Protocol J2T-JE-KGAL (a)

A Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Lebrikizumab When Used in Combination with Topical Corticosteroid Treatment in Japanese Patients with Moderate-to-Severe Atopic Dermatitis

NCT04760314

Approval Date: 22-Jan-2021

Title Page

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Lebrikizumab When Used in Combination with Topical Corticosteroid Treatment in Japanese Patients with Moderate-to-Severe Atopic Dermatitis

Protocol Number: J2T-JE-KGAL

Amendment Number: a

Compound: Lebrikizumab (LY3650150)

Study Phase: 3

Short Title: Safety and Efficacy of Lebrikizumab in Combination with Topical Corticosteroids in Japanese Patients with Moderate-to-Severe Atopic Dermatitis

Acronym: ADhere-J

Sponsor Name: Eli Lilly Japan K.K.

Legal Registered Address: Eli Lilly Japan K.K., Kobe Hyogo Japan

Regulatory Agency Identifier Number(s): Not available

Approval Date: Protocol Electronically Signed and Approved by Lilly on 19 November 2020.

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	*19-Nov-2020*

Amendment [a]

Overall Rationale for the Amendment:

The overall changes and rationale for changes made to this protocol are described in the following table. Note that minor edits have been made throughout the protocol, which are not captured in the table.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities; Induction Period	Days from Randomization for Visit 2 has been revised from 1 to 0.	Definition of Days from Randomization for Visit 2 changed.
1.3. Schedule of Activities; Induction Period, Health Outcome Measures and Other Questionnaires	Definitions of baseline for Itch, Sleep-Loss, Skin Pain and POEM have been added.	Clarification
1.3. Schedule of Activities; Induction Period, Laboratory Testing and 8.2.7. Hepatitis B Testing and Monitoring	Language describing the participants who will not be required to undergo HBV DNA monitoring at screening has been revised from "or" to "and" and now states: "Participants who are HBsAg negative, HBcAb negative, and HBsAb positive with a documented history of hepatitis B vaccination will not be required to undergo HBV DNA monitoring at screening"	To correct the definition of participants who will be required the hepatitis B DNA monitoring.
8.2.8. Hepatic Safety	Language describing the hepatic monitoring for pediatric participants has been added. Threshold for performing close hepatic monitoring and comprehensive hepatic	To follow the latest Lilly safety monitoring standards for hepatic monitoring.

Section # and Name	Description of Change	Brief Rationale
	elevation has been updated in total bilirubin.	
9.4.2.4. Treatment Compliance	Definition of treatment compliance has been added.	Clarification
10.1.6. Data Quality Assurance	Language related to quality tolerance limits has been added.	To follow the latest Lilly requirement for quality tolerance limits.
10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Language describing still birth in the collection of pregnancy information has been revised from ">20 weeks gestational age" to "≥20 weeks gestational age" and now states: "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"	To follow the latest Lilly required language for still birth.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Lebrikizumab When used in Combination with Topical Corticosteroid Treatment in Japanese Patients with Moderate-to-Severe Atopic Dermatitis

Short Title: Safety and Efficacy of Lebrikizumab in Combination with Topical Corticosteroids in Japanese Patients with Moderate-to-Severe Atopic Dermatitis

Rationale:

The use of lebrikizumab for atopic dermatitis (AD) is supported by numerous preclinical studies demonstrating that AD is characterized by the increased expression of interleukin (IL)-13 in skin. Moreover, clinical studies (Phase 2a Study GS29250 and Phase 2b Study DRM0-AD01) with lebrikizumab demonstrated significant clinical benefit in participants with AD. Additional detailed discussion of the lebrikizumab studies is provided in the lebrikizumab Investigator's Brochure (IB).

Objectives and Endpoints

Objective	Endpoints
Primary	
• To test the hypothesis that lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W is superior to placebo in reducing signs and symptoms of AD at Week 16 in Japanese participants with moderate-to-severe AD when used in combination with TCS treatment	• Proportion of participants achieving EASI-75 at Week 16 • Proportion of participants achieving an IGA score of 0 or 1 and a reduction of ≥2 points from baseline to Week 16
Major Secondary	
• To compare the efficacy and health outcome measures of lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W to placebo during the 16-week Induction Period in Japanese participants with moderate-to-severe AD when used in combination with TCS treatment	• Percentage change in EASI score from baseline to Week 16 • Proportion of participants achieving EASI-90 at Week 16 • Proportion of participants with an Itch NRS score of ≥4 points at baseline who achieve a ≥4-point reduction from baseline to Weeks 1, 2, 4 and 16

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

Overall Design

Study J2T-JE-KGAL is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study, which is 68 weeks in treatment duration. The study is designed to evaluate the safety and efficacy of lebrikizumab when used in combination with topical corticosteroid (TCS) treatment compared with placebo in combination with TCS treatment using a 16-week induction treatment and a 52-week Long-Term Maintenance Period of lebrikizumab for Japanese participants with moderate-to-severe AD.

The 16-week Induction Period will be double blinded and double dummy. All study intervention injections in the Induction Period will be administered by site staff in the clinic. After completion of the Week 16 visit, participants (responders) originally assigned to lebrikizumab 250 mg every 2 weeks (Q2W) will be re-randomized to either lebrikizumab 250 mg Q2W or lebrikizumab 250 mg every 4 weeks (Q4W), and participants originally assigned to 250 mg lebrikizumab Q4W or placebo will stay on the originally assigned treatment for the Maintenance Period. Non-responders at Week 16 and participants who used rescue therapy in the Induction Period will move to the Escape Arm from Week 16.

Treatment regimen assignment will remain blinded during the Maintenance Period.

Participants who do not maintain a ≥50% reduction from baseline in Eczema Area and Severity Index score (EASI-50) response at certain time points in the Maintenance Period will be assigned to an Escape Arm and will receive lebrikizumab 250 mg Q2W as open-label treatment through Week 68.

During the Maintenance Period, participants will be instructed to self-administer study intervention. Administration by the participants or caregiver is recommended. If the participant or caregiver is not able to administer any dose throughout the study, study site staff may administer the injection.

Participants who terminate early or complete the 68-week treatment period will receive a safety follow-up visit, which includes vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS), self-harm supplement and self-harm follow-up form, and pharmacokinetic (PK) and immunogenicity samples.

Disclosure Statement: This is a parallel-group treatment study with 3 arms that is participant and investigator blinded.

Number of Participants:

Approximately 280 participants will be randomized in a 3:2:2 ratio to lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, or placebo (120 participants: 80 participants:80 participants).

Intervention Groups and Duration:

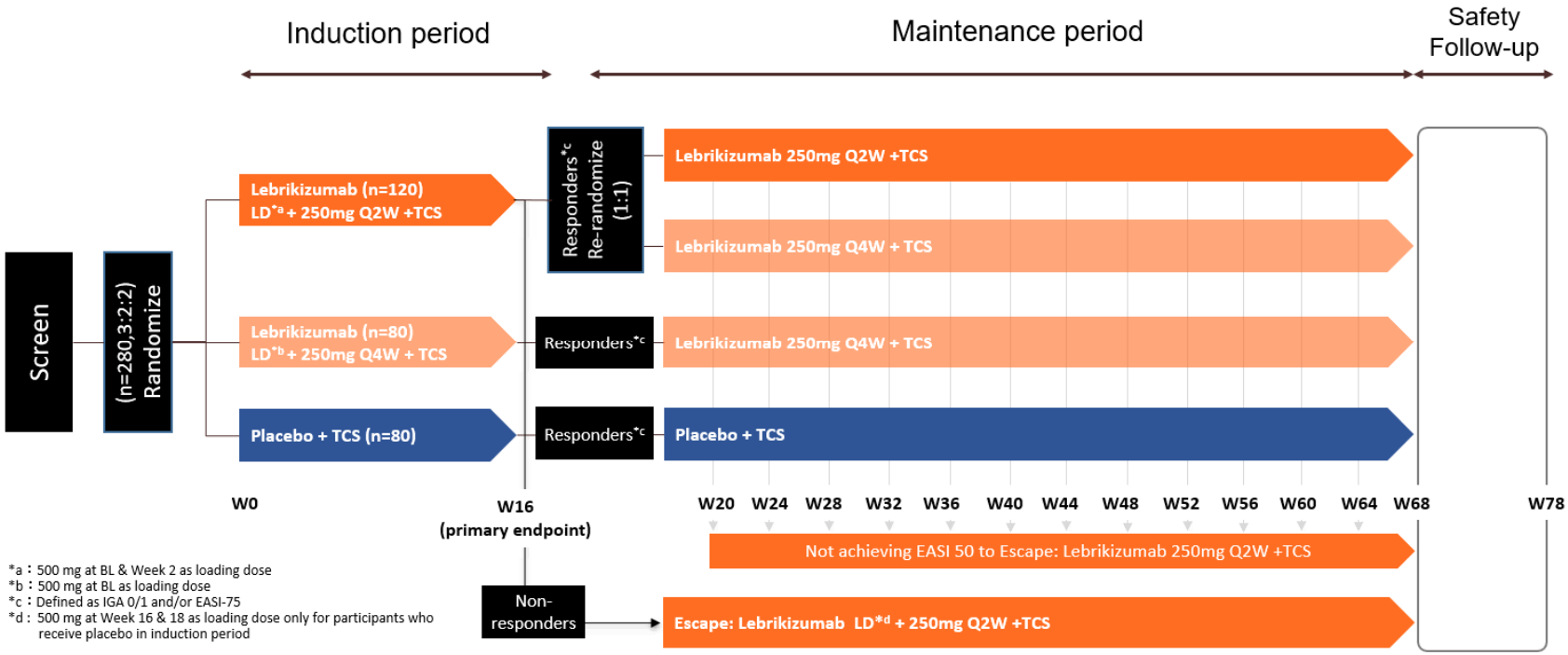
The study treatment period is 68 weeks followed by a safety follow-up visit 10 weeks later (78 weeks in total).

Approximately 280 participants, including approximately 15 adolescent participants (≥12 to <18 years and weighing ≥40 kg) will be randomized in a 3:2:2 ratio to treatment:

- 250 mg lebrikizumab (loading dose of 500 mg given at baseline and Week 2) by subcutaneous (SC) injection Q2W
- 250 mg lebrikizumab (loading dose of 500 mg given at baseline) by SC injection Q4W, or
- placebo.

Data Monitoring Committee: Yes

1.2. Schema



Participants to use mid- and low-potency TCS or TCIs which will be used in treatment period ≥7 days prior to the Baseline visit (Day 1).
Low-potency TCS or TCIs may be used for sensitive areas only.
Participants who receive rescue treatment in the induction period will be eligible to continue to the Escape arm and receive 250 mg lebrikizumab Q2W.
At Week 16, site personnel will instruct the participant or their caregiver on the proper injection technique.
At Week 16 and Week 18, participants or their caregiver will administer study intervention under site personnel supervision.

1.3. Schedule of Activities (SoA)

Study Schedule Protocol J2T-JE-KGAL
Induction Period: Screening Through Week 16

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

Study Schedule Protocol J2T-JE-KGAL
Induction Period: Screening Through Week 16

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
Safety											
Vital signs	X	X	X	X	X	X	X	X	X	X	
Physical examination including height and weight	X									X	
12-lead ECG (single)	X										Performed locally. Abnormalities recorded as AEs.
Chest x-ray (posterior-anterior view)	X										Will be performed locally at screening if applicable (Section 8.2.5). Abnormalities recorded as AEs.
Prior therapy	X										
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	
Investigator Scales											
IGA, EASI	X	X	X	X	X	X	X	X	X	X	
SCORAD		X	X	X	X	X	X	X	X	X	

Study Schedule Protocol J2T-JE-KGAL
Induction Period: Screening Through Week 16

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
Health Outcome Measures and Other Questionnaires											
Itch, Sleep-Loss, Skin Pain (daily)	X	X (Will be collected daily via an electronic participant diary)									The baseline for the daily assessments will be the average score of the 7 days prior to randomization.
POEM (weekly)	X	X (Will be collected weekly via an electronic participant diary)									The baseline for the weekly assessments will be the score acquired closest to randomization.
DLQI/CDLQI		X		X		X		X		X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
WPAI-AD		X				X				X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
HADS	X	X		X		X		X		X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
C-SSRS ‘Baseline/Screening’	X										
C-SSRS ‘Since Last Visit’		X	X	X	X	X	X	X	X	X	
Self-Harm Supplement Form	X	X	X	X	X	X	X	X	X	X	
Self-Harm Follow-up Form	X	X	X	X	X	X	X	X	X	X	Only required if triggered by the Self-Harm Supplement Form.

Study Schedule Protocol J2T-JE-KGAL
Induction Period: Screening Through Week 16

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
Health Outcome Measures and Other Questionnaires											
ACQ-5	X	X								X	Participants who report comorbid asthma prior to enrollment only. Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
Laboratory Testing											
TB test	X										TB test(s), including PPD, QuantiFERON®-TB Gold, and T-SPOT®. See Exclusion Criterion [17] for description of TB testing. Performed locally and not captured in eCRF.
Read PPD if applicable (48-72 hours post PPD)	X										Participant must return and PPD test read 48 to 72 hours after Visit 1 (post PPD).

