

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

[a] All ULN values should be age adjusted (AAULN) for participants <18 years of age.

[b] Hepatic signs or symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, and rash.

For Adult Participants (≥18 years old)

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

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, 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, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

For Adolescent Participants (<18 years old)

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio and direct bilirubin, if total bilirubin was elevated.

Based on the participant's age, medical history, and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for viral hepatitis A, B, C, E; autoimmune hepatitis; and/or an abdominal imaging study, for example, ultrasound, MRI, or computed tomography scan. Consider additional tests, based on the medical history and clinical picture, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr

virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Special care should be taken to prioritize more pertinent blood tests and minimize the volume of blood taken during hepatic evaluation. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a pediatric hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy as deemed appropriate for the clinical condition and participant's age.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection in hepatic safety CRF should be performed in study participants who meet 1 or more of the following 5 conditions:[a]

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests, if baseline ALT <1.5x ULN
   - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevated TBL to ≥2x ULN, if baseline TBL <1.5x ULN (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests, if baseline ALP <1.5x ULN
   - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be a SAE
5. Discontinuation of study drug due to a hepatic event

NOTE: the interval between the 2 consecutive blood tests should be at least 2 days.

[a] All ULN values should be age adjusted (AAULN) for participants <18 years of age.

8.2.3. Hepatitis B Testing and Monitoring

As specified in the SoA (Section 1.3), initial testing for HBV infection includes HBsAg and hepatitis B core antibody (HBcAb).

- If HBsAg is positive, the participant is excluded.
- If HBsAg is negative and HBcAb is negative, the participant is not excluded.
- If HBsAg is negative and HBcAb 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 months during the study as described in the SoA.

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 7.1.2 and 7, and the participant should be referred for appropriate follow-up medical care.

8.2.4. Hepatitis C Testing

As specified in the SoA (Section 1.3), initial testing for HCV infection includes testing for antibodies to HCV (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 polymerase chain reaction 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 discontinued (Section 7), and the participant should receive appropriate follow-up medical care.

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

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

- AEs
- SAEs, and
- 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 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 or 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 PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate nature and/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 paper form	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 paper form	SAE paper form
SAE[a] – 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	At least 18 weeks after the last dose of study intervention	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC 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	PC form	

Abbreviations: AE = adverse event; ICF = informed consent form; N/A = not applicable; PC = product complaint SAE = serious adverse event.

[a] Serious adverse event 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 request a consent or assent to release information from the pregnant female partner directly, and
  - within 24 hours after obtaining this consent or assent, 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 Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, they 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.

Prior to continuation of study intervention following pregnancy, the following must occur:

- The sponsor and the relevant institutional review board/independent ethics committee (IRB/IEC) give written approval.
- The participant gives signed informed consent (or assent, as applicable).
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and the participant's offspring.

8.3.3. Adverse Events of Special Interest

The following TEAEs will be designated AE 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 data. Participant records must include any follow-up information regarding these AESI. Study intervention should be discontinued if an AE is deemed persistent and if continuation of study intervention would not be in the best interest of the participant. Discuss discontinuation of study intervention with the sponsor or designee prior to implementation.

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 10.9, Appendix 9).

8.3.4. Facial Dermatitis

Completion of the facial dermatitis follow-up CRF page is required for each facial dermatitis event reported as an AE or SAE.

8.3.5. Hypersensitivity

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.

8.3.6. Injection Site Reactions

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

If an injection site reaction is reported by a participant or site staff, the injection site reaction CRF will be used to capture additional information about this reaction, for example, injection site pain, degree and area of erythema, induration, pruritis, and edema.

8.4. Pharmacokinetics

At the visits and times specified in the SoA, venous blood samples will be collected and stored for potential analysis of serum concentrations of lebrikizumab.

Samples will be stored at a facility designated by the sponsor and may be assessed at a later date at a laboratory approved by the sponsor using a validated enzyme-linked immunosorbent assay method.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual data and time (24-hour clock time) of each sample and the most recent lebrikizumab dose prior to PK blood draw must be recorded.

Sample retention is described in Section 10.1.11. Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last participant visit for the study. During this time, samples remaining after the bioanalysis may be used for exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A blood sample for DNA isolation will be collected from participants.

