Protocol: J2T-MC-KGAK

A Phase 3, 16-week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Impact of Lebrikizumab on Vaccine Responses in Adult Patients with Moderate-to-Severe Atopic Dermatitis

NCT04626297

Approval Date: 05-Aug-2020

Title Page

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Protocol Number: J2T-MC-KGAK/DRM06-AD18

Amendment Number: This is the initial protocol.

Compound: lebrikizumab (LY3650150/DRM06)

Study Phase: 3

Short Title: A Phase 3, 16-week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Impact of Lebrikizumab on Vaccine Responses in Adult Patients with Moderate-to-Severe Atopic Dermatitis

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 119866

EudraCT: 2020-002572-12

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 05-Aug-2020 GMT

Medical Monitor Name and Contact Information will be provided separately.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3, 16-week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Impact of Lebrikizumab on Vaccine Responses in Adult Patients with Moderate-to-Severe Atopic Dermatitis

Short Title: same as the protocol title

Rationale:

Study J2T-MC-KGAK (KGAK) is a Phase 3, randomized, double-blind, placebo-controlled study to assess the impact of lebrikizumab on vaccine immune responses in adult patients with moderate-to-severe atopic dermatitis (AD). This study will evaluate the effect of lebrikizumab treatment on 2 vaccines commonly used in adults with moderate to severe AD:

- Tdap: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi), and
- MCV: Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline).

In addition, this study will further assess the efficacy and safety of lebrikizumab in patients with moderate-to-severe AD.

Objectives and Endpoints

Objectives	Endpoints
Co-Primary	
• To compare the seroresponses to the Tdap and MCV between lebrikizumab-treated and placebo-treated participants with moderate-to-severe AD	*The percentage of participants who:* 1. Develop a **booster response to tetanus toxoid** 4 weeks after the administration of the Tdap vaccine (Week 16) Booster response is defined as: o ≥4-fold increase in anti-tetanus toxoid IgG antibody concentration if the pre-vaccination level was >0.10 IU/mL and ≤2.7 IU/mL; OR o ≥2-fold increase in anti-tetanus toxoid IgG antibody concentration if the pre-vaccination level was >2.7 IU/mL; OR o ≥4-fold increase in anti-tetanus toxoid IgG antibody concentration and a post-vaccination level ≥0.10 IU/mL if the pre-vaccination level was ≤0.10 IU/mL
	2. Have **positive antibody response to MCV (group C serum bactericidal antibodies)** 4 weeks after the administration of the vaccine (Week 16) Positive antibody response to MCV is defined as: o post-vaccination hSBA titer ≥4 times the LLOQ, if the pre-vaccination hSBA titer is less than the LLOQ; OR o post-vaccination hSBA titer ≥4 times the pre-vaccination titer, if the pre-vaccination hSBA titer is greater than or equal to the LLOQ

Objectives	Endpoints
Secondary	
• To compare the efficacy of lebrikizumab with that of placebo in treatment of participants with moderate-to-severe AD, as measured by:	*Percentage of participants at Week 16 achieving:* • an IGA score of 0 or 1 and a reduction of ≥2 points from baseline • EASI-75 • EASI-90 • ≥4-point improvement from baseline in Pruritus NRS score *Percentage change from baseline to Week 16 in:* • EASI • Pruritus NRS score *Change from baseline in:* • Percent BSA • Sleep-Loss score
• To compare the patient-reported outcomes between lebrikizumab-treated and placebo-treated participants with moderate-to-severe AD, as measured by:	*Change from baseline by visit in:* • PROMIS® Anxiety measure • PROMIS® Depression measure

Abbreviations: AD = atopic dermatitis; BSA = Body Surface Area; EASI = Eczema Area and Severity Index; EASI-75 = ≥75% reduction from baseline in EASI score; EASI-90 = ≥90% reduction from baseline in EASI score; hSBA = human complement serum bactericidal assay; IGA = Investigator Global Assessment; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline); NRS = Numeric Rating Scale; PROMIS = Patient-Reported Outcomes Measurement Information System; Tdap = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi).

Overall Design

KGAK will last approximately 16 weeks and will have 3 study periods:

- Screening
- Treatment
- Safety follow-up

Depending on the preference of the study site or the study participant, some of the study visits may be performed either remotely or on site, as indicated in the Schedule of Activities (SoA). In addition, provisions for exceptional circumstances (such as pandemics or natural disasters) are provided in Appendix 10.9.

Remote visits may be conducted as follows:

- virtually (i.e., via telephone or telemedicine tools), *and*
- at a mobile location (e.g., a participant's home), if permitted by local laws and regulations.

Participants will receive lebrikizumab or matching placebo via subcutaneous injection. The lebrikizumab doses will be as follows:

- At randomization/baseline and Week 2: loading dose of 500 mg
- At Weeks 4 through 14: 250 mg once every 2 weeks (Q2W)

During remote visits, study participants will have an option of administering the study drug either themselves, or having a caregiver or a mobile home health care provider administer it. Prior to at-home administration, participants and/or caregivers will be adequately trained on the study drug administration at the clinical site.

Both vaccines will be administered at Week 12 at the clinical site. Vaccine injections will be given per local vaccination guidelines and practices and:

- should not be injected in body locations with active AD or other skin lesions
- should be injected in a location different from that for the study drug administration

Disclosure Statement: This is a parallel, 2-arm treatment study that is double-blinded.

Number of Participants:

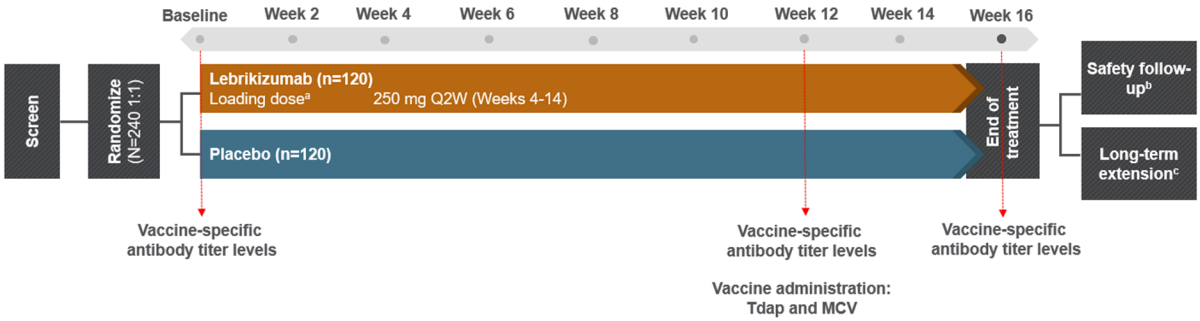
Approximately 240 participants will be randomly assigned to study drug.

Intervention Groups and Duration:

Participants will be randomized in 1:1 ratio to receive either lebrikizumab or placebo. All of the participants will receive both of the vaccines (Tdap and MCV).

Data Monitoring Committee: Yes; a Data Safety Monitoring Board (DSMB) will be used in this study. (A DSMB is a type of Data Monitoring Committee.)

1.2. Schema



Abbreviations: MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline); Q2W = once every 2 weeks; Tdap = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi).

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

[b] The safety follow-up will occur at Week 26 (or approximately 12 weeks after last study drug injection). See Section 4.4 for completion of study definitions.

[c] If eligible, participants can continue to the long-term extension study (DRM06-AD07/J2T-DM-KGAA). See Section 4.4 for completion of study definitions.

1.3. Schedule of Activities (SoA)

The SoA described below should be followed for all participants enrolled in Study KGAK. However, for those participants whose participation in this study is affected by exceptional circumstances (such as pandemics or natural disasters), please refer to Appendix 10.9 for additional guidance.

Notes:
- Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance.
- For early terminations (ETs) that occur before the last visit in treatment period, see the activities listed for ET in this table.
- Visit 801 is only for study participants who are terminating early or not rolling into the long-term extension study (DRM06-AD07/J2T-DM-KGAA).

Visit number	1	2	3*	4	5*	6*	7*	8	9*	10	ET	V801*	Comments
Weeks from randomization	Screening (-4)	Baseline /Day 1	2	4	6	8	10	12	14	16	ET	Safety follow-up Week 26 (or approximately 12 weeks after last study drug injection)	* = visit may be conducted remotely or on site, per preference of the study site or participant. See Section 4.1 for details about remote visits.
Days from randomization	≤30	—	15	29	43	57	71	85	99	113	N/A		
Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
Informed consent	X												
Inclusion and exclusion criteria, review and confirm	X	X											
Demographics	X												
Preexisting conditions and medical history	X												
Prespecified medical history (indication and history of interest)	X												
Review of immunization record	X												Applies only to Tdap, MCV, BCG, or any live (attenuated) vaccine.

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Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
Prior treatments for AD	X												Includes medications and procedures.
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	Includes medications of special interest such as TCS and TCI and procedures.
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	Collection for AEs associated with vaccinations will begin at Week 12. For AESIs, additional data are collected (Section 8.3.6).
Physical Evaluation													
Height	X									X			

Notes:

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Days from randomization	≤30	—	15	29	43	57	71	85	99	113	N/A		
Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
Weight	X									X	X		
Vital signs	X	X		X				X		X	X	X	See Section 8.2.2 for details.
Physical examination	X									X	X		See Section 8.2.1 for details. Additional symptom-directed physical examinations may be conducted at the discretion of the investigator.