Study Schedule Protocol J2T-JE-KGAL
Induction Period: Screening Through Week 16

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
Laboratory Testing											
Hematology, clinical chemistry	X	X		X		X		X		X	See Appendix 2, Clinical Laboratory Tests, for details.
Estradiol or testosterone		X								X	Collect estradiol in adolescent female participants only. Collect testosterone in adolescent male participants only.
Lipids (fasting)		X								X	Participants should not eat or drink anything except water for 12 hours prior before sample collection. If a participant attends these visits in a nonfasting state, this will not be considered a protocol violation.
Pregnancy test	serum	urine		urine		urine		urine		urine	For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests will be performed locally and not captured in eCRF.
FSH	X										For female participants who are >40 to ≤55 years of age.

Study Schedule Protocol J2T-JE-KGAL
Induction Period: Screening Through Week 16

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
Laboratory Testing											
HIV, HCV, HBV screening tests	X										For participants who are positive for HCV antibody, a follow-up test for HCV RNA will be performed automatically. Participants who are positive for HCV antibody and negative for HCV RNA may be enrolled.
HBV DNA	X			X		X		X		X	Participants who are HBsAg negative and positive for HBcAb (and/or HBsAb) will automatically have an HBV DNA test performed at screening. Participants who are HBsAg negative, HBcAb negative, and HBsAb positive with a documented history of hepatitis B vaccination will not be required to undergo HBV DNA monitoring at screening. If screening HBV DNA is negative, defined as undetectable HBV DNA, the participant is not excluded, and HBV DNA monitoring is required per the schedule. (Section 8.2.7).

Study Schedule Protocol J2T-JE-KGAL
Induction Period: Screening Through Week 16

	Screening	Induction Period									Comments
Visit Number	1	2	3	4	5	6	7	8	9	10	
Weeks from Randomization	–	0	2	4	6	8	10	12	14	16	
Days from Randomization	–	1	14	28	42	56	70	84	98	112	
Visit Tolerance Interval (days)	-7 to -30	–	±3	±3	±3	±3	±3	±3	±3	±3	
Laboratory Testing											
Beta-D-glucan	X										
Urinalysis	X	X								X	
Lebrikizumab PK samples		X		X				X		X	PK samples should be collected prior to dosing on days of dosing. Additional samples can be collected for any participants experiencing a hypersensitivity reaction during study (Section 8.3.7).
Immunogenicity samples		X		X				X		X	Immunogenicity samples should be collected prior to dosing on days of dosing. Additional sample can be collected for any participants experiencing a hypersensitivity reaction during study (Section 8.3.7).
Genetic samples		X									Collected at Visit 2. Sample collection can be rescheduled to any other visit if blood volume is limited at Visit 2.
TARC		X		X		X		X		X	

Study Schedule Protocol J2T-JE-KGAL
Maintenance Period: Week 18 to Week 40/Escape Arm

	Maintenance Period							Comments
Visit Number	11	12	13	14	15	16	17	
Weeks from Randomization	18	20	24	28	32	36	40	
Days from Randomization	126	140	168	196	224	252	280	
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	
IWRS entry	X	X	X	X	X	X	X	
Dispense background TCS	X	X	X	X	X	X	X	
Weigh (tube with cap) and record returned background TCS	X	X	X	X	X	X	X	
Dispense IP for home treatment		X	X	X	X	X	X	
IP returned and compliance assessed			X	X	X	X	X	
Administer study intervention	X	X (every 2 weeks)						At Visit 11, participants or their caregiver will administer study intervention under site personnel supervision. Subsequent administration will be administered by participants or their caregiver at home. At Visit 11, for participants in the Escape Arm: 2 injections. All other visits: 1 injection.
Safety								
Vital signs	X	X	X	X	X	X	X	
Physical examination including height and weight					X			
Concomitant medications/procedures	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	
Investigator Scales								
IGA, EASI	X	X	X	X	X	X	X	
SCORAD	X	X	X	X	X	X	X	

Study Schedule Protocol J2T-JE-KGAL
Maintenance Period: Week 18 to Week 40/Escape Arm

	Maintenance Period							Comments
Visit Number	11	12	13	14	15	16	17	
Weeks from Randomization	18	20	24	28	32	36	40	
Days from Randomization	126	140	168	196	224	252	280	
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	
Health Outcomes Measures and Other Questionnaires								
Itch, Sleep-Loss, Skin Pain	X (Will be collected daily via an electronic participant diary)							
POEM (weekly)	X (Will be collected weekly via an electronic participant diary)							Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
DLQI/CDLQI		X	X	X	X	X	X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
WPAI-AD				X			X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
HADS		X	X	X	X	X	X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
C-SSRS 'Since Last Visit'	X	X	X	X	X	X	X	
Self-Harm Supplement Form	X	X	X	X	X	X	X	
Self-Harm Follow-up Form	X	X	X	X	X	X	X	Only required if triggered by the Self-Harm Supplement Form.
Laboratory Testing								
Hematology, clinical chemistry		X		X		X		See Appendix 2, Clinical Laboratory Tests, for details.
Estradiol or testosterone					X			Collect estradiol in adolescent female participants only. Collect testosterone in adolescent male participants only.
Lipids (fasting)					X			Participants should not eat or drink anything except water for 12 hours prior to sample collection. If a participant attends these visits in a nonfasting state, this will not be considered a protocol violation.
Pregnancy test	urine	urine	urine	urine	urine	urine	urine	Urine pregnancy tests will be performed locally and not captured in the eCRF. If required per investigator judgment, local regulations, and/or institutional guidelines, additional pregnancy testing can occur during the study treatment period.

Study Schedule Protocol J2T-JE-KGAL
Maintenance Period: Week 18 to Week 40/Escape Arm

	Maintenance Period							Comments
Visit Number	11	12	13	14	15	16	17	
Weeks from Randomization	18	20	24	28	32	36	40	
Days from Randomization	126	140	168	196	224	252	280	
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	
Laboratory Testing								
HBV DNA		X	X	X	X	X	X	If screening HBV DNA is negative, defined as undetectable HBV DNA, the participant is not excluded, and HBV DNA monitoring is required per the schedule (Section 8.2.7).
Urinalysis					X			
Lebrikizumab PK samples			X		X			PK samples should be collected prior to dosing on days of dosing. Additional sample can be collected for any participants experiencing a hypersensitivity reaction during the study (Section 8.3.7).
Immunogenicity samples			X		X			Immunogenicity samples should be collected prior to dosing on days of dosing. Additional sample can be collected for any participants experiencing a hypersensitivity reaction during the study (Section 8.3.7).
TARC		X	X	X	X	X	X	

Study Schedule Protocol J2T-JE-KGAL
Maintenance Period: Week 44 to Week 68/Escape Arm

	Maintenance Period							Safety Follow-Up	Comments
Visit Number	18	19	20	21	22	23	24/ET	801	
Weeks from Randomization	44	48	52	56	60	64	68	78	
Days from Randomization	308	336	364	392	420	448	476	546	
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	±5	
IWRS entry	X	X	X	X	X	X	X	X	
Dispense background TCS	X	X	X	X	X	X			
Weigh (tube with cap) and record returned background TCS	X	X	X	X	X	X	X		
Dispense IP for home treatment	X	X	X	X	X	X			
IP returned and compliance assessed	X	X	X	X	X	X	X		
Administer study intervention	X (every 2 weeks)								Administered by participants or their caregiver. No administration at Visit 24/ET (Week 68).
Safety									
Vital signs	X	X	X	X	X	X	X	X	
Chest x-ray (posterior-anterior view)			X				X		X-ray at Visit 20, Visit 24, and at ET will be performed locally if more than 12 weeks have elapsed since the previous x-ray was obtained and not captured in the eCRF.
Physical examination including height and weight			X				X		
Concomitant medications/procedures	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	
Investigator Scales									
IGA, EASI	X	X	X	X	X	X	X	X	
SCORAD	X	X	X	X	X	X	X	X	

Study Schedule Protocol J2T-JE-KGAL
Maintenance Period: Week 44 to Week 68/Escape Arm

	Maintenance Period							Safety Follow-Up	Comments
Visit Number	18	19	20	21	22	23	24/ET	801	
Weeks from Randomization	44	48	52	56	60	64	68	78	
Days from Randomization	308	336	364	392	420	448	476	546	
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	±5	
Health Outcome Measures and Other Questionnaires									
Itch, Sleep-Loss, Skin Pain (daily)	X (Will be collected daily via an electronic participant diary)								Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
POEM (weekly)	X (Will be collected weekly via an electronic participant diary)								Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
DLQI/CDLQI	X	X	X	X	X	X	X	X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
WPAI-AD			X				X		Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
HADS	X	X	X	X	X	X	X	X	Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.
C-SSRS ‘Since Last Visit’	X	X	X	X	X	X	X	X	
Self-Harm Supplement Form	X	X	X	X	X	X	X	X	
Self-Harm Follow-up Form	X	X	X	X	X	X	X	X	Only required if triggered by the Self-Harm Supplement Form.
ACQ-5			X				X		Will be collected as eCOA data. Will be completed by the participant prior to any clinical assessments on days of study visits.

Study Schedule Protocol J2T-JE-KGAL
Maintenance Period: Week 44 to Week 68/Escape Arm

	Maintenance Period							Safety Follow-Up	Comments
Visit Number	18	19	20	21	22	23	24/ET	801	
Weeks from Randomization	44	48	52	56	60	64	68	78	
Days from Randomization	308	336	364	392	420	448	476	546	
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	±5	
Laboratory Testing									
Hematology, clinical chemistry	X		X		X		X		
Estradiol or testosterone			X				X		Collect estradiol in adolescent female participants only. Collect testosterone in adolescent male participants only.
Lipids (fasting)			X				X		Participants should not eat or drink anything except water for 12 hours prior to sample collection. If a participant attends these visits in a nonfasting state, this will not be considered a protocol violation.
Pregnancy test	urine	urine	urine	urine	urine	urine	urine	urine	Urine pregnancy tests will be performed locally and not captured in the eCRF. If required per investigator judgment, local regulations, and/or institutional guidelines, additional pregnancy testing can occur during the study treatment period.
HBV DNA			X		X		X		If screening HBV DNA is negative, defined as undetectable HBV DNA, the participant is not excluded, and HBV DNA monitoring is required per the schedule (Section 8.2.7).
Urinalysis			X				X		

Study Schedule Protocol J2T-JE-KGAL
Maintenance Period: Week 44 to Week 68/Escape Arm

	Maintenance Period							Safety Follow-Up	Comments
Visit Number	18	19	20	21	22	23	24/ET	801	
Weeks from Randomization	44	48	52	56	60	64	68	78	
Days from Randomization	308	336	364	392	420	448	476	546	
Visit Tolerance Interval (days)	±5	±5	±5	±5	±5	±5	±5	±5	
Laboratory Testing									
Lebrikizumab PK samples			X				X	X	PK samples should be collected prior to dosing on days of dosing. Additional sample can be collected for any participants experiencing a hypersensitivity reaction during study (Section 8.3.7).
Immunogenicity samples			X				X	X	Immunogenicity samples should be collected prior to dosing on days of dosing. Additional sample can be collected for any participants experiencing a hypersensitivity reaction during study (Section 8.3.7).
TARC	X	X	X	X	X	X	X		

Abbreviations: ACQ-5 = Asthma Control Questionnaire-5; AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI/CDLQI = Dermatology Life Quality Index/Children's Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eCOA = electronic clinical outcome assessment; eCRF = electronic case report form; ET = early termination; FSH = follicle-stimulating hormone; HADS = Hospital Anxiety Depression Scale; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGA = Investigator's Global Assessment; IP = investigational product; IWRS = interactive web response system; PK = pharmacokinetic; POEM = Patient-Oriented Eczema Measure; PPD = purified protein derivative; SCORAD = SCORing Atopic Dermatitis; TARC = thymus and activation-regulated chemokine; TB = tuberculosis; TCS = topical corticosteroids; WPAI-AD = Work Productivity and Activity Impairment-Atopic Dermatitis.

2. Introduction

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

2.1. Study Rationale

The use of lebrikizumab for AD is supported by numerous preclinical studies demonstrating that AD is characterized by the increased expression of IL-13 in skin. Moreover, clinical studies (Phase 2a Study GS29250 and Phase 2b Study DRM06-AD01) with lebrikizumab demonstrated significant clinical benefit in participants with AD. Additional detailed discussion of the lebrikizumab studies is provided in the lebrikizumab IB.

2.2. Background

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

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

Epidemiology of Pediatric Atopic Dermatitis

Atopic dermatitis is one of the most common chronic medical diseases; 15% to 30% of children and 2% to 10% of adults are affected, and the prevalence appears to have increased over the past 2 to 3 decades (Williams et al. 2008), with some geographic variability. With respect to disease severity, about 67% of pediatric patients with AD have mild disease, 14% to 26% have moderate disease, and 2% to 7% have severe disease (Silverberg 2017). Approximately 85% of all cases of AD begin before age 5, with up to 70% of children having spontaneous remission before adolescence (Illi et al. 2004; Bieber 2008; Hua et al. 2014).

Clinical Manifestations

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

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

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

Patients with AD have a high disease burden, and their quality of life is significantly affected. In one study, AD was shown to have a greater negative effect on patient mental health than diabetes and hypertension (Zuberbier et al. 2006). Patients with moderate-to-severe AD have a higher prevalence of social dysfunction and sleep impairment, which are directly related to the severity of the disease (Williams et al. 2008). Depression, anxiety, and social dysfunction not only affect patients with AD but also affect their caregivers (Zuberbier et al. 2006). Compared with patients with psoriasis, another common and debilitating skin disease, patients with AD have lower physical vitality, social functioning, role-emotional, and mental health scores (Kiebert et al. 2002).