See Appendix 10.5 for Information regarding genetic research and Section 10.1.11 for details about sample retention and custody.

8.7. Biomarkers

- Serum samples will be collected to discern responder variability within the study and to track response variability to lebrikizumab. Biomarkers will include but not limited to CCI [redacted] Samples will be collected according to the schedule described in the SoA and as detailed in laboratory manual provided separately to sites.
- The sponsor may store samples according to Section 10.1.11. Additionally, with participants' consent, samples may be used for further research by the sponsor or others such as universities or other companies to contribute to the understanding of AD or other diseases, the development of related or new treatments, or research methods.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA, venous blood samples will be collected for the purpose of determining antibody production against lebrikizumab. To aid interpretation of these results, a blood sample for PK analysis will be collected at the same time points.

All samples for immunogenicity should be taken predose when applicable and possible. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample collection will be recorded. Immunogenicity samples will be stored at a facility designated by the sponsor and may be later assessed by a validated assay designed to detect ADAs in the presence of lebrikizumab at a laboratory designated by the sponsor. Samples may also be used for the development and control of an immunogenicity assay.

Treatment-emergent ADAs are defined in Section 9.3.6.4.

Sample retention is described in Section 10.1.11.

8.9. Health Economics

Health economics and/or medical resource utilization will not be collected as part of this study.

9. Statistical Considerations

The SAP will be finalized prior to first participant visit, 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.

9.1. Statistical Hypotheses

The primary objective is to evaluate efficacy of lebrikizumab 250 mg Q2W on reducing skin sign of AD, measured by percentage of participants who achieve at least 75% improvement in baseline EASI at Week 16 in participants with moderate-to-severe AD who were previously treated with dupilumab. There is no hypothesis testing planned nor inference statistical analysis planned.

9.2. Analyses Sets

Participant Analysis Set	Description
ITT population	All enrolled participants. Participants will be included in the analyses according to the planned intervention.
Safety population	All participants who are exposed to study intervention.

Abbreviation: ITT = intent-to-treat.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed SAP describing the statistical methodologies will be developed by Lilly or its designee.

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 CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

All analyses will be descriptive. Frequencies, percentages, and 90% CI for percentages will be reported for discrete efficacy endpoints. Mean, standard deviation, minimum, Q1, median, Q3, maximum, and the number of participants will be reported for continuous efficacy endpoints. AEs, discontinuation, and other categorical safety data will be summarized using frequencies and percentage. Continuous vital signs, body weight, and other continuous safety variables including laboratory variables will be summarized descriptively as well.

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

The primary endpoint is EASI-75 response rate at Week 16. The primary clinical question of interest is: What is the intervention effect in percentage of participants achieving EASI-75 after 16 weeks of lebrikizumab 250 mg intervention in participants with moderate-to-severe AD who

have been previously treated with dupilumab and who remain on study treatment until Week 16. There are no intercurrent events since participants who initiate rescue medication are discontinued from the study and hence study treatment. Therefore, participants who stay on study treatment through Week 16 will not have an intercurrent event such as initiating rescue medication or permanently discontinuing treatment. All observed data will be included in summary statistics. All summary statistics will be based on observed data.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Secondary endpoints outlined in the objective will be analyzed similarly to the primary endpoint of the primary estimand, that is, using all observed data. For categorical endpoints related to reaching a threshold, analyses will be evaluated in participants who satisfy baseline minimum value (for xx-point improvement, baseline value need to be ≥xx) in intent-to-treat set.

9.3.4. Exploratory Endpoint(s) Analysis

Other exploratory endpoints specified in Section 3 will be summarized using all observed data.

9.3.5. Safety Analyses

All safety data will be descriptively summarized using the safety population.

Treatment-emergent AEs are defined as AEs that first occurred or worsened in severity after the first dose of study treatment. The number of TEAEs as well as the number and percentage of participants who experienced at least 1 TEAE will be summarized using MedDRA (Medical Dictionary for Regulatory Activities) for each system organ class (or a body system) and each preferred term. SAEs and AEs that lead to discontinuation of study intervention will also be summarized.