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Days from randomization	≤30	—	15	29	43	57	71	85	99	113	N/A		
Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
Patient Education													
Diary education	X												
Train participant and/or caregiver on study drug administration		X											Applicable only when participant chooses to self-administer the study drug or have a caregiver administer it.
Patient Diary (Electronic)													
Patient diary dispensed	X												The electronic patient diary will be used to record the following: • Patient-reported outcomes (PROs) • Information about at-home study drug administration
PRO diary compliance check		X	X	X	X	X	X	X	X	X	X		This diary compliance check includes checking for completion of the PRO assessments. For details about

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Days from randomization	≤30	—	15	29	43	57	71	85	99	113	N/A		
Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
													those assessments, see Section 8.1.3 and the PRO section of the SoA.
Drug Administration diary compliance check			X		X	X	X		X				This diary compliance check includes checking for study drug compliance. Participant will need to complete this diary any time the study drug is administered at home (regardless of who administered the drug at home—the participant, caregiver, or mobile home health care provider).
Diary return (patient to site)										X	X		Participant would need to visit the site to return the electronic diary. Participants need to return the electronic diary device only if they are not rolling into the long-term extension study (DRM06-AD07/J2T-DM-

Notes:

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Days from randomization	≤30	—	15	29	43	57	71	85	99	113	N/A		
Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
													KGAA).
Patient-Reported Outcomes (Electronic Diary at Home)													
Pruritus NRS	Daily (should be completed at approximately the same time every day)												Initial electronic diary entries for Pruritus NRS should be completed a minimum of 4 of 7 days before randomization. PROs should be completed prior to any other study assessments.
Sleep-Loss	Daily (should be completed at approximately the same time every day)												Initial electronic diary entries for Sleep-Loss should be completed a minimum of 4 of 7 days before randomization. PROs should be completed prior to any other study assessments.
Skin Pain NRS	Daily (should be completed at approximately the same time every day)												Initial electronic diary entries for Skin Pain NRS should be completed a minimum of 4 of 7 days before randomization.

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Days from randomization	≤30	—	15	29	43	57	71	85	99	113	N/A		
Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
													PROs should be completed prior to any other study assessments.
Patient-Oriented Eczema Measure (POEM)	Weekly												PROs should be completed prior to any other study assessments.
Patient-Reported Outcomes (Electronic Tablet on Site)													
PROMIS® (Patient-Reported Outcomes Measurement Information System) Anxiety Measure		X								X	X		PROs should be completed prior to any other study assessments.
PROMIS® Depression Measure		X								X	X		PROs should be completed prior to any other study assessments.
Clinician-Administered Assessments (Electronic Tablet on Site)													
Investigator Global Assessment (IGA)	X	X		X				X		X	X		The IGA must be conducted prior to conducting the EASI and BSA assessments.

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Days from randomization	≤30	—	15	29	43	57	71	85	99	113	N/A		
Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
Eczema Area and Severity Index (EASI)	X	X		X				X		X	X		
Body Surface Area (BSA)	X	X		X				X		X	X		
Laboratory Tests and Sample Collections													
Hematology	X			X				X		X	X		
Clinical Chemistry	X			X				X		X	X		
Urinalysis	X			X				X		X	X		
Serum pregnancy	X												Only for women of childbearing potential (Section 8.2.3.1 and Appendix 10.4).
Urine pregnancy (local)		X		X		X		X		X	X		Only for women of childbearing potential (Section 8.2.3.1 and Appendix 10.4).
HIV screening tests	X												
Hepatitis C Virus (HCV) screening tests	X												HCV RNA will be measured to confirm positive hepatitis C virus antibody

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Days from randomization	≤30	—	15	29	43	57	71	85	99	113	N/A		
Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
													(Section 8.2.6).
Hepatitis B Virus (HBV) screening tests	X												Includes testing for HBsAg, anti-HBc, and anti-HBs.
HBV DNA	X							X					Only for participants who are anti-HBc reactive and anti-HBs nonreactive at screening (Section 8.2.5).
Total IgG	X												
Total IgA	X												
Anti-tetanus toxoid IgG antibody		X						X		X			At Week 12, collect this sample before the vaccine administration.
Meningococcal Group C serum bactericidal antibodies (human complement serum bactericidal assay		X						X		X			At Week 12, collect this sample before the vaccine administration.

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Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
[hSBA])													
Pharmacokinetic (PK) samples		X		X				X		X	X	X	• Collect samples before dosing. See Section 8.5 for more information about the PK testing. • In case of systemic hypersensitivity reactions, additional PK samples will need to be collected (Section 8.2.4, Appendix 10.5).
Immunogenicity (ADA) samples		X		X				X		X	X	X	• Collect samples before dosing. See Section 8.9 for details. • In case of systemic hypersensitivity reactions, additional immunogenicity samples will need to be collected

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Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
													(Section 8.2.4, Appendix 10.5).
Stored Samples													
Pharmacogenetics sample		X											
Randomization and Dosing													
Randomization		X											
Administer study drug		X	X	X	X	X	X	X	X				During remote visits, participant can choose to self-administer the assigned study drug (lebrikizumab or placebo) or have a caregiver or the mobile home health care provider administer it. See Section 6.1.4 for more information about at-home administration. Participants and/or caregivers need to be adequately trained on injection technique prior to administering injections.

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Visit interval tolerance (days)		—	±3	±3	±3	±3	±3	±3	±3	±3	N/A	±3	
													Mobile home health care provider would observe the participant's or caregiver's first attempt at administering the study drug.
Administer vaccines: Tdap and MCV								X					See Section 6.1.2 for location of vaccine injections.
Participant/caregiver returns study drug and injection supplies				X		X	X	X		X	X		If study drug was administered at home by participant or caregiver, the injection supplies should be saved and returned at the next on-site visit.

Abbreviations: AD = atopic dermatitis; ADA = antidrug antibodies; AESI = adverse event of special interest; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; BCG = Bacillus Calmette-Guerin; HBsAg = hepatitis B surface antigen; IgA = immunoglobulin A; IgG = immunoglobulin G; MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline); N/A = not applicable; NRS = Numeric Rating Scale; SoA = Schedule of Activities; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; Tdap = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi); V = visit.

2. Introduction

2.1. Study Rationale

To date, no vaccine-response studies have been conducted for lebrikizumab. Because lebrikizumab suppresses interleukin (IL)-13 signaling, a potential immunomodulator effect, there is a need to assess immune response to vaccinations in patients receiving this drug.

Study J2T-MC-KGAK (KGAK) is a Phase 3, randomized, double-blind, placebo-controlled study to assess the impact of lebrikizumab on vaccine immune responses in adult patients with moderate-to-severe atopic dermatitis (AD). This study will evaluate the effect of lebrikizumab treatment on 2 vaccines commonly used in adults with moderate to severe AD:

- Tdap: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi), and
- MCV: Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline).

In addition, this study will further assess the efficacy and safety of lebrikizumab in patients with moderate-to-severe AD.

2.2. Background

Atopic dermatitis is a complex disease that is considered an autoimmune disorder (Mitterman et al. 2004) and is determined by genetic, environmental, and immunologic factors (Werfel et al. 2016; Simon et al. 2019). Atopic dermatitis is one of the most common chronic medical diseases; 2% to 20% of adults are affected, and the prevalence appears to have increased over the past 3 to 4 decades (Williams et al. 2008), with some geographic variability.

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 is considered a major contributor to the development of early childhood AD (Bieber 2008; Tanei 2009; Bieber 2012; Flohr and Irvine 2013).

Reduced epithelial barrier function, which represents the first line of protection against the environment, is thought to lead to sensitization to environmental allergens, associated with elevated immunoglobulin E (IgE). Elevated IgE is present in up to 80% of all patients with AD, particularly in children (Werfel et al. 2016), and is consistent with the presence in the skin of the following:

- Type 2 cytokines:
    - IL-4
    - IL-5
    - IL-9

  - IL-13
  - IL-25
  - IL-31
  - IL-33, and
  - thymic stromal lymphopoietin (TSLP), 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 ubiquitous presence of IL-13 in the skin of patients with AD supports the evaluation of anti-IL-13 therapies in patients with AD.

2.2.1. Clinical Manifestations of Atopic Dermatitis

Clinically, AD is characterized by xerosis, erythematous crusted eruption (dermatosis), lichenification, and intense pruritus (Bieber 2008). These symptoms, along with the distribution, chronicity, and history of skin lesions, form the basis for diagnosing 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 puberty onwards) is less predictable than the infantile stage. 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 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 1 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

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).

2.2.2. Treatment for Atopic Dermatitis

The therapeutic approach to AD consists primarily of trigger avoidance, skin hydration with bathing, the use of moisturizers, and anti-inflammatory therapies consisting predominantly of topical corticosteroids (TCS). In many patients, treatment with TCS provides some measure of symptomatic relief but does not always adequately control the disease. In those patients who have 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, and mycophenolate mofetil. These medicines are not available for patients across the globe. In the US, only cyclosprone is approved for treatment of moderate-to-severe AD. Recently, an anti-IL-4R monoclonal antibody that inhibits signaling for both IL-4 and IL-13, dupilumab, was approved for the treatment of adult and adolescent patients with moderate-to-severe AD.

In spite of these treatments, AD remains a major societal burden and a significant unmet medical need.

2.2.2.1. Lebrikizumab

Lebrikizumab is a humanized monoclonal immunoglobulin (Ig) G4 antibody (huIgG4) with a mutation in the hinge region that increases stability. Lebrikizumab binds specifically to soluble human IL-13 with high affinity, and potently inhibits IL-13 signaling through the IL-4Rα/IL-13Rα1 complex. Because lebrikizumab binds to IL-13 in a non-receptor binding domain (i.e., a portion of the molecule not involved in binding to its receptor), antibody-bound IL-13 can still bind its receptor (IL-13Rα1), but the engaged receptor complex cannot be activated.

2.3. Benefit/Risk Assessment

Atopic dermatitis remains an important public health challenge. Therefore, there is a continuing need to develop additional treatment options that offer alternatives to and potential improvements upon existing therapies.

Clinical benefit

The use of lebrikizumab for the treatment of AD is supported by numerous preclinical studies demonstrating that AD is characterized by the increased expression of IL-13 in skin. Moreover, Phase 2 efficacy studies in lebrikizumab (GS29250 [TREBLE], GS29735 [ARBAN], and DRM06-AD01) demonstrated significant clinical benefit in patients with AD.