Treatment for Atopic Dermatitis

The therapeutic approach to AD consists primarily of trigger avoidance, skin hydration with bathing, and use of moisturizers and anti-inflammatory therapies consisting predominantly of TCS. In many patients, treatment with TCS provides some measure of symptomatic relief but does not always adequately control the disease. In patients with persistent moderate-to-severe disease not responding adequately to TCS, the step-up options include topical calcineurin inhibitors (TCIs), phototherapy, and immunosuppressive agents such as oral

corticosteroids, cyclosporine, azathioprine, methotrexate (MTX), and mycophenolate mofetil (MMF). Among these immunosuppressive agents, only cyclosporine is approved in Japan for the treatment of patients with severe adult AD who do not respond to conventional treatments and have eruptions with marked inflammation involving 30% or more of the body surface area (BSA). The use of cyclosporine is limited to short-term (8 to 12 weeks) and intermittent administration involving a 2-week or much longer period of discontinuation if long-term administration is necessary. Recently, in 2018, a clinically efficacious and relatively safe treatment, anti-IL-4R monoclonal antibody, dupilumab, was approved for the treatment of adult patients with moderate-to-severe AD. More recently, in 2020, the topical Janus kinase (JAK) inhibitor delgocitinib was approved for the treatment of AD. Despite these treatments, there remains a major societal burden for those with AD and a significant unmet medical need for treatment.

2.3. Benefit/Risk Assessment

As of October 2019, lebrikizumab has been given to 311 healthy people and more than 4200 study participants to study various diseases. More than 400 patients with AD have taken lebrikizumab. In Phase 2 studies, treatment-emergent adverse events (TEAEs) reported in 2% to 10% of participants included nasopharyngitis, upper respiratory tract infection, all conjunctivitis, headache, herpes infections, injection site reactions, pruritus, diarrhea, and anxiety. No anaphylaxis or serious infections were reported as TEAEs in participants with AD.

Lebrikizumab may increase the risk of malignancy and serious infections. These have not been reported in the AD studies.

Serious adverse effects and death can occur in study participants. No deaths have been reported in AD studies with lebrikizumab.

In AD study participants, higher levels of eosinophils have been observed without resultant adverse events (AEs). Conjunctivitis, herpes infection or zoster, and parasitic infection or an infection related to an intracellular pathogen are the adverse events of special interest (AESI [Section 8.3.6]). These reactions, if they occur, will prompt additional testing and data collection and are among the reasons that a participant might be discontinued from study intervention.

To minimize study participant risk in this study (J2T-JE-KGAL), enrolled participants will receive study intervention doses at the clinic to enable appropriate predose safety assessments and postdose monitoring during the Induction Period.

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

Phase 2 efficacy studies of lebrikizumab (GS29250 [TREBLE], and DRM06-AD01) demonstrated significant clinical benefit in participants with AD.

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

In this Phase 3 study, adolescent participants (≥12 to <18 years weighing ≥40 kg) will be included and will receive the same doses of lebrikizumab as adult participants. Pharmacokinetic

analyses of SC doses of lebrikizumab reveal similar kinetics for adults and adolescents ≥12 to <18 years. Although maximal exposures are CCI [redacted] 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, we expect a similar exposure response relationship in this age group compared to adults based on partial extrapolation and propose to include adolescent participants in this study. We also expect that the adolescent AD participants ≥40 kg will respond to lebrikizumab with a similar overall safety profile as adult participants.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of lebrikizumab are in the IB. In Section 2.2, more details about pediatric populations are given.

3. Objectives and Endpoints

Objective	Endpoints
Primary	
• To test the hypothesis that lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W is superior to placebo in reducing signs and symptoms of AD at Week 16 in Japanese participants with moderate-to-severe AD when used in combination with TCS treatment	• Proportion of participants achieving EASI-75 at Week 16 • Proportion of participants achieving IGA score of 0 or 1 and a reduction of ≥2-points from baseline to Week 16
Major Secondary	
• To compare the efficacy and health outcome measures of lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W to placebo during the 16-week Induction Period in Japanese participants with moderate-to-severe AD when used in combination with TCS treatment	• Percentage change in EASI score from baseline to Week 16 • Proportion of participants achieving EASI-90 at Week 16 • Proportion of participants with an Itch NRS score of ≥4-points at baseline who achieve a ≥4-point reduction from baseline to Weeks 1, 2, 4 and 16
Other Secondary	
• To measure lebrikizumab exposure and assess the relationship between exposure and immunogenicity	• Average serum lebrikizumab concentration at steady state • Lebrikizumab serum trough concentrations associated with ADA titer
• To evaluate the efficacy and health outcome measures of lebrikizumab 250 mg Q2W and lebrikizumab 250 mg Q4W during the 16-week Induction and 52-week Maintenance periods in Japanese participants with moderate-to-severe AD when used in combination with TCS treatment	• Percentage change from baseline in EASI score by visit • Proportion of participants with EASI-50, EASI-75, and EASI-90 by visit • Proportion of participants maintaining EASI-75 by visit during the 52-week Maintenance Period among those originally randomized to lebrikizumab 250 mg Q2W and lebrikizumab 250 mg Q4W who achieved EASI-75 at Week 16 • Proportion of participants with an IGA score of 0 or 1 and a reduction of ≥2 points from baseline by visit

	• Proportion of participants maintaining an IGA score of 0 or 1 with a ≥2-point improvement from baseline by visit during the 52-week Maintenance Period among those originally randomized to lebrikizumab 250 mg Q2W and lebrikizumab 250 mg Q4W who achieved and IGA score of 0 or 1 with a ≥2-point improvement from baseline at Week 16 • Change from baseline in Itch NRS score by visit • Proportion of participants with an Itch NRS score of ≥4 points at baseline who achieve a ≥4-point reduction from baseline by visit • Change from baseline in Skin Pain NRS score by visit • Number of Skin Pain-Free (Skin Pain NRS = 0) days • Proportion of participants with a Skin Pain NRS score of ≥4 points at baseline who achieve a ≥4-point reduction from baseline by visit • Change from baseline in percent BSA by visit • Change from baseline in Sleep-Loss score by visit • Proportion of participants achieving a ≥4-point improvement in DLQI/CDLQI score from baseline by visit • Proportion of participants achieving DLQI/CDLQI score of 0 or 1 by visit • Change from baseline in DLQI/CDLQI by visit • Change from baseline in POEM by visit • Change from baseline in WPAI-AD score by visit • Change from baseline in HADS score by visit • Change from Baseline in ACQ-5 score to Week 16 in participants who have self-reported comorbid asthma • Percentage change from Baseline in SCORAD by visit • Proportion of TCS/TCI-free days over the 16-week and 68-week study periods

	• Total amount of TCS used over the 16-week and 68-week study periods • Time (days) to TCS/TCI-free use over the 16-week and 68-week study periods
• To assess the growth of adolescent participants treated with lebrikizumab	• Mean changes in growth parameters (height, weight, and BMI) over the course of treatment

Abbreviations: ACQ-5 = Asthma Control Questionnaire-5; AD = atopic dermatitis; ADA = anti-drug antibody; BMI = body mass index; BSA = body surface area; DLQI/CDLQI = Dermatology Life Quality Index/Children's Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-50 = ≥50% reduction from baseline in EASI score; EASI-75 = ≥75% reduction from baseline in EASI score; EASI-90 = ≥90% reduction from baseline in EASI score; HADS = Hospital Anxiety Depression Scale; IGA = Investigator's Global Assessment; NRS = numeric rating scale; POEM = Patient-Oriented Eczema Measure; Q2W = every 2 weeks; Q4W = every 4 weeks; SCORAD = SCORing Atopic Dermatitis; TCS/TCI = topical corticosteroid/topical calcineurin inhibitor; WPAI-AD = Work Productivity and Activity Impairment – Atopic Dermatitis.

4. Study Design

4.1. Overall Design

Study Design

Study KGAL is a randomized, double-blind, placebo-controlled, parallel-group study, which is 68 weeks in treatment duration. The study is designed to evaluate the safety and efficacy of lebrikizumab when used in combination with TCS treatment compared with placebo in combination with TCS treatment using a 16-week induction treatment and a 52 week long-term Maintenance Period of lebrikizumab for Japanese participants with moderate-to-severe AD.

Study Population

Participants are eligible for the study if they

- are ≥18 years or an adolescent (≥12 to <18 years of age and weighing ≥40 kg) with moderate-to-severe AD for at least 1 year, defined according to the American Academy of Dermatology Consensus Criteria (Eichenfield et al. 2014) (Appendix 7)
- have an EASI score ≥16
- have an Investigator's Global Assessment (IGA) score ≥3, and
- have an AD involvement in ≥10% of BSA

Investigators should review vaccination status in adolescent participants (≥12 to <18 years) and determine the benefit/risk of their participation. No changes in start or resumption of vaccine is required, and pediatric participants will follow the Japan immunization guidelines, with the exception of live vaccines. If a participant has received a live vaccine within 12 weeks of the baseline visit or intends to receive a live vaccine during the study or up to 125 days after the last dose of investigational product (IP), the participant is not eligible for the study (see exclusion criterion [29]).

Induction Period

During the 16-week Induction Period, approximately 280 participants, including approximately 15 adolescent participants (≥12 to <18 years and weighing ≥40 kg), will be randomized in a 3:2:2 ratio to treatment:

- 250 mg lebrikizumab (loading dose of 500 mg given at baseline and Week 2) by SC injection Q2W
- 250 mg lebrikizumab (loading dose of 500 mg given at baseline) by SC injection Q4W, or
- placebo.

Participants will be stratified at randomization according to age (adolescent participants ≥12 to <18 years vs ≥18 years) and disease severity (IGA 3 vs 4). Daily use of mid-potency TCS (low-potency TCS and/or TCI for sensitive areas) will be initiated at least 7 days prior to baseline in all participants (not allowed to be tapered or stopped during the Screening Period). Mid-potency TCS, low-potency TCS, and TCIs may be tapered or stopped after baseline, as needed, based on treatment response.

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

Maintenance Period

After completion of the Week 16 visit:

- Participants receiving 250 mg lebrikizumab Q2W
    i. who achieve an IGA 0 or 1 and/or a ≥75% reduction in EASI score (≥EASI-75) response at Week 16 will be randomly allocated to receive 250 mg lebrikizumab Q2W or 250 mg lebrikizumab Q4W, in a 1:1 fashion;
    ii. who achieve neither an IGA 0 or 1 nor a <75% reduction in EASI score (<EASI-75) response at Week 16 will move to the Escape Arm.
- Participants receiving 250 mg lebrikizumab Q4W
    i. who achieve an IGA 0 or 1 and/or an EASI-75 response (≥EASI-75) at Week 16 will continue 250 mg lebrikizumab Q4W;
    ii. who achieve neither an IGA 0 or 1 nor an EASI-75 response (<EASI-75) at Week 16 will move to the Escape Arm.
- Participants receiving placebo
    i. who achieve an IGA 0 or 1 and/or an EASI-75 response (≥EASI-75) at Week 16 will continue to receive placebo;
    ii. who achieve neither an IGA 0 or 1 nor an EASI-75 response (<EASI-75) at Week 16 will move to the Escape Arm and will receive a loading dose of 500 mg lebrikizumab at Week 16 and Week 18.

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

Escape Arm

In the Escape Arm, participants will receive 250 mg lebrikizumab Q2W.

Escape Arm from Week 16:

- Participants who achieve neither an IGA 0 or 1 nor an EASI-75 response (<EASI-75) at Week 16 will move to the Escape Arm.
- Participants who receive rescue treatment in the Induction Period will also be eligible to continue to the Escape Arm at Week 16.
- Participants who required systemic rescue medication in the Induction Period must discontinue study intervention and must wait for the rescue medication washout (≥5 half-lives of the medication) prior to entering the Escape Arm.
- Only participants who receive placebo in the Induction Period will receive a loading dose of 500 mg lebrikizumab at Week 16 and Week 18 followed by 250 mg lebrikizumab Q2W. Participants not achieving an EASI-50 response at 2 consecutive visits in the Escape Arm after Week 32 of treatment will be discontinued from the study.

Escape Arm after Week 20:

- Participants who do not maintain an EASI-50 response at Week 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 or 64 in the Maintenance Period will be assigned to an Escape Arm and receive lebrikizumab 250 mg Q2W as open-label treatment thorough Week 68.
- Participants not achieving an EASI-50 response at 2 consecutive visits in the Escape Arm after 8 weeks of treatment will be discontinued from the study.

During the Maintenance Period, participants will be instructed to self-administer study intervention. Administration by the participant or caregiver is recommended. If the participant or caregiver is not able to administer any dose throughout the study, study site staff may administer the injection.

- At Week 16, site personnel will instruct participants or their caregiver on the proper injection technique.
- At Week 16 and Week 18, participants or their caregiver will administer study intervention under site personnel supervision.
- Subsequent administration will be administered by participants or their caregiver at home.