All clinical laboratory results will be descriptively summarized. Individual results that are outside of normal reference ranges will be flagged in data listings. Quantitative clinical hematology, chemistry, and urinalysis variables obtained at the baseline to postbaseline visits will be summarized as changes from baseline. Categorical variables, including the incidence of abnormal values and incidence of AEs of special interest, will be summarized by frequency and percentage of participants in corresponding categories. Shift tables might be presented for selected measures.

Observed values and changes from baseline (predose or screening if missing) for vital signs and physical characteristics will be descriptively summarized by time point.

The SAP may include additional safety analyses if needed.

9.3.6. Other Analyses

9.3.6.1. Subgroup Analyses

Subgroup (subpopulation) analyses of the primary endpoint and selected secondary endpoints at Weeks 16 and 24 *may be* conducted for intended-to-treat set. Subgroup to be evaluated may include baseline severity, sex, age, race, and reasons for discontinuation for previously treated with dupilumab.

Definitions for the levels of the subgroup variables and any additional subgroup analyses will be defined in the SAP if applicable. All analyses will be descriptive and should be treated as exploratory.

9.3.6.2. Biomarker Analyses

Biomarker analyses will be described in the SAP.

9.3.6.3. Pharmacokinetic Analyses

PK samples will be stored and may be later assessed. If assessed, PK analyses may be described in the SAP.

9.3.6.4. Immunogenicity Assessments

Immunogenicity samples will be stored and may be later assessed. If assessed, the frequency and percentage of participants with preexisting anti-drug antibody (ADA) and who are treatment-emergent ADA positive (TE ADA+) to lebrikizumab will be tabulated.

Treatment-emergent ADAs are defined as participants

- with a 2-fold (1 dilution) increase in titer than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA), or
- with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA).

The distribution of titers and frequency of neutralizing antibodies (if assessed) for TE ADA+ participants may also be tabulated.

The relationship between the presence of ADA and PK parameters, efficacy response, or safety to lebrikizumab may also be assessed.

Additional details may be provided in the SAP.

9.4. Interim Analysis

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

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

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

9.5. Sample Size Determination

Based on available data, the anticipated EASI-75 response rate is approximately 50%. A total sample size of 120 enrolled participants will provide >95% probability that the 2-sided 90% CI of the EASI-75 response rate with half-width is at most 10%.

With a total sample size N = 120, example point estimate of response rates and corresponding 2-sided 90% CI based on Wilson (Score) method are summarized in the table below. The values are provided as reference rather than a basis of any decision criteria.

Estimated 90% CI with Sample Size of 120 Participants

Example Point Estimates	Lower Bound of 90% CI	Upper Bound of 90% CI
40%	32.9%	47.5%
45%	37.7%	52.5%
50%	42.6%	57.4%
55%	47.5%	62.3%
60%	52.5%	67.1%

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 International Ethical Guidelines
    - Applicable ICH GCP Guidelines
    - International Organization for Standardization 14155
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/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, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- 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 participant, or the participant's legally authorized representative, and answer all questions regarding the study.
- 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 Code of Federal Regulations 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 or parent(s) 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 while on study, will need to re-consent.
- Participants (or their legally acceptable representative, parent(s), or legal guardian) must be reconsented to the most current version of the ICF(s) during their participation in the study.
- 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. Any participant 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.

- The participant must be informed 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 data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. 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.

Data

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

10.1.6. 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.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined 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).
- Study monitors will perform ongoing source data verification 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 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, 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 sponsor or its representatives, and/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 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 investigator or designee 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, the skin assessment using the Fitzpatrick Skin Type scale will be collected by the authorized study personnel via a paper source document and will be transcribed by the authorized study personnel into the EDC system.

Additionally, electronic clinical outcomes assessment (COA) data (participant-focused outcome instrument) will be directly recorded by the participant/investigator site personnel, into an instrument (for example, handheld smart phone or tablet). The electronic COA 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 system(s) 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 system(s). 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 PC management system.

10.1.7. 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 Section 10.1.6.

10.1.8. 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:

- Discontinuation of further study intervention development

For site termination:

- 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
- 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.

10.1.9. 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.

10.1.10. Investigator Information

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

10.1.11. 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.