The lebrikizumab doses and regimen planned for Study KGAK were selected based on analyses of pharmacokinetic (PK), safety, and efficacy data from Phase 1 and Phase 2 studies and nonclinical safety data. In addition, the doses and regimen used here are identical to ongoing Phase 3 registration trials.

Safety profile and mitigation plan

Blinded trial-level safety reviews will be conducted at periodic intervals throughout the study. An external data safety monitoring board (DSMB) will conduct safety analyses to review unblinded safety data. These monitoring and risk-mitigation actions, along with regular review of adverse events (AEs) and laboratory data, will assist in the evaluation and management of potential risks associated with lebrikizumab administration.

Both of the vaccines (Tdap and MCV) used in this study will be administered according to their approved labelling.

Additional information

More detailed information about the known and expected benefits and risks and reasonably expected AEs of lebrikizumab may be found in the Investigator's Brochure (IB).

3. Objectives and Endpoints

Objectives	Endpoints
Co-Primary	
• To compare the seroresponses to the Tdap and MCV between lebrikizumab-treated and placebo-treated participants with moderate-to-severe AD	*The percentage of participants who:* 1. Develop a **booster response to tetanus toxoid** 4 weeks after the administration of the Tdap vaccine (Week 16) Booster response is defined as: o ≥4-fold increase in anti-tetanus toxoid IgG antibody concentration if the pre-vaccination level was >0.10 IU/mL and ≤2.7 IU/mL; OR o ≥2-fold increase in anti-tetanus toxoid IgG antibody concentration if the pre-vaccination level was >2.7 IU/mL; OR o ≥4-fold increase in anti-tetanus toxoid IgG antibody concentration and a post-vaccination level ≥0.10 IU/mL if the pre-vaccination level was ≤0.10 IU/mL
	2. Have **positive antibody response to MCV (group C serum bactericidal antibodies)** 4 weeks after the administration of the vaccine (Week 16) Positive antibody response to MCV is defined as: o post-vaccination hSBA titer ≥4 times the LLOQ, if the pre-vaccination hSBA titer is less than the LLOQ; OR o post-vaccination hSBA titer ≥4 times the pre-vaccination titer, if the pre-vaccination hSBA titer is greater than or equal to the LLOQ

Objectives	Endpoints
Secondary	
• To compare the efficacy of lebrikizumab with that of placebo in treatment of participants with moderate-to-severe AD, as measured by:	*Percentage of participants at Week 16 achieving:* • an IGA score of 0 or 1 and a reduction of ≥2 points from baseline • EASI-75 • EASI-90 • ≥4-point improvement from baseline in Pruritus NRS score *Percentage change from baseline to Week 16 in:* • EASI • Pruritus NRS score *Change from baseline in:* • Percent BSA • Sleep-Loss score
• To compare the patient-reported outcomes between lebrikizumab-treated and placebo-treated participants with moderate-to-severe AD, as measured by:	*Change from baseline by visit in:* • PROMIS® Anxiety measure • PROMIS® Depression measure
Exploratory	
Exploratory objectives and endpoints may include the following assessments. The endpoints will be detailed in the SAP. • Skin Pain NRS • POEM	

Abbreviations: AD = atopic dermatitis; BSA = Body Surface Area; EASI = Eczema Area and Severity Index; EASI-75 = ≥75% reduction from baseline in EASI score; EASI-90 = ≥90% reduction from baseline in EASI score; hSBA = human complement serum bactericidal assay; IGA = Investigator Global Assessment; IgG = immunoglobulin G; LLOQ = lower limit of quantitation; MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline); NRS = Numeric Rating Scale; POEM = Patient-Oriented Eczema Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; SAP = Statistical Analysis Plan; Tdap = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi).

Note: For distinction between the clinician-administered assessments and patient-reported outcomes, see the Schedule of Activities (Section 1.3), as well as Sections 8.1.2 and 8.1.3.

4. Study Design

4.1. Overall Design

Study KGAK is a Phase 3, 16-week, randomized, double-blind, placebo-controlled, parallel-group trial. The study will evaluate whether treatment with lebrikizumab compared with placebo affects seroresponses to non-live vaccines in patients with moderate-to-severe AD. In addition, the study will further assess the efficacy and safety of lebrikizumab compared with placebo in treating this patient population.

Study periods

KGAK has 3 study periods:

- Screening (Visit 1: ≥1 day)
- Treatment (Visits 2-10: 16 weeks)
- Safety follow-up (Visit 801: at Week 26 or approximately 12 weeks after last treatment)

See the Schedule of Activities (SoA) (Section 1.3) for additional details about the study periods and visit-specific assessments. A schematic of the study design is presented in Section 1.2.

Visit types

Depending on the preference of the study site or the study participant, some of the study visits may be performed either remotely or on site.

Remote visits may be conducted as follows:

- virtually (i.e., via telephone or telemedicine tools), *and*
- at a mobile location (e.g., a participant's home), if permitted by local laws and regulations.

See the table below for details about the visit types.

Study visit	Study week	Visit type
1	-4	On site only
2	Baseline	On site only
3	2	Remote or on site
4	4	On site only
5	6	Remote or on site
6	8	Remote or on site
7	10	Remote or on site
8	12	On site only
9	14	Remote or on site
10/early termination (ET)	16	On site only
801	Week 26 (or approximately 12 weeks after last treatment)	Remote or on site

Treatment groups

Participants found to be eligible according to all of the study entry criteria will be randomly assigned in a 1:1 ratio to receive either lebrikizumab or placebo (see Section 6.1 for dose and administration details).

Participants will be stratified at randomization according to their disease severity (i.e., IGA score of 3 vs 4). If the study is conducted in multiple countries, participants will also be stratified according to the geographical region.

Vaccine products

All participants will receive 2 vaccine injections at Week 12. For details, see Section 6.1.2.

Eligibility for long-term extension study

Participants who complete this 16-week study will be eligible to continue to a separate long-term extension study (DRM06-AD07/J2T-DM-KGAA). For "completion of study" definition, see Section 4.4. For rescue medications allowed at entry into the long-term extension study, see Section 6.5.3.

4.2. Scientific Rationale for Study Design

Vaccine types and timing of vaccine administration

When evaluating a new immunomodulatory agent for potential use in AD patients, it is important to understand any potential effects the new treatment may have on the immune response to vaccines. This study will use 2 different, commonly used vaccines (Tdap and MCV) to test the effect of the study drug on both the T-independent B-cell responses and T-dependent B-cell responses.

Both placebo- and lebrikizumab-treated participants will be immunized with the 2 vaccines after 12 weeks of treatment, to allow study drug to reach steady-state levels. Serum antibody levels will be determined at 4 weeks following vaccination to allow for a maximal antibody response.

Demographics collection

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

Safety monitoring

Safety monitoring, complaint handling, and all AEs and serious adverse events (SAEs) will be collected as specified in this protocol. This study will collect the safety information to further characterize the safety profile of lebrikizumab.

4.2.1. Participant Input into Design

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

No participant input was provided for this study design.

4.3. Justification for Dose

The lebrikizumab dosing regimen of 500 mg loading dose at baseline and Week 2, followed by 250 mg Q2W, was selected based on an evaluation of safety, efficacy, and PK data from the DRM06-AD01 and DRM06-AD03 trials. This is the same dosing and treatment regimen used in the ongoing Phase 3 studies of lebrikizumab.

4.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed all required visits of the study, namely:

- Completed all required visits through Week 16 and through the safety follow-up period
- Completed all required visits through Week 16 and rolls into the LTE study (DRM06-AD07/J2T-DM-KGAA)

The "end of the study" is defined as the date of the last visit or the last scheduled procedure shown in the SoA for the last participant in the study globally.

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:

Participant Characteristics

[1] Are male or female participants from 18 to 55 years of age.

Atopic Dermatitis Characteristics

[2] Have chronic AD (according to American Academy of Dermatology Consensus Criteria; Eichenfield et al. 2014; Appendix 10.8) that has been present for ≥1 year before the screening visit (Visit 1).

[3] Have Eczema Area and Severity Index (EASI) score ≥16 at the baseline visit (randomization; Visit 2).

[4] Have Investigator Global Assessment (IGA) score ≥3 (scale of 0 to 4) at the baseline visit (randomization; Visit 2).

[5] Have ≥10% Body Surface Area (BSA) of AD involvement at the baseline visit (randomization; Visit 2).

Prior/Concomitant Therapy and Vaccinations

[6] Have a history of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable.

[7] Have not received any tetanus-containing vaccine within approximately 5 years of randomization (Visit 2).

[8] Have never received a meningococcal conjugate vaccine or have received not more than 1 prior MCV dose at least 4 years prior to randomization (Visit 2), of a vaccine containing 1 or more meningococcal serogroups (serogroups A, C, W, Y).

Reproductive Characteristics

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

a. Female participants of childbearing potential: must agree to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method during the treatment period and for at least 18 weeks after the last dose of study drug.

   Women of non-childbearing potential (non-WOCBP) may participate without any contraception requirements. For definitions of women of childbearing potential (WOCBP) and non-WOCBP, see Appendix 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 (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion and bilateral tubal ligation
- vasectomized partner, or
- sexual abstinence.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

b. Male participants are not required to use any contraception except in compliance with specific local government study requirements.

Informed Consent

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

Other

[11] Participants must be willing and able to comply with all study visits and study-related procedures and questionnaires.

5.2. Exclusion Criteria

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

Medical Conditions

[12] Have a history of anaphylaxis, as defined by the Sampson criteria (Sampson et al. 2006).

[13] Have an uncontrolled chronic disease that might require multiple intermittent uses of oral corticosteroids, e.g., co-morbid severe uncontrolled asthma (as defined by the investigator).

[14] Have an active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotoxoals, or antifungals within 2 weeks before the baseline visit (randomization; Visit 2), or superficial skin infections within 1 week before the baseline visit.

NOTE: Participants may be rescreened after infection resolves (Section 5.4.1).