Efficacy, Health Outcomes, and Safety Assessments

Efficacy and health outcomes will be measured through

- IGA
- EASI
- SCORing Atopic Dermatitis (SCORAD)
- BSA involvement
- Itch Numeric Rating Scale (NRS)
- Sleep-Loss Scoring System
- Skin Pain NRS
- TCS/TCI use
- C-SSRS self-harm assessment
- Quality of life and impact of disease (these will be assessed using the Patient-Oriented Eczema Measure [POEM], Dermatology Life Quality Index/Children's Dermatology Life Quality Index [DLQI/CDLQI], Work Productivity and Activity Impairment – Atopic Dermatitis [WPAI-AD], and Hospital Anxiety Depression Scale [HADS]), and
- Asthma Control Questionnaire-5 (ACQ-5) (to be completed by participants reporting comorbid asthma at study entry).

Safety will be assessed in all participants by

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

- chest x-ray
- concomitant medications, and
- monitoring of hormone levels and growth parameters (adolescents only).

Serum samples will be collected for PK analysis and immunogenicity.

Participants who terminate the study early or complete the 68-week treatment period will receive a safety follow-up visit at which vital signs will be measured, C-SSRS self-harm supplement and self-harm follow-up form will be completed, and PK and immunogenicity samples will be collected.

4.2. Scientific Rationale for Study Design

The use of lebrikizumab for AD is supported by numerous preclinical studies demonstrating that AD is characterized by the increased expression of IL-13 in skin. Moreover, clinical studies (Phase 2a Study GS29250 and Phase 2b Study DRM06-AD01) with lebrikizumab demonstrated significant clinical benefit in participants with AD. Additional detailed discussion of the lebrikizumab studies is provided in the lebrikizumab IB.

4.3. Justification for Dose

For Study KGAL, a dosing regimen of 500 mg lebrikizumab administered as a loading dose at baseline and Week 2, followed by 250 mg Q2W lebrikizumab and a dosing regimen of 500 mg lebrikizumab administered as a loading dose at baseline, followed by 250 mg Q4W lebrikizumab was selected for the Induction Period (baseline to Week 16) based on an evaluation of safety, efficacy, and PK data from the DRM06-AD01 and DRM06-AD03 studies. The DRM06-AD03 PK study conducted in healthy adults demonstrated that a single 2-mL (250 mg) SC injection of lebrikizumab delivered comparable levels of lebrikizumab as two 1-mL (125 mg) SC injections. This simulated the conditions under which study intervention will be administered in Phase 3, further supporting the dose and treatment regimen for KGAL, lebrikizumab 250 mg Q2W with a loading dose of 500 mg given at baseline and Week 2 and lebrikizumab 250 mg Q4W with a loading dose of 500 mg given at baseline.

Following the Induction Period, Study KGAL will assess the long-term safety and efficacy of both a 250-mg lebrikizumab Q2W dosing regimen and a 250-mg lebrikizumab Q4W dosing regimen to determine whether one or both regimens, of which one involves less frequent dosing, may be effective in maintaining disease control over an extended period.

Adolescent Participants

Adolescent participants (≥12 to <18 years weighing ≥40 kg) will be included in Study KGAL and will receive the same doses of lebrikizumab described above for adults. The justification for this approach is described below.

Both adults and adolescent participants have similar disease characteristics, typified by prominent Type 2 skin inflammation and similar clinical manifestations. In addition, both groups tend to have similar efficacy outcomes in response to therapies, including dupilumab (Simpson et al. 2018; Treister and Lio 2019). Pharmacokinetic modeling and simulations of lebrikizumab dosing (population PK modeling of pooled data from 2259 adult asthma participants and a subsequent external posterior predictive check with lebrikizumab PK data from the

DRM06-AD01 study in adult AD participants) revealed similar kinetics for adult and adolescent participants (≥12 to <18 years). The maximal exposures are predicted to be CCI [redacted] in adolescent participants than in adult participants for any given dose due to the lower adolescent weight ranges and lebrikizumab exposure dependence on weight; however, the safety profile in adolescent participants, based on the exposure-response relationship analysis and on partial extrapolation, is comparable to that observed in adults.

4.4. End of Study Definition

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

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

Weight

6. Body weight ≥40 kg.

Sex

7. Male or non-pregnant, non-breastfeeding female.

   Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   a. For women of childbearing potential (WOCBP): 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 lebrikizumab.

      NOTE: A WOCBP is defined in Appendix 4, Section 10.4.

      NOTE: The following are highly effective contraceptive methods: combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; bilateral tubal ligation; partner who has undergone vasectomy; or sexual abstinence. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (for example, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

      If the highly effective contraceptive methods are contraindicated or strictly declined by patient, acceptable birth control methods may be considered. These may include combination of both of the following methods:

      - male or female condom with spermicide, or
      - cap, diaphragm, or sponge with spermicide.

   b. Male patients are not required to use contraception.

Informed Consent

8. Capable of giving signed informed consent or have a legal guardian who is willing and able to provide written informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

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

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

5.2. Exclusion Criteria

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

Medical Conditions

9. Have a history of anaphylaxis as defined by National Institute of Allergy and Infectious Disease criteria (Sampson et al. 2006).
10. Have uncontrolled chronic disease that might require bursts of oral corticosteroids, for example, comorbid severe uncontrolled asthma (defined by a history of ≥2 asthma exacerbations within the past 12 months requiring systemic [oral and/or parenteral] corticosteroid treatment or hospitalization for >24 hours at Visit 1 and 2).
11. Have an active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit or superficial skin infections within 1 week before the baseline visit.

    NOTE: participants may be re-screened after infection resolves.

12. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (for example, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution or unusually frequent, recurrent, or prolonged infections, per the investigator's judgment.
13. Have known hepatitis B infection or test positive for hepatitis B virus (HBV) at screening, defined as: (1) positive for hepatitis B surface antigen (HBsAg); (2) positive for hepatitis B core antibody (HBcAb) and positive confirmatory polymerase chain reaction (PCR) for HBV DNA, regardless of hepatitis B surface antibody (HBsAb) status; or (3) positive for HBcAb and/or positive for anti-HBsAb and a confirmatory PCR for HBV DNA.
    Participants whose results are HBcAb positive and/or HBsAb positive and HBV DNA negative may be eligible to continue screening per investigator judgment. Such participants will be monitored for HBV during the study as detailed in Section 8.2.7.
14. Have known hepatitis C infection or test positive for hepatitis C virus (HCV) at screening, defined as a positive test result for hepatitis C antibody (anti-HCVAb) plus a positive confirmatory test result for HCV (for example, HCV RNA).
    Participants whose results are anti-HCVAb positive and HCV RNA negative are eligible to continue screening per investigator judgment.

    NOTE: Participants who have documented anti-HCV treatment for a past HCV infection AND are HCV RNA negative are eligible to continue screening per investigator judgment.

15. Have a history of pneumocystis pneumonia (PCP) or a positive beta-D-glucan test at screening and a confirmed diagnosis of PCP.
16. Have active endoparasitic infections or are at high risk of contracting these infections.
17. Have evidence of active tuberculosis (TB) or latent tuberculosis infection (LTBI).
    a. have evidence of active TB, defined in this study as follows:
        i. documented by a positive purified protein derivative (PPD) test (≥5 mm induration between approximately 48 and 72 hours after application, regardless of vaccination history), medical history, clinical features, and abnormal chest x-ray at screening;
        ii. QuantiFERON®-TB Gold test or T-SPOT® TB test may be used instead of the PPD test. Participants are excluded from the study if the test is not negative and there is clinical evidence of active TB.

Exception: Participants with a history of active TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such participants would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON-TB Gold test, or T-SPOT TB test but must have a chest x-ray at screening.

    b. have evidence of untreated/inadequately or inappropriately treated LTBI, defined in this study as follows:
        i. documented to have a positive PPD test (≥5 mm induration between approximately 48 and 72 hours after application, regardless of vaccination history), no clinical features consistent with active TB, and a chest x-ray with no evidence of active TB at screening; or
        ii. PPD test is positive and the participant has no medical history or chest x-ray findings consistent with active TB. The participant may have a QuantiFERON-TB Gold test or T-SPOT TB test. If the test results are not negative, the participant will be considered to have LTBI (for purposes of this study); or
        iii. QuantiFERON-TB Gold test or T-SPOT TB test may be used instead of the PPD test. If the test results are positive, the participant will be considered to have LTBI. If the test is not negative, the test may be repeated once within approximately 2 weeks of initial testing. If results of the repeated test are not negative, the participant will be considered to have LTBI (for purposes of this study). Participants who have an indeterminate QuantiFERON-TB Gold test (not negative) may either repeat the QuantiFERON-TB Gold test or undergo T-SPOT TB testing. Purified protein derivative testing after an indeterminate QuantiFERON-TB Gold test is not allowed.

Exception: A participant who has evidence of LTBI may be enrolled if he or she completes at least 4 weeks of appropriate treatment prior to randomization and agrees to

complete the remainder of treatment during the study. If a participant is not able to complete at least 4 weeks of appropriate treatment prior to randomization, the participant may be re-screened.

Exception: Participants with a history of LTBI who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such participants would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON-TB Gold test, or T-SPOT TB test but must have a chest x-ray at screening.

18. Have a history of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
19. Have presence of skin comorbidities (for example, sclerosis, psoriasis, or lupus erythematosus) that may interfere with study assessments.
20. Have presence of significant uncontrolled neuropsychiatric disorder, are clinically judged by the investigator to be at risk for suicide, or have a "yes" answer to any of the following:
    a. Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS
    b. Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS, or
    c. any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, and preparatory act or behavior) on the "Suicidal Behavior" portion of the C-SSRS and the ideation or behavior occurred within 2 months prior to Visit 1.

    NOTE: A participant does not necessarily have to be excluded if they have self-injurious behavior that would be classified as nonsuicidal self-injurious behavior. If this situation arises, the participant should be referred to a psychiatrist or appropriately trained professional as indicated.
21. Have a history of malignancy, including mycosis fungoides, within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix or completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin with no evidence of recurrence in the past 12 weeks.
22. Have severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the participant's participation in the study or any other medical or psychological condition that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant because of his/her participation in this clinical study, may make the participant's participation unreliable, or may interfere with study assessments.

Prior/Concomitant Therapy

23. Have received a dose of lebrikizumab in any prior lebrikizumab clinical study.
24. Have had an important side effect from TCS (for example, intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects), as assessed by the investigator or treating physician, that would prevent further use.
25. Had treatment with high-potency topical corticosteroids, JAK inhibitors (topical) or phosphodiesterase 4 inhibitor within 7 days prior to the baseline visit (Visit 2).
26. Had treatment with any of the following agents within 4 weeks prior to the baseline visit:
    a. immunosuppressive/immunomodulating drugs (for example, systemic corticosteroids, cyclosporine, MMF, interferon γ (IFN-γ), JAK inhibitors, azathioprine, MTX, or
    b. Phototherapy and photochemotherapy for AD.
27. Had treatment with the following prior to the baseline visit:
    a. an investigational intervention within 8 weeks or within 5 half-lives (if known), whichever is longer
    b. dupilumab within 8 weeks
    c. B-cell–depleting biologics, including rituximab, within 6 months, or
    d. other biologics within 5 half-lives (if known) or 16 weeks, whichever is longer.
28. Have regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit.
29. Have been exposed to a live vaccine within 12 weeks prior to the baseline visit or are expected to need/receive a live vaccine during the study or up to 125 days after the last dose of IP.

    NOTE: Booster vaccination for measles, mumps, and rubella or varicella-zoster virus may be considered if it is essential based on local guidelines and/or in the opinion of the investigator.

Prior/Concurrent Clinical Study Experience

30. Participated in a prior lebrikizumab clinical study.

Diagnostic assessments

31. Have any of the following specific abnormalities in screening laboratory tests:
    a. serum creatinine, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2× upper limit of normal (ULN)
    b. alkaline phosphatase (ALP) ≥2× ULN
    c. total bilirubin (TBL) ≥1.5× ULN
    d. hemoglobin <10.0 g/dL (<100.0 g/L)
    e. total white blood cell (WBC) count <2500 cells/µL (<2.50×10^3/µL or <2.50 GI/L)
    f. neutropenia (absolute neutrophil count [ANC] <1200 cells/µL) (<1.20×10^3/µL or <1.20 GI/L)

g. lymphopenia (lymphocyte count <750 cells/μL) (<0.75×10^3/μL or <0.75 GI/L), or
h. thrombocytopenia (platelets <100,000/μL) (<100×10^3/μL or <100 GI/L).

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

Other Exclusions

32. Pregnant or breastfeeding women or women planning to become pregnant or breastfeed during the study.
33. Are Lilly employees or are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) 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 re-screened. Re-screened participants should be assigned a new participant number. When re-screening, participants who have previously completed screening chest radiography and/or TB tests according to the protocol do not need to repeat these procedures if they were performed within 90 days before their re-screening date of consent but may do so at the discretion of the investigator. All other screening procedures must be conducted at re-screening to ensure that all eligibility criteria are met. Individuals may be re-screened up to 1 time. The interval between re-screenings should be at least 4 weeks. Each time re-screening is performed, the individual or their parent or legal guardian must sign a new ICF.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

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

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

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

The tables below describe the dosing schedules for the Induction and Maintenance periods and the Escape Arm.

Table 1. Induction Period Dosing Schedule by Treatment Group

Treatment Assignment in Induction Period (Blinded)	Loading Dose (Baseline and Week 2)	Weeks 4, 8, and 12	Weeks 6, 10, and 14
Lebrikizumab 250 mg Q2W	Baseline: 2 active injections Week 2: 2 active injections	1 active injection	1 active injection
Lebrikizumab 250 mg Q4W	Baseline: 2 active injections Week 2: 2 placebo injections	1 active injection	1 placebo injection
Placebo	Baseline: 2 placebo injections Week 2: 2 placebo injections	1 placebo injection	1 placebo injection

Abbreviations: SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks.
Notes: Information provided in this table may change throughout the study. Injections are given SC.