Sample Type	Custodian	Retention Period after Last Participant Visit
Biomarkers	Sponsor or Designee	7 years
PK	Sponsor or Designee	1 year
Genetics	Sponsor or Designee	7 years
Immunogenicity	Sponsor or Designee	7 years

Abbreviation: PK = pharmacokinetics.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the central 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.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Absolute neutrophil count (calculation) (definition – include segs and bands or segs, bands and other immature cells)	
Leukocytes (WBCs)	
Differential	
Percent and absolutes count of:	
Neutrophils, segmented	
Neutrophils, bands	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	
Clinical Chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
ALP	

Clinical Laboratory Tests	Comments
ALT	
AST	
GGT	
BUN	
Creatinine	
CK	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
LDH	
Hormones (female)	
Serum pregnancy	Assayed by Lilly-designated laboratory
Urine pregnancy	Assayed and Evaluated locally
HIV and Hepatitis Serology	Assayed by Lilly-designated laboratory
HIV testing	
HCV testing:	
HCV antibody	
HCV RNA	
HBV testing:	
HBV DNA	Performed only for participants who test positive for HBcAb
HBcAb	
HBsAg	
HBsAb	
Exploratory Biomarkers	Assayed by Lilly-designated laboratory Results will not be provided to the investigative sites
CCI	
Immunoglobulins	Assayed by Lilly-designated laboratory Results will not be provided to the investigative sites
IgE (Serum)	
Genetics Sample	Assayed by Lilly-designated laboratory Results will not be provided to the investigative sites
Exploratory Biomarker storage samples	Assayed by Lilly-designated laboratory Results will not be provided to the investigative sites
Serum	

Clinical Laboratory Tests	Comments
Immunogenicity (ADA) samples	Assayed by Lilly-designated laboratory Results will not be provided to the investigative sites
Anti-LY3650150 antibodies	
Pharmacokinetic Samples – LY3650150 concentration	Assayed by Lilly-designated laboratory Results will not be provided to the investigative sites

Abbreviations: ADA = anti-drug antibodies; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; GGT = Gamma-glutamyl transferase; 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; IgE = immunoglobulin E; IL = interleukin; LDH = lactic dehydrogenase; PK = pharmacokinetics; RBC = red blood cells; WBC = white blood cells.

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 predose 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	Tryptase
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 anti-drug antibodies
	Lebrikizumab concentration

[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

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization (ISO) 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.3.1. Definition of AE

AE Definition
• 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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. • An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, electrocardiogram, radiological scans, 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 preexisting 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. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an

AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of 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/disorder being studied or expected progression, signs, or symptoms of the disease/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 preexisting 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:

a. Results in death

b. 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.

c. 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 preexisting condition that did not worsen from baseline is not considered an AE.
d. 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.
e. Is a congenital anomaly/birth defect • Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
f. 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.
g. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

Product Complaint
A PC 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 PCs: o Deficiencies in labeling information, and o Use errors for device or drug-device combination products due to ergonomic design elements of the product.

- PCs related to study interventions used in clinical trials are collected in order 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 PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC 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/PC 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/PC 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 PC information is reported on the Product Complaint Form.

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

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.
- There may be instances when copies of medical records for certain cases are requested by 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 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 adverse event 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 adverse event 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 adverse event 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 pre-defined 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 IB in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to 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 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 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 Sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via Paper Form
• Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the medical monitor or the SAE coordinator. • 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 SAE form.

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 suspected unexpected serious adverse reactions 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 will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Women of child-bearing potential (WOCBP)

Females are considered WOCBP if they have had at least 1 cycle of menses.

Any amount of spotting or bleeding should be considered menarche.

Women not of child-bearing potential (WNOCBP)

Females are considered WNOCBP if they

- have a congenital anomaly such as Mullerian agenesis
- are infertile due to surgical sterilization, or
- are postmenopausal.

Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.

Postmenopausal

The postmenopausal state is defined as ≥1 year without a menstrual period confirmed by follicle stimulating hormone test.

10.4.2. Contraception Guidance

Guidance for WOCBP

This outlines the rules for WOCBP to ensure they do not become pregnant during the study.