[15] Have had any of the following types of infection within 3 months of screening or develop any of these infections before randomization (Visit 2):

- Serious (requiring hospitalization, and/or intravenous or equivalent oral antibiotic treatment)
- Opportunistic (as defined in Winthrop et al. 2015)

  NOTE: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.

- Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
- Recurring (including, but not limited to herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis)

  NOTE: Participants with only recurrent, mild and uncomplicated orolabial and/or genital herpes may be discussed with the sponsor's medical monitor to determine whether the participants meet this exclusion criterion.

[16] Have a current or chronic infection with hepatitis B virus (HBV) (Section 8.2.5).

[17] Have a current infection with hepatitis C virus (HCV) (i.e., positive for HCV RNA; Section 8.2.6).

[18] Have known liver cirrhosis and/or chronic hepatitis of any etiology.

[19] Are diagnosed with active endoparasitic infections or at high risk of these infections.

[20] Have a known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per the investigator's judgement.

[21] Have a history of human immunodeficiency virus (HIV) infection or positive HIV serology at screening (Visit 1).

[22] Have presence of skin comorbidities that may interfere with study assessments.

[23] Have a history of malignancy, including mycosis fungoides, within 5 years before screening (Visit 1), 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.

[24] Have a severe concomitant illness(es) that in the investigator's judgement would adversely affect the patient's participation in the study. Have any other medical or psychological condition that in the opinion of the investigator may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant because of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments.

[25] Have a prior history of Guillain-Barre syndrome.

[26] Are allergic to latex.

[27] Have a history of past vaccination allergy or Arthus-type hypersensitivity.

[28] Have an uncontrolled seizure disorder.

[29] Have known hypogammaglobulinemia or a screening serum immunoglobulin G (IgG) or immunoglobulin A (IgA) concentration less than the lower limit of the reporting laboratory's reference range.

Prior/Concomitant Therapy and Vaccines

[30] Have been treated with TCS, calcineurin inhibitors, or phosphodiesterase-4 inhibitors such as crisaborole within 1 week prior to the baseline visit (randomization; Visit 2).

[31] Have been treated with any of the following agents within 4 weeks prior to the baseline visit (randomization; Visit 2):

a. Immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon gamma(IFN-γ), Janus kinase inhibitors, azathioprine, methotrexate, etc.)
b. Phototherapy and photochemotherapy (PUVA) for AD

[32] Have been treated with the following prior to the baseline visit (randomization; Visit 2):

a. An investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer
b. B Cell-depleting biologics, including rituximab, within 6 months
c. Other biologics within 5 half-lives (if known) or 8 weeks, whichever is longer

[33] Have used prescription moisturizers within 7 days of the baseline visit (randomization; Visit 2).

[34] Have regularly used (more than 2 visits per week) a tanning booth or parlor within 4 weeks of the screening visit (Visit 1).

[35] Have received a Bacillus Calmette-Guerin (BCG) vaccination or treatment within 12 months of screening (Visit 1), or have been treated with a live (attenuated) vaccine within 12 weeks of the baseline visit (randomization; Visit 2) or planned during the study.

[36] Have a contraindication to the Tdap vaccine or MCV.

Diagnostic Assessments

[37] In the investigator's opinion, have any clinically significant laboratory results from the chemistry, hematology, or urinalysis tests obtained at the screening visit (Visit 1).

Prior/Concurrent Clinical Study Experience

[38] Have received a dose of lebrikizumab in any prior lebrikizumab clinical study.

[39] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Other Exclusions

[40] Are pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.

[41] 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.

[42] Are employees of Eli Lilly and Company (Lilly) or are employees of a third-party involved in study that requires exclusion of their employees.

5.3. Lifestyle Considerations

All study participants should be instructed not to donate blood or blood products as follows:

- within 2 to 4 weeks of study entry
- during the study, and
- for at least 18 weeks after the last dose of the study drug.

No other lifestyle considerations are applicable to this study.

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 drug. 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 SAE.

5.4.1. Rescreening for Individuals Who Failed Screening

Informed consent for rescreenings

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

Rescreening after failure to meet study entry criteria

An individual who does not meet the criteria for participation in this study due to deviation from the exclusion criterion [14] (acute infection requiring treatment) may be rescreened **one time** after the reason for the screen failure has resolved and if the sponsor has approved the rescreening.

An individual who does not meet the criteria for participation in this study for other reasons may be rescreened **one time** if the reason for the screen failure has resolved and if the sponsor has approved the rescreening.

Rescreening for administrative reasons

An individual may be rescreened **one time** for an administrative reason, including, for example, but not limited to, falling out of the screening window because of scheduling conflicts. The sponsor does not need to approve rescreening for an administrative reason. The rescreening can start immediately after the administrative reason has resolved.

Procedures to be repeated at rescreening

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

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.

In this protocol, the collective term "study intervention" applies both to the study drug (lebrikizumab or placebo; Section 6.1.1) and the vaccine products (Section 6.1.2).

6.1. Study Interventions Administered

6.1.1. Study Drugs

This study involves administration of lebrikizumab and placebo, as shown:

Study Drug Name	Lebrikizumab	Placebo[b]
Dosage Formulation	250 mg (2 mL)[a]	To match lebrikizumab
Dosage Levels and Frequency	Baseline and Week 2: 500 mg loading dose Weeks 4-14: 250 mg Q2W	To match lebrikizumab
Routes of Administration	subcutaneous injection	subcutaneous injection

Abbreviation: baseline = randomization (Visit 2); Q2W = once every 2 weeks.

[a] All study drug (lebrikizumab and placebo) will be supplied as a sterile prefilled syringe with needle safety device (PFS-NSD). Each prefilled syringe is intended for a single 2 mL dose (250 mg) administered subcutaneously.

[b] Placebo solution is identical in appearance and content to the active solution except for lebrikizumab.

For drug administration information, see Sections 6.1.3 and 6.1.4.

6.1.2. Vaccine Products

At Week 12, after the pre-dose vaccine titers have been drawn, one dose of each of the 2 commercially available vaccines will be administered to all participants still on study drug:

- Tdap
- MCV

Participants whose study drug has been permanently discontinued before Week 12 will not receive the vaccines (Section 7.1.2).

Vaccine administration

Vaccine injections will be given per local vaccination guidelines and practices and:

- should not be administered at sites with active AD or other skin lesions
- should be injected in a location different from that for the study drug administration (Section 6.1.3).

6.1.3. Instructions for Administration in the Clinic

Study drug and vaccines will be administered to all study participants in the clinic by designated and trained site staff as specified in the SoA (unless the study participant has opted for at-home administration of the study drug; see the SoA and Section 6.1.4). Detailed instructions for study drug administration will be provided by the sponsor.

At Week 12, the study drug should be injected in a location different from that for vaccine administration.

6.1.4. Instructions for Administration at Home

During remote visits, study participants may opt to self-administer the study drug or have the mobile home health care provider administer it, if permitted by local laws and regulations. Participants may also opt to have their caregivers administer the study drug. Prior to at-home administration, participants and/or caregivers will be adequately trained on the study drug administration at the clinical site (as indicated in the SoA, Section 1.3).

Participants and/or their caregiver will be instructed on the proper injection technique, and the participant or their caregiver will demonstrate the proper injection technique prior to beginning at-home administration.

Instructions for Use with details of the injection procedures, as well as storage and handling of syringes, will be provided to the participant and/or their caregiver to take home. Participants who are not capable of administering study drug at home (or do not have a caregiver to administer the drug at home), or who prefer not to do so, may continue to receive study drug injections in the clinic.

Any time the study drug is administered at home, participants will enter the details about the injections in the electronic patient diary (see the SoA for details).

6.1.5. Packaging and Labeling

Lebrikizumab and placebo will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice (cGMP). Vaccines will be sourced as directed by the sponsor or its designee. Clinical trial materials will be labeled according to the country's regulatory requirements. All study interventions will be stored, inventoried, reconciled, and destroyed according to applicable regulations (see also Section 6.2).

Each prefilled syringe with needle safety device (PFS-NSD) will be packaged in a carton.

6.2. Preparation/Handling/Storage/Accountability

The Pharmacy Manual provides general instructions for the handling and storage of the study drug, as well as the site responsibility and accountability for the administered products. Additional trial-specific information is provided in other documents (see Sections 6.1.3 and 6.1.4). For storage information for lebrikizumab, refer to the investigational product label.

For vaccine-related information, refer to the local labels and guidelines.

Site responsibilities and accountability

- 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 personnel authorized by the primary investigator or by the sponsor 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 (unless the study drug will be administered at home by the participant or caregiver). At-home storage instructions are provided in the participants' Instructions for Use.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind study. The sponsor or designee, the investigator, study-site personnel, and the participant will be blinded to treatment assignment. The integrity of the clinical study will be maintained by observing the treatment blind.

Method of treatment assignment

The randomization ratio and stratification factors are described in Section 4.1.

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). Each study participant will be assigned a unique identification number.

Emergency unblinding

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study drug assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify the sponsor as soon as possible.

Unblinding and participant discontinuation

See Section 7.2.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision unless they opt for at-home administration of the study drug by themselves or their caregivers (see Section 6.1.4).

When administered in the clinic, the date and time of each dose will be recorded in the source documents and recorded in the electronic case report form (eCRF). When administered at home, participants will enter the details about the study drug injections in the electronic patient diary (see the SoA for details).

A participant will be considered compliant with the dosing regimen if the participant received 80% of the expected number of study drug injections while enrolled in the study.

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 the study participants.

- 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 it is a supplement or used as preventative care.

6.5.1. Permitted and Prohibited Treatments and Procedures

Permitted medications

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

In addition, TCS or TCI may be used during the study (low- or mid-potency only).

Participants may use TCS (described below) for AD symptoms starting at the baseline visit (randomization: Visit 2/Day 1).

Participants may taper or stop TCS use, as needed. If AD lesions return or a participant experiences a flare, TCS treatment may be resumed at the participant's discretion.

Low-potency TCS or TCIs may be used for sensitive areas only (i.e., face, neck, intertriginous, and genital areas).