Table 2. Maintenance Period Dosing Schedule by Treatment Group

Treatment Assignment in Induction Period (Blinded)	Treatment Assignment in Maintenance Period	Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, and 64	Weeks 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, and 66
Lebrikizumab 250 mg Q2W	Lebrikizumab 250 mg Q2W	1 active injection	1 active injection
	Lebrikizumab 250 mg Q4W	1 active injection	1 placebo injection
Lebrikizumab 250 mg Q4W	Lebrikizumab 250 mg Q4W	1 active injection	1 placebo injection
Placebo	Placebo	1 placebo injection	1 placebo injection

Abbreviations: SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks.
Notes: Information provided in this table may change throughout the study. Injections are given SC.

Participants Entering Escape Arm at Week 16

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

Participants who require high-potency topical or systemic rescue treatment for AD during the Induction Period will be eligible for treatment in the Escape Arm. Participants receiving systemic rescue medication in the Induction Period will be required to washout for 5 half-lives prior to initiating treatment in the Escape Arm.

Participants who are eligible for the Escape Arm at Week 16 will receive blinded loading doses at Week 16 and 18, based on their prior treatment assignment, followed by 250 mg lebrikizumab Q2W through Week 68 in the Escape Arm in an open-label fashion. Participants not achieving an EASI-50 response at 2 consecutive visits in the Escape Arm after Week 32 of treatment will be terminated from the study.

Table 3. Escape Arm Dosing Schedule by Treatment Group

Treatment Assignment in Induction Period	Treatment Assignment in Maintenance Period	Escape Arm (Blinded: Week 16 and 18)	Escape Arm (Unblinded after Week 20)
Participants Entering Escape Arm at Week 16			
Lebrikizumab 250 mg Q2W	Escape Arm (Lebrikizumab 250 mg Q2W)	Week 16: 1 active and 1 placebo injection Week 18: 1 active and 1 placebo injection	One active injection Q2W during Weeks 20 to 66
Lebrikizumab 250 mg Q4W			
Placebo	Escape Arm (Lebrikizumab 250 mg Q2W)	Week 16: 2 active injections Week 18: 2 active injections	

Abbreviations: SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks.
Notes: Information provided in this table may change throughout the study. Injections are given SC.

Participants Entering Escape Arm at Week 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, or 64

Participants who do not maintain an acceptable response (have an EASI score <50% of baseline) at Week 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, or 64 in the Maintenance Period will be eligible for treatment in the Escape Arm and will receive 250 mg lebrikizumab Q2W through Week 68 in the Escape Arm in an open-label fashion. Participants not achieving an EASI-50 response at 2 consecutive visits after 8 weeks of treatment in the Escape Arm will be discontinued from the study.

6.1.1. Background Medication (Topical Treatment for AD)

Background medication allowed during the study is described below.

All participants will be instructed to use a mid-potency TCS (hydrocortisone butyrate ointment 0.1%, or equivalent-potency TCS) for AD symptoms starting ≥7 days prior to the baseline visit (Day 1). Low-potency TCS (prednisolone cream 0.5% or equivalent-potency TCS) and/or TCI may be used for sensitive areas only (that is, face, neck, intertriginous, and genital areas) ≥7 days prior to the baseline visit (Day 1). Background medication is not allowed to be tapered or stopped until the baseline visit (Day 1).

Participants may taper or stop background medication use based on treatment response after baseline visit (Day 1). If AD lesions return or a participant experiences a flare, the background medication may be resumed at the participant and/or investigator's discretion.

Where possible, a mid-potency TCS (hydrocortisone butyrate ointment 0.1%) and a low-potency TCS (prednisolone cream 0.5%) will be provided by the sponsor for use in this study. If these specific TCS treatments are unavailable, an alternate, equivalent-potency TCS may be provided by the site.

Topical corticosteroid use, when the TCS is supplied by the sponsor, should be recorded via weight of returned tubes as indicated in the SoA (Section 1.3). The investigator must keep an accurate record of the number of tubes received, dispensed/used, and returned to the sponsor or designee. The sponsor or designee will provide forms to facilitate inventory control. All accountability forms and treatment logs must be retained in the investigator's permanent study

file, and these records must be available for inspection at any time by the sponsor, its designees, or by regulatory agencies.

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

6.2. Preparation/Handling/Storage/Accountability

Investigational products will be supplied by Lilly or its representative, in accordance with current good manufacturing practices, and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

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

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Follow storage and handling instructions stated on the IP label. Detailed instructions regarding preparation and handling of IPs will be provided by the Sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Method of Treatment Assignment

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

Participants who achieve an IGA 0 or 1 and/or an EASI-75 response (≥EASI-75) at Week 16 and do not use rescue therapy during the Induction Period are defined as responders. The responders originally assigned to lebrikizumab 250 mg Q2W will be re-randomized to either lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W. The responders originally assigned to 250 mg lebrikizumab Q4W or placebo will stay on their originally assigned treatment in the double-blind Maintenance Period at Visit 10 (Week 16).

Participants who achieve neither an IGA 0 or 1 nor an EASI-75 response (<EASI-75) at Week 16 and participants who require high-potency topical or systemic rescue treatment for AD during the Induction Period will be eligible for treatment in an Escape Arm. Participants who are eligible for the Escape Arm will receive blinded loading doses at Week 16 and Week 18, based on their prior treatment assignment, followed by 250 mg lebrikizumab Q2W through Week 68 in the Escape Arm in an open-label fashion.

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

visits as summarized in the SoA (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

Emergency Unblinding

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining whether unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

Unblinding and Participant Discontinuation

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

6.4. Study Intervention Compliance

When participants are dosed at the site (first 16 weeks), they will receive study intervention directly from the investigator or designee, under medical supervision. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

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 and checking the IP during the site visits and will be documented in the source documents and eCRF.

A record of the study intervention dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, will also be recorded in the eCRF.

The date, time, and injection location of each dose administered will be recorded in the source documents and in the eCRF.

6.5. Concomitant Therapy

All medications (including over the counter drugs, vitamins, and antacids) and over the counter emollient(s) taken/used at screening and throughout the study must be recorded. 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 participating in the study.

- Medication entries should be specific to product name (if a combination drug product) and spelled correctly.
- The brand and specific product name for any over the counter emollient(s) should be noted and spelled correctly.

- Information on the dose, unit, frequency, route of administration, start date, discontinuation date, indication, and reason for use will be recorded.
- The use of any concomitant medication must relate to an AE listed on the AE eCRF or the participant's medical history, unless the medication is a supplement or used as preventive care

6.5.1. Permitted and Prohibited Treatments and Procedures

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

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

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

The use of systemic corticosteroids for the treatment of AD is prohibited and requires permanent discontinuation of IP. If used for treatment of an AE (for example, worsening of an existing condition such as asthma exacerbation), the corticosteroid will still be treated as rescue medication per Section 6.5.3.

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

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

Cannabinoid treatments for AD are prohibited. Planned or anticipated major medical procedures or surgeries should be avoided during the study. See Section 6.5.3 for details on approved rescue medications and timing of use.

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

6.5.2. Moisturizers

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

6.5.3. Rescue Treatment for Atopic Dermatitis

The goal of this Phase 3 study is to demonstrate the efficacy and safety of lebrikizumab when used in combination with TCS for AD. However, add-on rescue therapies may be needed if the participant experiences clinical worsening of symptoms that are intolerable.

All rescue treatment usage must be recorded in the eCRF.

Induction Period

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

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

Maintenance Period

Intermittent use of high-potency TCS treatments for AD is permitted during the Maintenance Period but must be communicated to the investigator and documented as concomitant medications. Participants who may require short-term systemic treatment for symptoms of AD during the Maintenance Period will be assessed on a case-by-case basis and must be discussed with the Medical Monitor prior to initiating treatment. Participants requiring long-term systemic treatment for symptoms of AD in the Maintenance Period must be discontinued from the study.

Escape Arm

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

6.6. Dose Modification

Not applicable.

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

In rare instances, it may be necessary for a participant to permanently discontinue study intervention.

These sections describe reasons for a participant's

- permanent discontinuation of study intervention (Section 7.1), or
- discontinuation (withdrawal) from the study (Section 7.2).

Discontinuation of specific sites or the study as a whole ("stopping rules") are handled as part of regulatory, ethical, and study oversight considerations in Appendix 10.1, Section 10.1.8.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If systemic treatments (for example, oral corticosteroids, phototherapy, cyclosporine) are required in the Induction Period, study intervention must be discontinued by Week 16. These participants can be eligible to continue in the Escape Arm after completion of Week 16 but must wait for the washout (≥5 half-lives of the treatment) prior to entering the Escape Arm.

Study intervention may be permanently discontinued during the study.

Participants who permanently discontinue study intervention early will undergo early termination (ET) procedures, which include

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

7.1.1. Criteria for Permanent Discontinuation of Study Intervention

Data collection and safety follow-up when study intervention is permanently discontinued

If study intervention is permanently discontinued, the participant will remain in the study to have an ET visit and posttreatment follow-up visits, as shown in the SoA (Section 1.3).

See the SoA (Section 1.3) for data to be collected at the time of discontinuation and follow-up and for any further evaluations that need to be completed. Safety follow-up is as outlined in the SoA (Section 1.3) and in Section 8.2 ("Safety Assessments) and Section 8.3 ("Adverse Events and Serious Adverse Events") of the protocol.

Criteria for permanent discontinuation of study intervention

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

Safety considerations

- The participant develops any of the following conditions during the study:
  - malignancy (except for successfully treated basal or squamous cell skin carcinoma)
  - HIV/acquired immune deficiency syndrome (AIDS)

– active TB infection or untreated LTBI (Section 8.2.6)

– HCV RNA positive (Section 5.2 and exclusion criterion [19]), or

– HBV DNA positive and clinical assessment consistent with HBV reactivation

NOTE: The HBV DNA result is to be confirmed if initial positive test result is below the level of quantification (Section 8.2.7). The participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study intervention. 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.

- The participant answered "yes" to Question 4 or Question 5 on the Suicidal Ideation portion of the C-SSRS **or** answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

  NOTE: A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

- The investigator, after consultation with the sponsor's designated Medical Monitor, determines that a systemic hypersensitivity reaction has occurred and is related to study intervention administration.
- The participant has any of the following results:

  – total WBC count <2000 cells/μL (<2.00×10^3/μL or 2.00 GI/L)

  – absolute lymphocyte count (ALC) <500 cells/μL (<0.5×10^3/μL or <0.5 GI/L), or

  – platelet count <50,000 cells/μL (<50×10^3/μL or <50 GI/L).

- Investigator-confirmed diagnosis of PCP during the study.
- 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.

Hepatic event or liver test abnormality

- Participants who are discontinued from study intervention because of a hepatic event or liver test abnormality should have additional hepatic safety data collected via the hepatic eCRF. Discontinuation of study intervention for abnormal liver test results should be considered by the investigator when a participant meets 1 of the conditions listed below after consultation with the sponsor's designated Medical Monitor (see Section 10.2).

  – ALT or AST ≥8× ULN

  – ALT or AST ≥5× ULN for more than 2 weeks

  – ALT or AST ≥3× ULN and TBL ≥2× ULN or international normalized ratio (INR) ≥1.5

– ALT or AST ≥3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash

– ALP ≥3× ULN

– ALP ≥2.5× ULN and TBL ≥2× ULN, or

– ALP ≥2.5× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash.

NOTE: Participants who are discontinued from IP because of a hepatic event or liver test abnormality should have additional hepatic safety data collected via the hepatic safety eCRF.

Other reasons

- Unblinding: If an investigator, blinded site personnel who are performing assessments, or participant is unblinded to a participant's treatment assignment, the participant must be discontinued from the study intervention and continue to posttreatment follow-up. For cases in which there are ethical reasons for the participant to continue on study intervention, the investigator must obtain specific approval from the sponsor's designated Medical Monitor.

7.1.2. Criteria for Temporary Discontinuation of Study Intervention

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to the IP. For example, IP should be temporarily interrupted if the patient experiences a cardiovascular AE considered to be related to study treatment, graded as moderate (Grade 2 according to Common Terminology Criteria for Adverse Events version 3.0), and that does not resolve promptly with supportive care. Except in cases of emergency, it is recommended that the investigator consult with Lilly (or its designee) before temporarily interrupting therapy for reasons other than those predefined in this section.

For the abnormal laboratory findings and clinical events (regardless of relatedness) listed in Table 4, specific guidance is provided for temporarily interrupting treatment and when treatment may be restarted. Retest frequency and timing of follow-up laboratory tests to monitor the abnormal finding is at the discretion of the investigator. Investigational product that was temporarily interrupted because of an AE or abnormal laboratory value not specifically covered in Table 4 may be restarted at the discretion of the investigator.