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	• 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
Pregnancy testing	Have a negative serum test result at screening (or upon a participant that reaches menarche during the trial and is sexually active) followed by a negative urine result within 24 hours prior to treatment exposure. See the protocol SoA for subsequent pregnancy testing requirements.

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

Examples of different forms of contraception

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female 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, 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
	  o condom with spermicide
	  o diaphragm with spermicide, or
	  o female condom with spermicide.
	NOTE: The barrier method must include use of a spermicide, that is, condom with spermicide, diaphragm with spermicide, and female condom with spermicide, to be considered effective.

Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal • post coital douche, and • lactational amenorrhea

Guidance for all men

Males may participate in this trial.

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to lebrikizumab or moderate-to-severe AD and related diseases. They may also be used to develop tests or assays including diagnostic tests related to lebrikizumab and moderate-to-severe AD. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to lebrikizumab or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on lebrikizumab continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic Evaluation Testing

See Section 8.2.2 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.

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.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody
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, segmented	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA [a]
Basophils	**Hepatitis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA [a]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	**Hepatitis E virus (HEV) testing:**
Direct bilirubin	HEV IgG antibody
Alkaline phosphatase (ALP)	HEV IgM antibody
Alanine aminotransferase (ALT)	HEV RNA [a]
Aspartate aminotransferase (AST)	**Anti-nuclear antibody (ANA)**
Gamma-glutamyl transferase (GGT)	**Anti-smooth muscle antibody (ASMA)** [b]
Creatine kinase (CK)	**Anti-actin antibody** [c]
Hepatic Coagulation Panel	**Immunoglobulin IgA (quantitative)**
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgG (quantitative)**
Urine Chemistry	**Immunoglobulin IgM (quantitative)**
Drug screen	**Epstein-Barr virus (EBV) testing:**
Haptoglobin	EBV antibody

[a] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

[b] Not required if anti-actin antibody is tested.

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

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

[a] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.7. Appendix 7: 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.

10.8. Appendix 8: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Refer to Appendix 3 for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.9. Appendix 9: 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 *Vibrio vulnificus*)
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) (*Rhizopus*, *Mucor,* and *Lichtheimia*), *Scedosporium*/*Pseudallescheria boydii*, *Fusarium*
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).

10.10. Appendix 10: 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 GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

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 if written sponsor approval is given.

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 written sponsor approval is given.

The screening procedures per the SoA in the protocol should be followed (starting at Visit 1) to ensure participant eligibility by the baseline 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. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance and written approval 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
Weeks 2-14	±7 days
Week 16	±7 days
Post-treatment safety follow-up (12 weeks after last dose)	±14 days

For participants whose visits have extended windows, subsequent dosing should be a minimum of 7 days apart if the visit window is expanded due to exceptional circumstances.

NOTE: 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.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visit window adjustments, and or rescreening were affected by exceptional circumstances.

10.11. Appendix 11: Abbreviations and Definitions

Term	Definition
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
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.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
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
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee. A data monitoring committee, or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
Device deficiencies	equivalent to product complaint
EASI	Eczema Area and Severity Index

EDC	electronic data capture system
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.
FLG	filaggrin
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HE	hand eczema
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IGA	Investigator's Global Assessment
IL	interleukin
IL-4Rα	IL-4 receptor alpha
IL-13Rα1	IL-13 receptor alpha 1
IMP	Investigational Medicinal Product
informed consent	A process by which a participant voluntarily confirms their 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.
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.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, 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/IEC	Institutional Review Board/Independent Ethics Committee

ITT	intention 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 participant 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.
IWRS	interactive web-response system
JAK	Janus kinase
LOR	loricrin
NIMP	non-investigational medicinal product
NRS	Pruritus Numeric Rating Scale
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PDE4	phosphodiesterase-4
PD/PK	pharmacodynamics/pharmacokinetics
PPS	per-protocol set: The set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QTc	corrected QT interval
QoL	Quality of Life
SC	subcutaneous
SCORAD	SCORing Atopic Dermatitis
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
TARC	thymus- and activation-regulated chemokine

TBL	total bilirubin
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
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.
Th1	T-helper type 1
Th2	T-helper type 2
Th17	T-helper type 17
WOCBP	women of child-bearing potential

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