Participants may use the following TCS, if needed:

- a mid-potency TCS: triamcinolone acetonide cream 0.1%, and
- a low-potency TCS: hydrocortisone 1% cream (for use on sensitive skin areas, e.g., face).

All TCS use should be recorded in the eCRF.

Prohibited medications and procedures

The introduction of medications or therapies for other medical conditions known to affect AD (e.g., systemic corticosteroids, mycophenolate-mofetil, IFN-y, Janus kinase inhibitors, cyclosporine, azathioprine, methotrexate, phototherapy or photochemotherapy, or phosphodiesterase-4 inhibitors such as crisaborole) are not permitted during the study.

The use of systemic corticosteroids for the treatment of AD is prohibited and requires permanent discontinuation of study drug (Section 7.1.2). If used for treatment of AEs (for example, worsening of existing condition, such as asthma exacerbation), it will be treated as rescue medication as per the Section 6.5.3.

Acute severe 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 trial.

Cannabinoid treatments for AD are prohibited.

Planned or anticipated major medical procedures or surgeries should be avoided during the trial.

See Section 6.5.3 for details on approved rescue medications and timing of use.

6.5.2. Background Treatment: Non-Medicated Moisturizers

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

Non-medicated moisturizers are to be used during the study. The participants may continue their current over-the-counter moisturizer regimen, if approved by the investigator.

All moisturizer use should be recorded in the eCRF.

6.5.3. Rescue Treatment for Atopic Dermatitis

During this study, add-on rescue therapies may be needed if the participant experiences clinical worsening of symptoms that are intolerable.

Participants will be eligible to receive rescue treatment with any locally approved AD treatments at the discretion of the investigator. Investigators are encouraged to provide rescue therapy in a staged fashion, using a greater intensity of treatment compared to that which the participant was using, for example:

- high-potency TCS, or
- treating with:
    - oral corticosteroids
    - systemic nonsteroid immunosuppressants, or
    - phototherapy.

Refer to Section 7.1.2 for discontinuation criteria associated with systemic rescue treatment.

Participants using topical or systemic rescue medication who complete the study through Week 16 will be eligible to continue to a separate long-term extension study after the Week 16 visit has been completed.

All rescue treatment usage must be captured in the eCRF.

6.6. Dose Modification

Dose modifications of lebrikizumab are not allowed in this study.

6.7. Intervention after the End of the Study

Participants who complete Study KGAK through Week 16 will be assessed for eligibility to enter a separate long-term extension study (DRM06-AD07/J2T-DM-KGAA). If a participant does not meet enrollment criteria for the long-term extension study or does not opt to continue into that study, he or she will be asked to complete the post-treatment follow-up period as described in the SoA (Section 1.3), which will complete his or her study participation.

Lebrikizumab will not be available to the KGAK study participants unless they enter the long-term extension study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

The sections below describe reasons for a participant's:

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

Discontinuation of specific sites or the trial as a whole is handled as part of regulatory, ethical, and trial oversight considerations in Appendix 10.1, Section 10.1.9.

7.1. Discontinuation of Study Intervention

Study drug may be permanently discontinued or temporarily withheld during the study.

7.1.1. Criteria for Temporary Discontinuation of Study Drug

Cases that may merit temporary withholding of the study drug should be discussed with the medical monitor. The medical monitor, in consultation with the investigator, will determine when it is appropriate to recommence study drug.

Participants who require a temporary withholding of study drug after Week 6 will not receive the Tdap and MCV vaccinations at Week 12 unless approved by the medical monitor.

Participants who require a temporary withholding of study drug will not be eligible for entry into the long-term extension study unless they continue to complete study visits and assessments through Week 16.

Some possible reasons for temporarily withholding the study drug include, but are not limited to:

- Serious or opportunistic infections (Section 5.2 and Appendix 10.7). Study drug is to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment.
- Hepatitis B virus DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification: The sponsor's designated medical monitor should be contacted regarding study status of the participant. Hepatitis B virus DNA testing is to be repeated as soon as is feasible. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study drug (Section 7.1.2).
- Hepatic event or liver test abnormality: The study drug should be withheld and additional testing performed following consultation with the Lilly-designated medical monitor, if the results of repeat tests following elevated alanine aminotransferase (ALT), alkaline phosphatase (ALP) or total bilirubin level (TBL) include one of the following (Section 8.2.7):
    - ALT ≥3x upper limit of normal (ULN) and TBL <2x ULN
    - ALP ≥2x ULN and TBL <2x ULN

- TBL ≥2x ULN without increase from baseline in ALT/aspartate aminotransferase (AST)/ALP.

7.1.2. Criteria for Permanent Discontinuation of Study Drug

In rare instances, it may be necessary for a participant to permanently discontinue (definitively discontinue) study drug.

Possible reasons for permanent discontinuation of study intervention

Possible reasons that may lead to permanent discontinuation of the study drug include, but are not limited to, the following:

Investigator decision

- The investigator decides that the participant should be discontinued from study drug. Some examples may include:
  - Inter-current illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
  - Treatment-related AEs that are clinically significant, deemed persistent, in the judgment of the investigator
  - Unacceptable toxicity

Systemic hypersensitivity reaction

- If the investigator, after consultation with the sponsor-designated medical monitor, determines that a systemic hypersensitivity reaction has occurred related to study drug administration, the participant should be permanently discontinued from the study drug.
- If a participant experiences a hypersensitivity event determined by the investigator to relate to the vaccine products, the participant will not be permanently discontinued from the study drug.

Required reasons for permanent discontinuation of study intervention

Permanent discontinuation of study drug should occur in the following instances:

Use of systemic rescue treatment

- If a participant receives rescue treatment with a systemic corticosteroid, immunosuppressant, or phototherapy, the participant must permanently discontinue study drug.
- Participants who receive rescue treatment with topical steroids may continue treatment with study drug.
  NOTE: Participants who discontinue study drug due to rescue medication use should continue to attend all study visits through Week 16 and be assessed for safety and efficacy according to the SoA (as shown in the table at the end of this subsection).

Hepatic event or liver test abnormality

- Participants who are discontinued from the study drug due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF. Discontinuation of the study drug for abnormal liver tests **should be** considered by the investigator when a participant meets one of the following conditions after consultation with the sponsor-designated medical monitor (see Section 8.2.7):
  - ALT or AST ≥8 times ULN
  - ALT or AST ≥5 times ULN for more than 2 weeks
  - ALT or AST ≥3 times ULN and TBL ≥2 times ULN or international normalized ratio (INR) ≥1.5
  - ALT or AST ≥3 times ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant abdominal pain or tenderness, fever, and/or rash
  - ALP ≥3 times ULN
  - ALP ≥2.5 times ULN and TBL ≥2 times ULN, or
  - ALP ≥2.5 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, and/or rash

Other laboratory findings

- Total white blood cell (WBC) count <2000 cells/µL (<2.00 x 10^3/µL or <2.00 GI/L)
- Lymphocyte count <500 cells/µL (<0.50 x 10^3/µL or <0.50 GI/L)
- Platelet count <50,000 cells/µL (<50 x 10^3/µL or <50 GI/L)

Other safety considerations

- The participant develops any of the following conditions during the study:
  - **Malignancy** (except for successfully treated basal or squamous cell skin carcinoma)
  - **Serious or opportunistic infection** that in the opinion of the investigator merits the study drug being discontinued. Such infections may include, but are not limited to:
    - HIV/acquired immune deficiency syndrome (AIDS) infection
    - active TB infection or untreated latent TB infection (LTBI)
    - HCV RNA positive (Section 8.2.6)
    - HBV DNA positive (Section 8.2.5)

      NOTE: The HBV DNA result is to be confirmed if initial positive test result is positive but below the level of quantification (Section 7.1.1; Section 8.2.5). 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 drug. Timing of discontinuation from study drug 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.

If study drug is definitively discontinued, the participant will either remain in the study or not, as follows:

If the study drug is permanently discontinued due to systemic rescue treatment,	**If the study drug is permanently discontinued for other reasons,**
then participants stay in the study to: • complete all the remaining study visits and assessments through Week 16 **AND** • roll into the long-term extension study, if entry criteria are met **OR** • undergo the safety follow-up visit (V801).	then participants will not stay in the study and • undergo an ET visit **AND** • the safety follow-up visit (V801).

If the study drug is permanently discontinued before Week 12 and participants are continuing in the study, these study participants will not receive the vaccines at Week 12.

See the SoA for assessments to be performed at the time of the ET visit and safety follow-up. In addition to the SoA, safety follow-up is outlined in Section 8.2 (“Safety Assessments”) and Section 8.3 (“Adverse Events and Serious Adverse Events”) of the protocol.

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, legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study (see Section 8.3.5 and Appendix 10.4, Section 10.4.3)
- if enrollment in any other clinical study involving an investigational product 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

The participant must be discontinued from the study:

- if an investigator, site personnel performing assessments, or participant is unblinded

  NOTE: In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from the sponsor-designated medical monitor for the participant to continue in the study.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an ET visit should be conducted, as shown in the SoA. See SoA 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 identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study drug unless there are extenuating circumstances that make it medically necessary for the participant to continue on study drug. If the investigator and the sponsor-designated medical monitor agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor-designated medical monitor to allow the inadvertently enrolled participant to continue in the study with or without treatment with the study drug. Safety follow up is as outlined in Section 1.3 (Schedule of Activities), 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.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get the study drug. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

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

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

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

8.1. Efficacy Assessments

8.1.1. Primary Outcome Measures: Vaccine Responses

Seroresponses to vaccines will be assessed as follows:

- Tdap vaccine: a booster response as measured by tetanus toxoid-specific IgG antibodies
- MCV: a positive antibody response to Group C serum bactericidal antibodies

For details about the primary endpoints and definitions of the booster response and positive antibody response, see Section 3.

For details about the laboratory tests to support the primary outcome measure, see Appendix 10.2. For frequency of these tests, see the SoA (Section 1.3).