Table 4. Criteria for Temporary Interruption of Investigational Product

Hold IP if the Following Laboratory Test Results or Clinical Events Occur:	IP May Be Resumed When:
ANC <1000 cells/μL (<1.00×10^3/μL or <1.00 GI/L)	ANC ≥1200 cells/μL (≥1.20×10^3/μL or ≥1.20 GI/L)
Platelet count <75,000/μL (<75×10^3/μL or <75GI/L)	Platelet count ≥100,000/μL (≥100×10^3/μL or ≥100 GI/L)
ALT or AST >5× ULN[a]	ALT and AST return to <2× ULN, and IP is not considered to be the cause of enzyme elevation
Hemoglobin <8 g/dL (<80.0 g/L)	Hemoglobin ≥10 g/dL (≥100.0 g/L)
Infection that, in the opinion of the investigator, merits the IP being interrupted	Resolution of infection
Beta-D-glucan test is positive	Perform evaluation for PCP locally. Resume IP if evaluation is negative. (See Section 7.1.1 [Criteria for Permanent Discontinuation of Study Intervention] if PCP is confirmed.)

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; IP = investigational product; PCP = pneumocystis pneumonia; ULN = upper limit of normal.

a Repeat liver enzyme(s) and serum bilirubin tests 1 or 2 times weekly. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize. Monitor ALT and AST until levels return to <2× ULN.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- if a participant transitioned to the Escape Arm from Week 16 (use of rescue treatment in the Induction Phase or non-responder at Week 16) and does not achieve an EASI-50 response at 2 consecutive visits after Week 32
- if a participant is transitioned to the Escape Arm after Week 20 and does not achieve an EASI-50 response at 2 consecutive visits after 8 weeks of treatment

- if a participant requires long-term systemic treatment for symptoms of AD in the Maintenance Period (for example, non-responders), or
- if an investigator, site personnel performing assessments, or participant is unblinded.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

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, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with IP. Safety follow-up is as outlined in the SoA (Section 1.3), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

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 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.

Discontinuation of specific sites or of the study are handled as part of Appendix 1 (Section 10.1.8).

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy and Health Outcome Assessments

8.1.1. Efficacy Assessments

Eczema Area and Severity Index

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

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

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

Investigator's Global Assessment

The IGA is a static assessment and rates the severity of the participant's AD. The IGA is composed of a 5-point scale ranging from 0 (clear) to 4 (severe), and a score is selected using descriptors that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present. Assessors must be trained and certified by the sponsor prior to conducting this assessment. The IGA must be conducted prior to conducting the EASI. A single assessor should be assigned to each participant for as many visits as possible to avoid inter-assessor variability in scoring. The IGA is assessed by the investigator and completed using a tablet device at the study visit.

See the table below for the IGA.

Table 5. Investigator's Global Assessment

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

SCORing Atopic Dermatitis

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

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

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

The participant self-reported questionnaires will be administered via an electronic participant diary, electronic tablet, or will be paper-based. and will be administered in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

Itch Numeric Rating Scale

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

Sleep-Loss Scoring System

Sleep loss due to itch will be assessed by the participant. Participants rate their sleep based on a 5-point Likert scale (0 [not at all] to 4 [unable to sleep at all]). Assessments will be recorded daily by the participant using a handheld device.

Skin Pain Numeric Rating Scale

Skin Pain NRS is a participant-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." Overall severity of a participant's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours. The Skin Pain NRS assessment will be completed daily by the participant using a handheld device.

Patient-Oriented Eczema Measure

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

Dermatology Life Quality Index/Children's Dermatology Life Quality Index

The DLQI is a 10-item, validated questionnaire used to assess the impact of skin disease on the quality of life of an affected person. The 10 questions cover the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sports, work or study, close relationships, sex, and treatment, over the previous week. Questions are scored from 0 to 3, giving a possible total score range from 0 (meaning no impact of skin disease on quality of life) to 30 (meaning maximum impact on quality of life). A high score is indicative of a poor quality of life. Participants ≤16 years will complete the CDLQI and should continue to complete the CDLQI for the duration of the study. DLQI/CDLQI is completed by the participant in the study clinic. The DLQI/CDLQI assessment will be completed by the participant using a tablet device at the applicable study visit.

Work Productivity and Activity Impairment Questionnaire-Atopic Dermatitis

The WPAI-AD records impairment due to AD during the past 7 days. The WPAI-AD consists of 6 items grouped into 4 domains: absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism), and activity impairment. Scores are calculated as impairment percentages (Reilly et al. 1993), with higher scores indicating greater impairment and less productivity. The WPAI-AD assessment will be completed by the participant using a tablet device at the applicable study visit.

Hospital Anxiety Depression Scale

The HADS is a 14-item self-assessment scale that determines the levels of anxiety and depression that a participant is experiencing over the past week. The HADS uses a 4-point Likert scale (0 to 3) for each question and is intended for participants aged 12 to 65 years (Zigmond and Snaith 1983; White et al. 1999). Scores for each domain (anxiety and depression) can range from 0 to 21, with higher scores indicating greater anxiety or depression (Zigmond and Snaith 1983; Snaith 2003). The HADS assessment will be completed by the participant using a tablet device at the applicable study visit.

Asthma Control Questionnaire-5

Participants who report comorbid asthma prior to enrollment will complete the ACQ-5 in addition to other participant-reported outcomes in this study. The ACQ-5 has been shown to reliably measure asthma control and distinguish participants with well-controlled asthma (score ≤0.75 points) from those with uncontrolled asthma (score ≥1.5 points). The ACQ-5 consists of 5 questions that are scored on a 7-point Likert scale with a recall period of 1 week. The total ACQ-5 score is the mean score of all questions; a lower score represents better asthma control. The ACQ-5 assessment will be completed by the participant in the study clinic using a tablet device at the applicable study visit.

Columbia Suicide Severity Rating Scale

The C-SSRS captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine whether suicidal ideation and/or behavior has occurred. The C-SSRS is administered by an appropriately trained health care professional with at least 1 year of participant care/clinical experience. The tool was developed by the National Institute of Mental Health trial group as a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. For this study, the scale has been adapted (with permission from the scale authors) to include only the portion of the scale that captures the occurrence of the 11 preferred ideation and behavior categories. The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS assessment but was not captured during the nonleading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception for which the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed. This assessment will be administered by paper at the study visit.

Self-Harm and Follow-Up Supplement Forms

Suicide-related events (behavior and/or ideations) will be assessed and evaluated at every visit with the administration of the Self-Harm Supplement Form. The Self-Harm Supplement Form is a single question to enter the number of suicidal behavior events, possible suicide behaviors, or nonsuicidal self-injurious behaviors. If the number of behavioral events is greater than 0, the participant will complete of the Self-Harm Follow-Up Form. The Self-Harm Follow-Up form is a series of questions that provides a more detailed description of the behavior cases.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will be conducted at screening and will include, at a minimum, assessments of general appearance; head, ears, eyes, nose, and throat; and dermatological, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, and lymphatic body systems. Height and weight will also be measured and recorded.
- At subsequent study visits, a symptom-directed physical examination may be conducted at the discretion of the investigator.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

Findings will be recorded as medical history or AE in the eCRF.

8.2.2. Vital Signs

For each participant, vital sign measurements should be conducted according to the SoA (Section 1.3). Vital signs, including body temperature, respiratory rate (breath per minute), pulse (beats per minute), and blood pressure (mm Hg), will be obtained with the participant in the seated position, after sitting for at least 5 minutes. Any abnormal finding that is new or has worsened and is clinically significant, in the opinion of the investigator, will be recorded as an AE. Vital sign measurements will be recorded in the eCRF.

8.2.3. Electrocardiograms

A single 12-lead ECG will be obtained locally at screening. The ECG will be read by a qualified physician (the investigator or qualified designee) at the site to determine whether the participant meets the entry criteria.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for their timing and frequency. In the opinion of the investigator, if evaluating beta-D-glucan is medically necessary, the investigator may do so at any time during the study, including at screening and during the Safety Follow-Up Period.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. 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/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 laboratory manual and the SoA (Section 1.3).
    - If laboratory values from non-protocol–specified laboratory assessments performed at the institution's 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 the results must be recorded in the CRF.

Laboratory tests will be analyzed using a central laboratory and will be transferred to the clinical database.

In cases where required blood samples cannot be collected due to blood volume limitation relative to participant size/age, the investigator must consult with Lilly-designated medical personnel to determine which samples to collect. This will not be considered a protocol violation but will need to be documented in the medical record.

8.2.5. Chest Radiography

A posterior-anterior chest x-ray will be performed locally at screening, unless one has been performed within the past 90 days, the x-ray and reports are available, and a repeat chest x-ray is not clinically indicated per investigator judgment. Additional chest x-rays will be performed at Week 52, Week 68, and/or at ET, if more than 12 weeks have elapsed since the previous study x-ray was obtained. This x-ray may be performed within 12 weeks if medically indicated. The chest x-ray will be reviewed by the investigator or his or her designee.

8.2.6. Tuberculosis Testing and Monitoring

All participants will undergo a TB test at screening (tuberculin skin test [TST] or IFN-γ release test). Refer to Exclusion Criterion [17] for details regarding TB testing.

Tuberculosis tests include PPD, QuantiFERON-TB Gold, and T-SPOT. At study sites where the QuantiFERON-TB Gold test or T-SPOT is available, either test may be used instead of the PPD TB test. The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally. (Note: Participants who have a documented history of completing an appropriate TB treatment regimen for LTBI with no risk of re-exposure since completion are eligible to participate in the study if other criteria are met. These participants should not undergo the protocol-specific TB testing (orthographic variants: TST = PPD, IGRA = QuantiFERON-TB

Gold and T-SPOT), unless advised to do so based on local guidelines, but must have a chest x-ray at screening.

8.2.7. Hepatitis B Testing and Monitoring

Participants who are HBsAg negative and positive for HBcAb and/or HBsAb will automatically have an HBV DNA test performed at screening. Participants who are HBsAg negative, HBcAb negative, and HBsAb positive with a documented history of hepatitis B vaccination will not be required to undergo HBV DNA monitoring at screening. If screening HBV DNA is negative, defined as undetectable HBV DNA, the participant is not excluded, and HBV DNA monitoring is required per the schedule.

If the result of the HBV DNA testing becomes positive at any time during the study, the participant will be permanently discontinued from IP (see Section 7.1.1) and should receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of participants with hepatitis (for example, infectious disease physician or hepatologist) should be consulted. The timing of discontinuation from IP and any other immunosuppressant therapy should be based on the recommendations of the consulting specialist physician in conjunction with the investigator and medical guidelines/standard of care.

8.2.8. Hepatic Safety

8.2.8.1. Close Hepatic Monitoring*

Laboratory tests (Appendix 2), including ALT, AST, ALP, total bilirubin (TBL), direct bilirubin, gamma-glutamyltransferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, 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
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants 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 participants with Gilbert's syndrome)

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

*All ULN values should be age adjusted (AAULN)

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, 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 laboratory results stabilize. Monitoring of ALT, AST, ALP and TBL should continue until levels normalize or return to approximate baseline levels. For pediatric participants, special care should be taken to minimize the volume of blood taken during hepatic monitoring.

8.2.8.2. Comprehensive Hepatic Evaluation*

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/symptoms**, or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms**, or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for participants with Gilbert's syndrome)

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

*All ULN values should be age adjusted (AAULN)

**Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, and/or 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-INR, 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 participant's history and initial results, further testing should be considered, in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance

cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or liver biopsy.

For Pediatric 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-INR 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, or E; autoimmune hepatitis; or an abdominal imaging study (for example, ultrasound, MRI, or CT scan). Consider additional tests, based on the medical history and clinical picture, including tests for HDV, CMV, EBV, 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, MRCP, ERCP, cardiac echocardiogram, or a liver biopsy as deemed appropriate for the clinical condition and participant's age.

8.2.8.3. Additional Hepatic Data Collection in Participants Who Have Abnormal Liver Test Results During the Study

Additional hepatic safety data collection (hepatic safety CRF) should be performed in study participants who meet 1 or more of the following 5 conditions:*

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

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

*All ULN values should be age adjusted (AAULN)

8.2.9. Growth Monitoring

Height, weight, and hormone levels (estradiol for females or testosterone for males) will be measured according to the SoA (Section 1.3) to allow for identification of potential effects on growth and development. Height and weight changes in adolescent participants at an individual level will be reviewed by the data monitoring committee (DMC) external to Lilly.

8.3. Adverse Events and Serious Adverse Events

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

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Product complaints (PCs) are covered in Section 8.3.8.

Adverse 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 the definition of an AE or SAE and remain responsible for following up AEs 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).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected from the signing of the ICF until the safety follow-up visit (Visit 801) at the time points specified in the SoA (Section 1.3).

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the AE CRF.

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to the sponsor begins after the participant has signed the ICF and has received study intervention. However, if an SAE occurs after signing the ICF, but prior to receiving lebrikizumab, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow up with each participant at subsequent visits/contacts. All SAEs, and AESI (as defined in Section 8.3.6) will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an 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 comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 125 days after the last dose.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

The following TEAEs will be designated AESI:

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

Adverse events of special interest should be reported to the sponsor or designee within 48 hours of knowledge of the event. Additional data, including medical history of first-degree relatives will be collected for AESI on study-specific AESI forms, which will be provided to the site. 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.

8.3.7. Hypersensitivity Events

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. Clinical manifestations of these reactions may include but are not limited to:

- rash
- pruritus (itching)
- dyspnea
- urticaria (hives)
- angioedema (for example, swelling of the lips and/or tongue)
- hypotension, and
- anaphylactic reaction.

If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

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 local standard of care.

In the case of generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Appendix 2. Laboratory results are provided to the sponsor via the central laboratory.

8.3.8. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention.