8.1.2. Secondary Outcome Measures: Efficacy

Each participant's AD will be assessed as specified in the SoA (Section 1.3). Whenever possible, the same assessor should perform all assessments on a given participant over the course of the study. The sponsor will administer training on the required efficacy assessments; detail on the specific instruments and training given are recorded in the study training materials.

All clinician-reported efficacy assessments will be captured on an electronic tablet during the site visits after all the patient-reported outcomes have been completed.

Appropriateness of assessments

All the assessments used in this study are relevant for the AD population. Some measures have been validated and are widely used, including the following:

- EASI (Hanifin et al. 2001)
- POEM (Charman et al. 2004)
- Skin Pain NRS (Newton et al. 2019; data on file)

8.1.2.1. Investigator Global Assessment (IGA)

The IGA is a static assessment and rates the severity of the participant's AD. The IGA is comprised of a 5-point scale ranging from 0 (clear) to 4 (severe), and a score is selected using descriptors that best describe the overall appearance of the lesions at a given time point. 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 and BSA assessments. A single assessor should be assigned to each individual participant for as many visits as possible, to avoid inter-assessor variability in scoring.

8.1.2.2. Eczema Area and Severity Index (EASI)

The EASI is a validated measure that evaluates 2 dimensions of AD: disease extent and clinical signs (Hanifin et al. 2001).

The EASI assesses extent of disease at 4 body regions and measures 4 clinical signs, each on a scale of 0 to 3:

(1) erythema

(2) induration/papulation

(3) excoriation, and

(4) lichenification.

The EASI is a composite index with scores ranging from 0 to 72, with the higher values indicating more severe or extensive disease.

Assessors must be trained and certified by the sponsor prior to conducting this assessment.

8.1.2.3. Body Surface Area (BSA)

The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. BSA will be determined by the investigator or designee using the participant palm = 1% rule.

Assessors must be trained and certified by the sponsor prior to conducting this assessment.

8.1.3. Patient-Reported Outcomes

The outcome measures used in this study are relevant to the AD population.

Participants will complete these assessments as follows, prior to the other study assessments; see also the SoA (Section 1.3):

- Electronic diary (completed at home):
  - Pruritus NRS (daily)
  - Sleep-Loss (daily)
  - Skin Pain NRS (daily)
  - POEM (weekly)
- Electronic tablet (provided at the site):

- PROMIS® Anxiety
- PROMIS® Depression

8.1.3.1. Pruritus Numeric Rating Scale (NRS)

Participants will assess pruritus using a Pruritus NRS. The Pruritus NRS is an 11-point scale used by patients to rate their worst itch severity over the past 24 hours, with 0 indicating "No itch" and 10 indicating "Worst itch imaginable."

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

8.1.3.2. Sleep-Loss

Participants will assess their Sleep-Loss due to pruritus. They will rate their sleep based on a 5-point Likert scale: 0 (not at all) to 4 (unable to sleep at all).

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

8.1.3.3. Skin Pain Numeric Rating Scale (NRS)

Skin Pain NRS (Newton et al. 2019) is a patient-administered, validated, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." Overall severity of a patient's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours.

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

8.1.3.4. Patient-Oriented Eczema Measure (POEM)

The POEM (Charman et al. 2004) is a 7-item, validated questionnaire used by the patient to assess disease symptoms over the last week. The patient is asked to respond to 7 questions on:

- skin dryness
- itching
- flaking
- cracking
- sleep loss
- bleeding, and
- weeping.

All 7 answers carry equal weight with a total possible score from 0 to 28 (answers scored as: No days = 0; 1–2 days = 1; 3–4 days = 2; 5–6 days = 3; everyday = 4). A high score is indicative of a poor quality of life.

Participants will capture the POEM responses weekly using an electronic diary at home.

8.1.3.5. Patient-Reported Outcomes Measurement Information System (PROMIS®): Anxiety and Depression

Patient-Reported Outcomes Measurement Information System is a set of person-centered measures that evaluates and monitors patient's physical, mental, and social health (PROMIS WWW).

The PROMIS® measures used in this study include Anxiety and Depression short forms, which assess the patients' symptoms over the previous week.

Participants will complete the PROMIS measures on an electronic tablet on site (see the SoA for frequency; Section 1.3).

PROMIS® Anxiety

This trial uses the PROMIS Short Form v1.0 – Anxiety -8a. The PROMIS® Anxiety short form assesses the following items (PROMIS Anxiety 2019):

- self-reported fear (fearfulness, panic)
- anxious misery (worry, dread)
- hyperarousal (tension, nervousness, restlessness), and
- somatic symptoms related to arousal (racing heart, dizziness).

Each question has 5 response options, with scores ranging from 1 to 5. The total scores range from 8 to 40, with the higher score indicating a higher level of anxiety.

PROMIS® Depression

This trial uses PROMIS Short Form v1.0 – Depression 8b. The PROMIS® Depression short form assesses the following items (PROMIS Depression 2019):

- self-reported negative mood (sadness, guilt)
- views of self (self-criticism, worthlessness)
- social cognition (loneliness, interpersonal alienation), and
- decreased positive affect and engagement (loss of interest, meaning, and purpose).

Somatic symptoms (such as changes in appetite or sleeping patterns) are not included. This helps eliminate potential confounding effects of these items when assessing participants with comorbid physical conditions.

Each question has 5 response options, with scores ranging from 1 to 5. The total scores range from 8 to 40, with the higher score indicating a higher level of depression.

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 cover general appearance and the following body parts and systems:

- dermatological
- head
- ears
- eyes
- nose
- throat
- respiratory
- cardiovascular
- abdominal
- neurological
- musculoskeletal, and
- lymphatic.

Height and weight will also be recorded.

At subsequent study visits, a symptom-directed physical examination may be conducted at the discretion of the investigator. Findings will be recorded as medical history or AE in the eCRF.

8.2.2. Vital Signs

Vital signs, including body temperature, respiratory rate (breaths per minute), pulse (beats per minute), and blood pressure (mmHg), will be obtained with the participant in the seated position, after sitting for at least 5 minutes. Any abnormal findings that are new or worsened in severity and 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. Clinical Safety Laboratory Assessments

See Appendix 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

Reviewing and recording test results

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 eCRF. 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.

Repeat testing after clinically significant abnormal findings

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 10.2, must be conducted in accordance with the laboratory manual and the SoA.

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 (e.g., SAE or AE or dose modification), then the clinically significant results will be reported as an AE in the AE section of the eCRF.

Blinding of laboratory test results

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel (Appendix 10.2).

8.2.3.1. Pregnancy Testing

Pregnancy testing is to be performed on WOCBP. Participants who are pregnant will be discontinued from the study (Section 7.2).

Visits and times

Serum pregnancy test will be done at screening only, and results will be confirmed by the central laboratory, as stated in Appendix 10.2.

Urine pregnancy testing will be performed locally at visits specified in the SoA (Section 1.3). If the specified visit includes study drug administration, the urine pregnancy test must be "negative" within 24 hours before the study drug is administered.

Urine pregnancy testing may be performed at additional time points during the study treatment period and/or follow-up period, at the discretion of the investigator or if this is required by local regulations.

8.2.4. Systemic Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. Vaccines may be associated with such hypersensitivity reactions, as well. 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 the study intervention. It is recommended that

participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Appendix 10.5. Laboratory results are provided to the sponsor via the central laboratory.

8.2.5. Hepatitis B Testing and Monitoring

Initial testing for HBV infection includes (CDC WWW):

- hepatitis B surface antigen (HBsAg)
- hepatitis B core (anti-HBc), and
- hepatitis B surface antibody (anti-HBs).

If …	**Then …**
HBsAg is positive	the participant is excluded.
HBsAg is negative and anti-HBs is positive (regardless of anti-HBc result) OR HBsAg, anti-HBs, and anti-HBc are all negative	the participant is not excluded.
anti-HBc is positive and HBsAg and anti-HBs are negative	further testing for HBV DNA is required: • If the screening HBV DNA is positive, the participant is excluded. • If the screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least every 3 months during the study (Section 1.3), with temporary withholding or permanent discontinuation of study intervention if HBV DNA is positive, as described in Sections 7.1.1 and 7.1.2, respectively.

Management of enrolled participants with detectable HBV DNA during the study

See Sections 7.1.1 and 7.1.2.

8.2.6. Hepatitis C Testing and Monitoring

Initial testing for HCV infection includes testing for antibodies to HCV:

- If anti-HCV is positive, a serum test for circulating HCV RNA is required.
- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the participant is excluded (see Section 5.2).

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

If HCV RNA is detected during the study, the study drug will be permanently discontinued (Section 7.1.2), and the participant should receive appropriate follow-up medical care.

8.2.7. Hepatic Safety Monitoring

Close hepatic monitoring

The laboratory tests listed in Appendix 10.6, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours, to confirm the abnormality and to determine whether it is increasing or decreasing, if these conditions occur:

If a participant with baseline...	**has the following elevations:**
ALT or AST <1.5 times ULN	ALT or AST ≥3 times ULN
ALP <1.5 times ULN	ALP ≥2 times ULN
TBL <1.5 times ULN	TBL ≥2 times ULN
ALT or AST ≥1.5 times ULN	ALT or AST ≥2 times baseline
ALP ≥1.5 times ULN	ALP ≥2 times baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for the possible causes of the abnormal liver tests should be initiated by the investigator in consultation with the sponsor's designated medical monitor. At a minimum, this evaluation should include a 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 lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

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

If a participant with baseline...	**has the following elevations:**
ALT or AST <1.5 times ULN	ALT or AST ≥3 times ULN with hepatic signs/symptoms*, or ALT or AST ≥5 times ULN
ALP <1.5 times ULN	ALP ≥3 times ULN
TBL <1.5 times ULN	TBL ≥2 times ULN
ALT or AST ≥1.5 times ULN	ALT or AST ≥2 times baseline with hepatic signs/symptoms*, or ALT or AST ≥3 times baseline
ALP ≥1.5 times ULN	ALP ≥2 times baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

*** Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, and/or rash.**

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

Based on the participant's history and initial results, further testing should be considered in consultation with the sponsor's 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 ethylglucuronide, and serum 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/ gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

8.2.7.1. Additional Hepatic Data Collection in Participants Who Have Abnormal Liver Tests During the Study

Additional hepatic safety data collection (hepatic safety eCRF) should be performed for participants who meet one or more of the following conditions:

- Elevation of serum ALT to ≥5 times ULN on two or more consecutive blood tests (if baseline ALT <1.5 times ULN)
    - In participants with baseline ALT ≥1.5 times ULN, the threshold is ALT ≥3 times baseline on 2 or more consecutive tests.
- Elevated TBL to ≥2 times ULN (if baseline TBL <1.5 times ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5 times ULN, the threshold should be TBL ≥2 times baseline.