The sponsor collects product complaints on IPs and intervention delivery systems used in clinical studies to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the IP so that the situation can be assessed.

NOTE: AEs/SAEs that are associated with a product complaint will follow the processes outlined in Section 8.3.3 and Appendix 3.

8.3.8.1. Time Period for Detecting Product Complaints

- Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the intervention is used.
- If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to an intervention provided for the study, the investigator will promptly notify the sponsor.

8.3.8.2. Prompt Reporting of Product Complaints to the Sponsor

- Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.
- The Product Complaint Form will be sent to the sponsor by a method designated by the sponsor.

8.3.8.3. Follow-Up of Product Complaints

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations, as indicated, to elucidate the nature and/or causality of the product complaint.
- New or updated information will be recorded on the originally completed form, with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

There are no data available on overdoses with lebrikizumab. No dose-related serious adverse drug reactions were observed in healthy volunteers who received single intravenous (IV) doses of up to 5 mg/kg, in patients with mild asthma who received multiple IV doses of up to 3 mg/kg or in participants with asthma or AD who received multiple SC doses of up to 500 mg.

In case of suspected overdose, hematology, chemistry, vital signs, and oxygen saturation should be monitored and supportive care provided as necessary. There is no known antidote for lebrikizumab.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.

2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until lebrikizumab can no longer be detected systemically (at least 18 days).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

- Whole venous blood samples will be collected for measurement of serum concentrations of lebrikizumab as specified in the SoA (Section 1.3).
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor.
- Instructions for the collection and handling of biological blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

8.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Serum concentrations of lebrikizumab will be assayed using a validated enzyme-linked immunosorbent assay method. Analyses of samples collected from placebo-treated participants are not planned. Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 2 years following last participant visit for the study. During this time, samples remaining after the bioanalysis may be used for exploratory metabolism studies or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

8.6. Pharmacodynamics

Samples collected (as specified in the SoA [Section 1.3) to measure thymus and activation-regulated chemokine (TARC) will be identified by the participant number (coded) and retained at a facility selected by Lilly or its designee for a maximum of 1 year following the last participant visit for the study at a facility selected by Lilly or its designee.

8.7. Genetics

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

See Appendix 5 for information regarding genetic research and Appendix 1 (Section 10.1.11) for details about sample retention and custody.

8.8. Biomarkers

Biomarkers will not be evaluated in this study.

8.9. Immunogenicity Assessments

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

Upon assay validation, ADAs may be characterized; treatment-emergent ADAs (TE-ADAs) are defined in Section 9.4.6.

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples are described in Appendix 1 (Section 10.1.11). Samples may also be used for development and control of an immunogenicity assay.

8.10. Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

The null hypothesis for the primary endpoint is that there is no difference between lebrikizumab 250 mg Q2W and placebo or lebrikizumab 250 mg Q4W and placebo in reducing the signs and symptoms of AD as measured by both the proportion of participants achieving IGA score of 0 or 1 and a reduction of ≥2-points from baseline to Week 16 and the proportion of participants achieving EASI-75 (≥75% reduction from baseline in EASI score) at Week 16.

9.2. Sample Size Determination

Approximately 280 participants will be randomized at a 3:2:2 ratio to lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, or placebo (120 participants: 80 participants: 80 participants). The inclusion of approximately 15 adolescents is based on enrollment feasibility in Japan.

The assumed IGA score of 0 or 1 at Week 16 response rates are 38% for lebrikizumab 250 mg Q2W, 33% for lebrikizumab 250 mg Q4W, and 13% for placebo. The assumed EASI-75 response rates at Week 16 are 58% for lebrikizumab 250 mg Q2W, 53% for lebrikizumab 250 mg Q4W, and 20% for placebo. The assumptions for lebrikizumab are based on the DRM06-AD01 Phase 2b study, and the proportion of participants who achieved an IGA score of 0 or 1 and proportion of participants who achieved EASI-75 response at Week 16 using the rescue medication nonresponse sensitivity analysis, adjusting for the allowed use of TCS. The placebo response rate is based on the review of historical TCS clinical studies in AD (Simpson et al. 2016). This study has >95% and >80% power to test the superiority of lebrikizumab 250 mg Q2W to placebo and lebrikizumab 250 mg Q4W to placebo in the co-primary endpoints based on a two-sided Fisher exact test with alpha of 0.05.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who signed informed consent/assent. Participant flow will be summarized.
Intent-to-Treat (ITT)	All randomized participants, even if the participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Participants will be analyzed according to the treatment group to which they were assigned. Unless otherwise specified, efficacy and health outcome analyses for the Induction Period will be conducted on this population.
Safety Population	All randomized participants who received at least 1 dose of study intervention during the Induction Period. Safety analyses for the Induction Period will be conducted on this population.

Population	Description
Per-Protocol Set (PPS)	All ITT participants who do not have a subset of important protocol deviations that impact the primary efficacy endpoint. Important protocol deviations are defined in a separate document referred to as "The KGAL Trial Issues Management Plan." Primary efficacy analysis for IGA 0/1 and EASI-75 will be repeated using the PPS.
Maintenance Period Primary Population	All participants who were randomized to lebrikizumab 250 mg Q2W at baseline visit and re-randomized to lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W (that is, participants who achieved an IGA of 0 or 1 and/or EASI-75 and were re-randomized at Week 16) or who were randomized to lebrikizumab 250 mg Q4W at baseline visit and continued lebrikizumab 250 mg Q4W (that is, participants who achieved an IGA of 0 or 1 and/or EASI-75 at Week 16) and received at least 1 dose of study intervention during the Maintenance Period. Participants will be analyzed according to the treatment to which they were assigned. Only information prior to escape will be presented. Efficacy, health outcome, and safety analyses for the Maintenance Period will be conducted primarily on the Maintenance Period Primary Population.
Maintenance Period Secondary Population	Participants who were randomized to placebo at baseline visit and participants who entered the Escape Arm at Week 16 due to not meeting IGA 0/1 and EASI-75 criteria or using rescue therapy during the Induction Period and received at least 1 dose of study intervention during the Maintenance Period. Selective efficacy analyses for the Maintenance Period will be conducted on the Maintenance Period Secondary Population.
Maintenance Period Escape Population	Maintenance Period Primary and Secondary Population who escaped to lebrikizumab 250 mg Q2W due to EASI-50 non-response at Weeks 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 or 64. Selective efficacy analyses for the Maintenance Period will be conducted on the Maintenance Period Escape Population to assess whether these participants re-gain EASI-50 response or achieve a higher level of response (for example, EASI-75) following re-treatment.

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

Abbreviations: EASI-75 = ≥75% reduction from baseline in Eczema Area and Severity Index IGA = Investigator's Global Assessment; Q2W = every 2 weeks; Q4 = every 4 weeks.

9.4. Statistical Analyses

9.4.1. General Considerations

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated, and all CIs will be given at a 2-sided 95% level.

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

For safety analyses during the Induction Period, the Baseline Period is defined as the time from the screening visit (Visit 1) to the date/time of the first injection in the Induction Period. Baseline will be the last scheduled non-missing assessment recorded during the baseline period. Unless specified otherwise, for the safety analyses during the Maintenance Period, baseline is defined as the last available value before the first injection in the Maintenance Period. In most cases, this will be the measure recorded at Week 16.

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

The primary estimand that will be used to analyze primary and secondary endpoints is a composite variable strategy where comparisons will not include data collected after intercurrent events of changes to background therapies or discontinuation due to lack of efficacy (ICH E9 [R1]).

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described

in the statistical analysis plan (SAP) and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

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

9.4.1.1. Missing Data Imputation

The primary method of handling missing efficacy data after intercurrent events will be as discussed below for both binary and continuous endpoints.

For participants who receive rescue medication (high-/ultra-high–potency TCS or systemic AD treatment) or withdraw from the study due to lack of efficacy, the participant's baseline value will be carried forward to the subsequent time points through Week 16. Markov Chain Monte Carlo multiple imputation will be used to handle the remaining missing data.

Sensitivity analyses will be addressed in the SAP.

9.4.1.2. Adjustment for Multiple Comparisons

The prespecified graphical multiple testing approach (Bretz et al. 2011) will be implemented to control the overall type I error rate at a 2-sided alpha of 0.05 for superiority tests for the hypotheses for the co-primary and major secondary endpoints.

The major secondary endpoints are as follows:

- percentage change in EASI score from baseline to Week 16
- proportion of participants achieving EASI-90 (≥90% reduction from baseline in EASI score) at Week 16, and
- proportion of participants with an Itch NRS of ≥4-points at baseline who achieve a ≥4-point reduction from baseline to Weeks 1, 2, 4 and 16.

The graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate across all endpoints (Alosh et al. 2014). The Week 16 endpoints of IGA 0/1 and EASI-75 represent a primary endpoint family. The graphical testing scheme will sequentially test the co-primary endpoints for lebrikizumab 250 mg Q2W to placebo first before proceeding to test the co-primary endpoints for lebrikizumab 250 mg Q4W to placebo and the major secondary endpoints during the Induction Period. Details of the specific graphical testing scheme (including testing order, interrelationships, type I error allocation, and the associated propagation) will be prespecified in the SAP prior to first unblinded efficacy analysis.

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

The number of randomized participants will be summarized. Frequency counts and percentages of all participants who are randomized, complete the study, discontinue the study intervention, or discontinue the study early will be presented. Reasons for discontinuing study intervention or the study will be summarized.

9.4.2.2. Participant Characteristics

Demographic data will be collected to demonstrate that the study population represents the target participant population. A summary of baseline participant characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported by treatment group using descriptive statistics. Other participant characteristics will be summarized by treatment group or listed, as deemed appropriate.

9.4.2.3. Concomitant Therapy

Current concomitant therapy (reported after randomization) will be summarized by treatment group and will be presented by Anatomical Therapeutic Chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) Drug Dictionary. Previous concomitant therapy (reported before randomization and after ICF) will be listed.

9.4.2.4. Treatment Compliance

Participants who are noncompliant will be listed by treatment. A participant will be considered compliant if he or she received ≥75% of the expected number of injections while enrolled in the study. The details of noncompliance will be defined in the SAP.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

The co-primary endpoints are the percentage of participants achieving IGA score of 0 or 1 and a reduction of ≥2-points from baseline to Week 16 and the percentage of participants achieving EASI-75 (≥75% reduction from Baseline in EASI score) at Week 16 and will be analyzed using the Cochran-Mantel-Haenszel test adjusted by randomization strata (disease severity: IGA 3 vs 4 and age: adolescent participants ≥12 to <18 years vs ≥18 years).

9.4.3.2. Secondary Analyses

For secondary binary efficacy and health outcome endpoints during the Induction Period, the CMH test will be used to compare the treatment groups while adjusting for the stratification factors (disease severity: IGA 3 versus 4, and age: adolescent participants ≥12 to <18 years versus ≥18 years).

Treatment comparisons of secondary continuous efficacy and health outcome endpoints during the Induction Period will be made using an analysis of covariance with the following in the model: treatment group, baseline value, and stratification factors.

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

More details will be specified in the SAP.

9.4.4. Safety Analyses

Safety analyses will include AEs, SAEs, AESI, vital signs, and laboratory analytes. The safety data will be summarized descriptively by treatment group. Categorical safety measures will be summarized with the number and percentage of participants. Continuous safety measures will be

summarized as mean change by visit. Exposure to study intervention will be calculated for each participant and summarized by treatment group.

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

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

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

Adverse events of special interest will be identified by a Standardised MedDRA Query (SMQ) or a Lilly-defined MedDRA PT listing.

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (Columbia Lighthouse Project Scoring and Data Analysis Guide [WWW]).

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

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

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

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

It is intended that data from this study will be combined with data from other studies to better characterize the PK of lebrikizumab, as well as to explore the relationship between exposure and efficacy and/or safety outcomes. Further details on PK and PK/pharmacodynamic (PD) analyses will be provided in the PK/PD analysis plan. The results of these analyses will be described in a separate PK/PD report.

9.4.6. Evaluation of Immunogenicity

For immunogenicity, upon assay validation, the frequency and percentage of participants with preexisting ADAs and with TE-ADAs to lebrikizumab will be tabulated. Participants who are

TE-ADA positive are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). The frequency of neutralizing antibodies may also be tabulated in TE-ADA positive participants. The relationship between the presence of antibodies and the PK parameters and PD response, including safety and efficacy to lebrikizumab, may be assessed.

9.4.7. Subgroup, Supplemental, and Other Exploratory Analyses

Subgroup analyses

Subgroup analyses will be conducted for the following subgroups: ≥12 to <18 years versus ≥18 years of age, sex, and baseline IGA score (3 or 4). Subgroup analyses will be conducted for the co-primary endpoints of IGA 0/1 and EASI-75 at Week 16 on the intent-to-treat (ITT) population.

Some additional subgroup analyses may be added to the SAP.

Supplemental analyses

Supplemental analyses will be performed on the co-primary endpoints using another composite variable strategy where comparisons will not include data collected after intercurrent events of changes to background therapies or discontinuation due to lack of efficacy ([ICH E9 [R1] Step 4 2019). For participants who receive rescue medication, their values while on rescue medication will be set to missing.

Analysis details will be described in the SAP.

Exploratory analyses

Exploratory analyses will be specified in the SAP.

9.5. Interim Analyses

The first database lock and unblinding will occur, and the interim analysis, including the Maintenance Period, will be performed at the time the last participant completes Week 52 or the ET visit (that is, a cutoff date). This database lock will include all data collected by the cutoff date. Because the study will be ongoing for the Maintenance and Follow-Up periods at the time of this database lock, the analysis will be referred to as an interim analysis. The analyses from the Week 52 database lock will be treated as a primary analysis for an initial regulatory submission in Japan because all primary and major secondary study objectives will be assessed at this time. The study will not be terminated early on the basis of efficacy following this interim analysis. The sponsor or designee could unblind a small team, including but not limited to medical, statistics, data management, regulatory to prepare for regulatory interactions, safety updates, and disclosures if needed, while the investigator, study-site personnel, and Lilly study members who are site facing and the participants will be blinded to treatment assignment until the final database lock.

The second database lock will occur, and the interim analysis, including the Maintenance Period, will be performed at the time the last participant completes Week 68 or the ET visit (that is, a cutoff date). This database lock will include all data collected by the cutoff date. The additional results from the Week 68 database lock will be submitted to the Japan Regulatory Agency during

the review period 6 months before the approval timing of lebrikizumab for the AD indication in Japan.

The final database lock will then be conducted after all participants have completed the Follow-Up Period.

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

9.6. Data Monitoring Committee

An independent DMC composed of members who are independent of the study sponsor and study investigators will monitor patient safety by conducting formal reviews of accumulated safety data that is blinded by treatment group; if requested, the DMC may have access to the treatment allocation code or any other data requested for the purposes of a risk-benefit assessment.

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

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

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (for example, advertisements) must be submitted to an institutional review board (IRB)/independent ethics committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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 serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, 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 (CTA).

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 his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that legally acceptable representative (parent/guardian) 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 authorized representative (parent/guardian). The acceptable parent/guardian obtaining the informed consent must also sign the ICF.
- Participants and their legally acceptable representative, parent(s), or legal guardian must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.
- Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.
- A copy of the ICF(s) must be provided to the participant or the participant's parent/guardian or legally acceptable representative and is kept on file.

Participants who are re-screened 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 his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the ICF.
- The participant must be informed that his/her 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 study, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and the European Union 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, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF 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 entered 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 CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives 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 electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the 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, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant/investigator site personnel, into an instrument (for example, handheld smart phone or tablet). The eCOA data will serve as the source documentation, and the investigator does not maintain a separate, written, or electronic record of these data.

Data collected via the sponsor-provided data capture system(s) will be stored at third-party (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 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/electronic transfers will be provided to the

investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.7. 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 the CRF or entered in the eCRF that 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

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

The sponsor 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:

- 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 of participants by the investigator
- Discontinuation of further study intervention development

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 assures 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

Physicians with a specialty in dermatology will participate as investigators in this clinical study.

10.1.11. Long-Term 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*
Long-term storage samples	Sponsor or Designee	15 years
Biomarkers	Sponsor or Designee	N/A
PK	Sponsor or Designee	2 years
Genetics/PD	Sponsor or Designee	15 years
Immunogenicity	Sponsor or Designee	15 years

Abbreviations: N/A = not applicable; PD = pharmacodynamics; PK = pharmacokinetics.

*Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed below will be performed by the central or local laboratory (as applicable) (patient characteristics appropriate reference ranges will be adapted [for example, age, sex).

- 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 regulation.
- 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.
- Pregnancy testing is described in the Schedule of Activities (Section 1.3), in Section 8.3.5, and in the table below.

Investigators must document their review of each laboratory safety report.

Laboratory test results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Chloride
Mean cell hemoglobin	Phosphorus/phosphate
Mean cell hemoglobin concentration	Bicarbonate
Leukocytes (WBC)	Total protein
Platelets	Albumin
	Total bilirubin
Differential WBC [Absolute counts and/or %] of:	Direct bilirubin
Neutrophils	Alkaline phosphatase (ALP)
Lymphocytes	Lactic dehydrogenase
Monocytes	Gamma-glutamyltransferase (GGT)
Eosinophils	Alanine aminotransferase (ALT)
Basophils	Aspartate aminotransferase (AST)
	Blood urea nitrogen (BUN)
	Creatinine
Urinalysis[a]	Uric acid
Specific gravity	Calcium
pH	Glucose (random)
Protein	Creatine kinase (CK)
Glucose	
Ketones	
Blood	**Lipid Panel** [a,b]
Urine leukocyte esterase	High-density lipoprotein (HDL)
Bilirubin	Low-density lipoprotein (LDL)
Nitrite	Triglycerides
Urobilinogen	Total cholesterol
Microscopic examination of sediment [c]	
	Pregnancy Test (females only)[d]
	(serum[a] /urine[e])
Hormones[a]	
Estradiol (adolescent females only)	**Serology**
Testosterone (adolescent males only)	HIV Antibody (HIV Ab)[a]
Follicle-stimulating hormone(FSH)[f]	Hepatitis B Core Antibody (HBcAb)[a]
	Hepatitis B Surface Antigen (HBsAg)[a]
	Hepatitis B Surface Antibody (HBsAb)[a]
	Hepatitis B DNA (HBV DNA)[a]
Pharmacogenetics[a,g]	Hepatitis C Antibody (HCV Ab)[a]
	TB Serology[h] (The QuantiFERON®-TB Gold test or T-SPOT®.TB test or TST)
Other tests	
Pharmacokinetic[a,g]	
Immunogenicity (anti- ebrikizumab Ab)[a,g]	
Beta D-glucan	
Thymus and activation-regulated chemokine (TARC)[a,g]	

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated laboratory.

b Participants should not eat or drink anything except water for 12 hours prior to test. If a participant attends these visits in a nonfasting state, this will not be considered a protocol violation.

c Test only if dipstick result is abnormal.

d Local- or investigator-designated laboratory.

e Urine pregnancy test to be performed only on women of childbearing potential and women with history of tubal ligation. Local testing. Result must be negative before dosing at each dosing visit.

f For female participants who are >40 to ≤55 years of age.

g Results will not be provided to the investigative sites.

h The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally.

Selected tests may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions. The samples should be collected as close as possible to the onset of the event.

After the participant has been stabilized, obtain a sample within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event, as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.

A follow-up sample should be obtained at the next regularly scheduled visit or after 4 weeks, whichever is later.

Hypersensitivity Tests[a]

Anti-LY antibodies (immunogenicity)	Tryptase[c]
Anti-PLBL2 antibodies	
LY concentration (PK)	N-methylhistamine
Drug-Specific IgE[b]	Complements o C3, C3a, and C5a
Basophil activation test[b]	Cytokine panel o IL-6, IL-1β, IL-10 (or any cytokine panel that includes these 3 cytokines)

Abbreviations: IgE = immunoglobulin E; IL = interleukin; LY = LY3650150; NMH = N-methylhistamine; PK = pharmacokinetic; PLBL2 = phospholipase B-like 2

[a] Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

[b] Will be performed if a validated assay is available.

[c] If a tryptase sample is obtained more than 2 hours after the event (that is, within 2-12 hours) or is not obtained because more than 12 hours have lapsed since the event, obtain urine for NMH testing. Note that for tryptase serum samples obtained within 2-12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine sample for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: 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 study intervention.

Events <u>Meeting</u> 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 conditions detected or diagnosed after study intervention administration, even though they 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 overdose should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfill the definition of an AE or SAE. Also, 'lack of efficacy' or 'failure of expected pharmacological action' also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
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 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

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE/SAE 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 information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. 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 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her 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 the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the site training documents.

SAE Reporting via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor or designee. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the site training documents.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal, unless permanently sterile (see below).

If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered women of childbearing potential:

- premenarchal, and
- premenopausal female with 1 of the following:
  - documented hysterectomy
  - documented bilateral salpingectomy, or
  - documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (for example, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female is defined as, women with:
  - 12 months of amenorrhea for women >55, with no need for follicle-stimulating hormone (FSH)
  - 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (for example, oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that induced amenorrhea)

Contraception Guidance

Contraception is described in Section 5.1, Inclusion Criteria [7].

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 lebrikizumab.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed up 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, including fetal status (presence or absence of anomalies) and 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 up 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, including fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered an adverse event (AE) or serious adverse event (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 stillbirth (occurring at ≥20 weeks gestational age) is always considered an SAE and will be reported as such.
- Any poststudy pregnancy-related SAE considered reasonably related to study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

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 institutional review boards (IRBs)/independent ethics committees (IECs) allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to lebrikizumab or AD and related diseases. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the 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 per local requirements.

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

Hepatic Evaluation Testing

See Section 8.2.8 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

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

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs [red blood cells])	Alkaline phosphatase (ALP)
Leukocytes (WBCs [white blood cells])	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyltransferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin (IgA [quantitative])
Hepatitis A virus (HAV) testing:	Immunoglobulin (IgG [quantitative])
HAV total antibody	Immunoglobulin (IgM [quantitative])
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)

Hematology	**Clinical Chemistry**
Hepatitis B core IgG antibody[a]	Anti-smooth muscle antibody (ASMA)[b]
Hepatitis B virus (HBV) DNA[c]	Anti-actin antibody[d]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[c]	EBV DNA[c]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[c]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[c]	HSV (Type 1 and 2) DNA[c]
Microbiology[a]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Assayed ONLY by investigator-designated local laboratory; no central testing available.

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

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

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

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 atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:

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

Exclusionary Features—It should be noted that a diagnosis of atopic dermatitis 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: 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.

Ethical Review Boards (ERBs), regulatory bodies and any other relevant local authorities, as required, will be notified as early as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study participants, urgent changes may be implemented before such communications are made, but all changes will be reported as soon as possible following implementation. If approval of ERBs, regulatory bodies, or both is required per local regulations, confirmation of this approval will be retained in the study records.

In the event written approval is granted by the sponsor for changes in study conduct, additional written guidance, if needed, will be provided by the sponsor.

Considerations for making a change

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

Informed Consent

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

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

Changes in Study Conduct During Exceptional circumstances

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

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

1. **Remote visits**

Visit 3 through Visit 9 and safety follow-up visit can be conducted remotely. In source documents and the CRF, the study site should capture the visit location and method, with a specific explanation for any data missing because of missed in-person site visits.

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

- AE and SAE reports
- concomitant medications, and
- compliance with the patient diary, and
- product complaints.

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

2. **Local laboratory testing option**

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

- PK samples
- Immunogenicity (ADA) samples
- Pharmacogenetics sample

These central laboratory testing may be collected at the next office visit.

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

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

3. **Study intervention and ancillary supplies (including participant diaries)**

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

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,
- arranging delivery of study supplies, and

- participants or their caregiver are appropriately trained on at-home administration of the study intervention (unless they have already received that training) before administering the study intervention at home. For training purposes, injection of IP will be self-administered by the participants or their caregiver under the supervision of the investigator. Participants or their caregiver will administer study intervention at home from the next study intervention. If the study intervention is administered at home, participants or caregiver will need to record the details about the injections.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.
- If the study intervention is administered at home, participants or caregiver will need to record the details about the injections.

4. Screening Period Guidance

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

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

5. 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 from the sponsor. This minimizes missing data and preserves the intended conduct of the study. The study may need to over enroll to obtain adequate sample size.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 3 through Visit 9	Within 7 days before the intended date, or up to 7 days after the intended date
Visit 10 through Visit 23	Within 14 days before the intended date, or up to 14 days after the intended date
Visit 24/ET and Visit 801	Within 7 days before the intended date, or up to 14 days after the intended date.

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

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

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

10.9. Appendix 9: Abbreviations

Term	Definition
ACQ-5	Asthma Control Questionnaire-5
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse events of special interest
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
blinding/masking	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CFR	Code of Federal Regulations
CK	creatine kinase
CMV	cytomegalovirus
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
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.
C-SSRS	Columbia-Suicide Severity Rating Scale
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee

EASI	Eczema Area and Severity Index
EASI-50	≥50% reduction from baseline in Eczema Area and Severity Index score
EASI-75	≥75% reduction from baseline in EASI score
EASI-90	≥90% reduction from baseline in EASI score
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERCP	endoscopic retrograde cholangiopancreatography
ET	early termination
FLG	filaggrin
GGT	gamma-glutamyltransferase
HADS	Hospital Anxiety Depression Scale
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN-γ	interferon γ
Ig	immunoglobulin

IGA	Investigator's Global Assessment
IL	interleukin
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IP	investigational product: a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
ITT	intent to treat: the principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participants allocated to a treatment group should be followed up, assessed, and analyzed as members of that group, irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
JAK	Janus kinase
LOR	loricrin
LTBI	latent tuberculosis infection
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MRCP	magnetic resonance cholangiopancreatography
MTX	methotrexate
NMH	N-methylhistamine
NRS	numeric rating scale
NSD	needle safety device

participant	equivalent to Clinical Data Interchange Standards Consortium (CDISC) term “subject”: an individual who participates in a clinical study, either as recipient of an investigational medicinal product or as a control
PCR	polymerase chain reaction
PCP	pneumocystis pneumonia
PD	pharmacodynamics
PFS	pre-filled syringe
PK	pharmacokinetics
POEM	Patient-Oriented Eczema Measure
PPD	purified protein derivative
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
QTLs	quality tolerance limits
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCORAD	SCORing Atopic Dermatitis
screen	The act of determining whether an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	schedule of activities
SOC	system organ class
SMQ	Standardised MedDRA Query
TARC	thymus and activation-regulated chemokine
TB	tuberculosis
TBL	total bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid(s)
TE-ADA	treatment-emergent anti-drug antibody

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

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