- Elevation of serum ALP to ≥2 times ULN on two or more consecutive blood tests (if baseline ALP <1.5 times ULN)
    - In participants with baseline ALP ≥1.5 times ULN, the threshold is ALP ≥2 times baseline on two or more consecutive blood tests.
- Hepatic event considered to be a SAE
- Discontinuation of study drug due to a hepatic event (Section 7.1.2)

Note that the interval between the two consecutive blood tests should be at least 2 days.

8.2.8. Serious Infections and Opportunistic Infections

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

8.3. Adverse Events and Serious Adverse Events

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

Adverse events in this study will be categorized based on their relatedness either to the study drug or vaccine products.

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 drug or the study (see Section 7).

Product complaints are covered in Section 8.3.7.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Collection of AEs and SAEs

All SAEs will be collected from the time of the participant’s signing of the ICF until participation in study has ended.

Likewise, all AEs will be collected from the from the signing of the study ICF until participation in study has ended.

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

Reporting of AEs and SAEs

Although all AEs after signing the ICF are recorded by the site in the eCRF/electronic data entry, SAE reporting to sponsor begins after the participant has signed the ICF and has received study drug. 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 10.3. 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 AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.3.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards 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 (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., 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

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Appendix 10.4 to collect data on the outcome for both mother and fetus.

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and for at least 18 weeks 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 10.4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest for this study include:

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

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

8.3.7. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges a deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released for distribution. When the ability to use the product safely is impacted, the following are also product complaints:

a. Deficiencies in labeling information, and
b. Use errors for device or combination products due to ergonomic design elements of the product.

Sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

Complaints are also collected on comparators and other materials supplied, as required and instructed for the study.

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

Product complaints will be reported by the investigator to the sponsor per instructions provided on the study specific Product Complaint Form.

8.4. Treatment of Overdose

In case of suspected overdose, hematology, chemistry, vital signs, and oxygen saturation should be monitored and supportive care provided as necessary.

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 weeks).

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

Study visits and times

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine the serum concentrations of lebrikizumab. The actual date and time (24-hour clock time) of dosing and sample collection must be recorded accurately on the appropriate forms.

Collection, handling, and analysis of samples

Instructions for the collection and handling of biological samples will be provided by the sponsor.

As stated in Appendix 10.2, samples will be analyzed at a laboratory approved by the sponsor. Concentrations of lebrikizumab will be assayed using a validated PK assay. Analyses of samples collected from participants who received placebo are not planned.

Additional and unused samples

Any excess samples collected for PK testing may be used for exploratory analyses such as bioanalytical methods development, assay validation or cross-validation exercises, protein binding, and/or metabolism work.

In the case of systemic allergic/hypersensitivity reactions, additional blood samples will be obtained for PK analyses (Section 8.2.4 and Appendix 10.5).

Genetic analyses will not be performed on these blood samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Unblinding

Drug concentration information that may unblind the study will not be reported to investigative sites or to personnel who are blinded to study data.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Appendix 10.1, Section 10.1.12. During the sample retention time, PK samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, and/or bioanalytical assay validation or bioanalytical method cross-validation exercises.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3), where local regulations allow.

Sample use

Samples will be used only for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will **not** be used for broad exploratory unspecified disease or population genetic analysis. 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.

Samples will be stored, and analysis may be performed on genetic variants thought to play a role in AD. In the event of an unexpected AE or the observation of unusual response, the samples may be analyzed to evaluate a genetic association with response to lebrikizumab. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response.

Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

Confidentiality

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site personnel. The sponsor will store the blood and/or DNA samples in a secure storage space with adequate measures to protect confidentiality.

Unblinding

Pharmacogenetic information that may unblind the study will not be reported to investigative sites or to personnel who are blinded to study data.

Sample retention

The samples will be retained at a facility selected by the sponsor or its designee. The samples will be retained as long as research on the study intervention or study indication continues, but no longer than the maximum retention time specified in Appendix 10.1, Section 10.1.12, or other period as per local requirements.

8.8. Biomarkers

Biomarkers will not be assessed in this *study*.

8.9. Immunogenicity Assessments

Visits and times

At the visits and times specified in the SoA (Section 1.3), predose venous blood samples will be collected to determine the antibody production against lebrikizumab.

The actual date and time (24-hour clock time) of each sample collection will be recorded.

To aid interpretation of these results, a predose blood sample for PK analysis will be collected at the same time points.

Sample collection, handling, and use

Instructions for the collection and handling of blood samples will be provided by the sponsor.

Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies (ADAs) in the presence of lebrikizumab at a laboratory approved by the sponsor, as indicated in Appendix 10.2. Antibodies may be further characterized for their ability to neutralize the activity of lebrikizumab.

Unblinding

Immunogenicity test information that may unblind the study will not be reported to investigative sites or to personnel who are blinded to study data.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples is described in Appendix 10.1, Section 10.1.12.

8.10. Medical Resource Utilization and Health Economics

Not applicable to this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

Study KGAK is a descriptive study with no planned hypothesis testing. Confidence intervals (CIs) will be used to compare seroresponses for lebrikizumab- and placebo-treated participants.

9.2. Sample Size Determination

Approximately 240 participants will be randomly assigned to study intervention (1:1 ratio for lebrikizumab:placebo) such that approximately 218 evaluable per protocol (PP) participants complete the study.

The sample size for this study was determined based on the following information:

- The percentage of study participants with positive response to the tetanus vaccination at Week 16 is 83.7% and 83.3% for active treatment and placebo, respectively (Blauvelt et al. 2019).
- The percentage of study participants with human complement serum bactericidal assay (hSBA)-Meningococcal C total seroresponse at Day 29 is 90% (Tipton et al. 2019, adjusted for adult population).

Assuming the observed booster response to tetanus toxoid for both lebrikizumab and placebo is 83% at Week 16, with 109 participants per arm, the Wald 2-sided 90% CI for the difference in booster response is (-0.08, 0.08).

Similarly, assuming the positive antibody response to MCV for both lebrikizumab and placebo is 90% at Week 16, with 109 participants per arm, the Wald 2-sided 90% CI for the difference in booster response is (-0.07, 0.07).

9.3. Populations for Analyses

The following participant populations are defined:

Population	Description
Intent-to-Treat (ITT)	All participants assigned to study drug, regardless of whether they take any doses of study drug, or if they took the correct study drug. Participants will be analyzed according to the treatment group to which they were randomly assigned.
Per Protocol (PP)	All participants in the safety population who complete the Week 16 (Visit 10) evaluation without any significant protocol violations.
Safety	All participants randomly assigned to study drug and who take at least 1 dose of study drug. Participants will be analyzed according to the study drug they actually received.
Pharmacokinetic Analysis	All randomized participants who received at least 1 full dose of

	study drug and at least 1 postbaseline evaluable PK sample.
Immunogenicity Analysis	A participant is evaluable for treatment-emergent ADA if there is at least 1 non-missing test result for ADA for both the baseline and the postbaseline visits.

Abbreviations: ADA = anti-drug antibody; PK = pharmacokinetic.

The PP population will include participants in the safety population without significant protocol deviations (i.e., any participant or investigator activity that could have possibly interfered with the therapeutic administration of the study drug or the precise evaluation of the study drug efficacy). Significant protocol deviations include the following:

- Used prohibited treatment that required permanent discontinuation of the study drug (see Section 7.1.2)
- Missed either one or both Week 12 or Week 16 study visits (Visits 8 and 10)
- Have not been compliant with the dosing regimen (i.e., participants must receive 80% of the expected injections of study drug and both of the vaccines during participation in the study)
- Exceeded the out-of-the-visit window at the Week 16 visit (Visit 10) by more than ±7 days

Additional significant protocol deviations may be specified in the Statistical Analysis Plan (SAP) prior to unblinding.

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 statistical processing will be performed using SAS® unless otherwise stated. The primary analysis of the co-primary endpoints will be performed for the PP participant population when all participants have completed Week 16. Analysis of the co-primary, secondary, and exploratory endpoints will be performed for the ITT participant population.

Descriptive statistics will be provided for all efficacy and safety endpoints. For categorical endpoints, the number and percentage of participants in each category will be presented. For continuous endpoints, descriptive statistics will include the following:

- the number of participants
- mean
- standard deviation (SD)
- median
- minimum, and
- maximum.

Participants' baseline characteristics related to efficacy analyses will be provided with descriptive statistics for each treatment group.

The Pruritus NRS weekly mean will be calculated as follows:

- The mean of each participant's baseline and post-baseline Pruritus NRS scores will be computed for each week based on the previous 7 days.
- The weekly mean will be calculated if a participant has responses for Pruritus NRS on at least 4 of the 7 days of the week.

If the participant has 3 or fewer Pruritus NRS responses, the mean value for that item will be considered missing. All Pruritus NRS efficacy endpoint analyses will be conducted on the weekly mean.

The Sleep-Loss weekly mean will be calculated similar to the Pruritus NRS weekly mean. All Sleep-Loss efficacy endpoint analyses will be conducted on the weekly mean.

The number of participants in each analysis set will be summarized. Reasons for study drug discontinuation and for study discontinuation during the treatment period will be summarized using frequencies and percentages by treatment group.

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 SAP and the clinical study report.

Additional exploratory analyses of the data may be conducted as deemed appropriate. The SAP will be finalized prior to unblinding. It will include a more technical and detailed description of the statistical analyses described in this section.

9.4.1.1. Participant Disposition

A detailed description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study and randomized, and number and percentage of participants who complete or discontinue the study or the study drug, both overall and by reason for discontinuation. A summary of important and significant protocol deviations will be provided.

9.4.1.2. Participant Characteristics

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

9.4.1.3. Concomitant Therapy

Previous and concomitant medications 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.

9.4.1.4. Exposure and Compliance

The extent of exposure to study drug in each treatment group will be summarized by total number of days of exposure, total number of injections, number of missed injections, and number and percentage of participants who are compliant.

The total number of vaccines of each type in each treatment group will be summarized by the total number of vaccines.

A participant will be considered compliant with the dosing regimen if the participant received 100% of the expected number of study drug injections and vaccines while enrolled in the study.

9.4.2. Co-Primary Analyses

The co-primary endpoints, as described in Section 3, will be analyzed for the PP participant population to compare the percentages of lebrikizumab-treated and placebo-treated participants using the methods for categorical endpoints described in Section 9.4.1. In addition, a 90% CI for the difference between treatment groups will be constructed using the stratified Newcombe approach (Yan and Su 2010; Kim and Won 2013). Missing values will not be imputed.

9.4.3. Secondary Analyses

Descriptive statistics, as described in Section 9.4.1, will be provided for the ITT participant population for the efficacy and quality-of-life measures described in Section 3.

For the anti-tetanus toxoid IgG antibody concentration and Meningococcal Group C serum bactericidal antibodies, the pre- and post-vaccination geometric mean titers will be analyzed.

9.4.3.1. Missing Data

The method of handling missing efficacy data will be as follows for endpoints:

Percentage of participants at Week 16 achieving:

- an IGA score of 0 or 1 and a reduction of ≥2 points from baseline
- ≥75% reduction from baseline in EASI score (EASI-75)
- ≥90% reduction from baseline in EASI score (EASI-90)
- ≥4-point improvement from baseline in Pruritus NRS score in participants with baseline score of ≥4

For participants who receive systemic rescue treatment or withdraw from the study due to lack of efficacy, values should be set to the participant's baseline value subsequent to this time through Week 16. The Markov Chain Monte Carlo (MCMC) multiple imputation will be used to handle the remaining missing data. Imputation will be conducted within each treatment group independently so the pattern of missing observations in one treatment group cannot influence the missing value imputation in the other treatment group. For each imputation process, 25 datasets with imputations will be calculated. Each complete data set will be analyzed with the specified analysis. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

For binary responses related to EASI and IGA, the binary response variables will be calculated based on the multiply imputed datasets that have been created. Because the MCMC algorithm is

based on the multivariate normal model, imputed values for IGA will not generally be one of the discrete values used in IGA scoring (0, 1, 2, 3, or 4). Therefore, to derive the binary IGA response variable, standard rounding rules will be applied to the imputed values. For example, if a participant has an IGA score imputed as 1.4 (and assuming a baseline IGA score of 3), the imputed value would be rounded down to 1, and the minimum change from baseline of 2 would have been met. This participant would be considered a responder. For derivation of an EASI-75 and EASI-90 responses, no rounding will be performed.

The imputed Week 16 EASI value will be compared directly to the observed baseline EASI value to determine whether a reduction of at least 75% was achieved for EASI-75. The imputed Week 16 EASI value will be compared directly to the observed baseline EASI value to determine whether a reduction of at least 90% was achieved for EASI-90. Imputation of continuous data will be analogous to that of binary variables; details will be provided in the SAP.

A total of 2 random seeds will be needed to impute IGA for the 2 treatment groups. The 2 seeds have been pre-specified by a random-number generator:

- IGA: Lebrikizumab 250 mg Q2W: Seed = 970309630
- IGA: Placebo Q2W: Seed = 1477266806

A total of 2 random seeds will be needed to impute Pruritus NRS for the 2 treatment groups. The 2 seeds have been prespecified by a random-number generator:

- NRS: Lebrikizumab 250 mg Q2W: Seed = 1611917356
- NRS: Placebo Q2W: Seed = 1087836192

A total of 2 random seeds will be needed to impute EASI for the 2 treatment groups. Those 2 random seeds have been prespecified by using a random-number generator:

- EASI: Lebrikizumab 250 mg Q2W: Seed = 353985587
- EASI: Placebo Q2W: Seed = 1828572477

9.4.4. Exploratory Analyses

Exploratory analyses will be described in detail in the SAP that is finalized prior to unblinding.

9.4.5. Safety Analyses

All AEs occurring during the study will be recorded and coded using the MedDRA dictionary. Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the date of the first injection of study drug. TEAEs will be summarized by treatment group, including the number of participants reporting an event, system organ class, preferred term, severity, relationship to study drug, and seriousness for the safety population. All SAEs as well as AEs that led to study discontinuation will be listed by participant.

9.4.6. Pharmacokinetic Analyses

Lebrikizumab PK data will be summarized using descriptive statistics.

Data from this study may 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. In this case, a separate PK analysis plan will be developed, and the results of these analyses will be described in a separate PK report.

9.4.7. Immunogenicity Data Analysis

The ADA variables will be analyzed using descriptive statistics. Drug concentration data will be examined and the influence of ADAs on individual concentration-time profiles will be evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

Listings and appropriate summary statistics will be provided for immunogenicity data. The frequency and percentage of participants with preexisting ADA and with treatment-emergent ADAs (TE-ADAs) to lebrikizumab may be tabulated.

Participants with TE-ADA 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 participants with TE-ADA.

The relationship between the presence of antibodies and the PK parameters and drug response (including safety and efficacy) to lebrikizumab may be assessed.

9.4.8. Other Analyses

Subgroup analyses will be conducted for the co-primary endpoints for the ITT participant population. Subgroups for the ITT participant population to be evaluated may include age, sex, race, and other as deemed appropriate.

Definitions of the subgroups and any subgroup-specific analyses will be provided in the SAP. All subgroup analyses will be considered exploratory.

9.5. Interim Analyses

No interim statistical analyses prior to participants' completing the Week 16 visit are planned for this study.

A database lock and unblinding will occur, and the primary analysis will be performed at the time (that is, a cut-off date) the last participant completes Week 16 or the ET visit of Study KGAK. This database lock will include all data collected by the cut-off date.

The final database lock and analyses will then be conducted after all the participants have completed the follow-up period of Study KGAK.

Depending on the regulatory submission timeline, the primary and final database locks may be combined; that is, one final database lock will occur after all the participants have either completed the follow-up period of Study KGAK, or discontinued the study early or entered the long-term extension study (DRM06-AD07/J2T-DM-KGAA).

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

9.6. Data Monitoring Committee (DMC)

The DSMB used across the lebrikizumab program will be used in this study. A DSMB is a type of DMC.

For details on the DSMB, refer to Appendix 10.1, Section 10.1.5.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 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.

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 authorized 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 written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

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

Participants who are rescreened are required to sign a new ICF and will be assigned a new participant number.

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 law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that 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. Committee Structure

As stated in Section 9.6, the DSMB used in this study is the same DSMB used across the lebrikizumab program.

This independent DSMB is comprised of members who are independent of the study sponsor and study investigators. This committee will monitor participant safety by conducting formal reviews of accumulated safety data that is blinded by treatment group. If requested, the DSMB may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The DSMB 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 DSMB 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 DSMB are described in the Lilly DSMB charter.

10.1.6. Dissemination of Clinical Study Data

Reports

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

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, SAP, clinical study report, blank or annotated CRFs, will be provided in a secure data sharing environment for up to 2 years per proposal.

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

10.1.7. Data Quality Assurance

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. Source data might include laboratory tests, medical records, and clinical notes.

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

Monitoring details describing strategy (e.g., 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 (e.g., 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 Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

Data Capture System

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

An electronic data capture system (EDC) will be used in this study for the collection of eCRF 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 eCRF.

Additionally, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant (electronic patient diary and electronic tablet on site) or investigator site personnel (electronic tablet on site). 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 sites. 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 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 sponsor will be encoded and stored in the global product complaint management system.

10.1.8. Source Documents

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

Data reported on 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 10.1.7.

10.1.9. Study and Site Start and Closure

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

The study or a study site will be discontinued if the sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP. 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 drug 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.

10.1.10. Publication Policy

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

10.1.11. Investigator Information

Physicians with a specialty in dermatology will participate as investigators in this clinical trial. Physicians and other qualified healthcare professionals with other specialties and experience in treatment of patients with AD may also participate as investigators.

10.1.12. 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[a]**
PK	Sponsor or Designee	Up to 1 year
Pharmacogenetics	Sponsor or Designee	Up to 7 years
Immunogenicity	Sponsor or Designee	Up to 15 years

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

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

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 SoA 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	**Comments**
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - Red Blood Cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - White Blood Cells)	
Differential	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Indirect bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Uric acid	
Total protein	
Albumin	

Clinical Laboratory Tests	**Comments**
Calcium	
Phosphorus	
Glucose	
Total cholesterol	
Lactic dehydrogenase (LDH)	
Urinalysis	Assayed by Lilly-designated laboratory.
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Hormones (female)	
Serum Pregnancy	Assayed by Lilly-designated laboratory.
Urine Pregnancy	Evaluated locally.
Serology	Assayed by Lilly-designated laboratory.
HIV testing	Assayed by Lilly-designated laboratory.
Hepatitis C Virus (HCV) testing:	Assayed by Lilly-designated laboratory.
HCV antibody	
HCV RNA	
Hepatitis B Virus (HBV) testing:	Assayed by Lilly-designated laboratory.
HBV DNA	
Hepatitis B core antibody (Anti-HBc)	
Hepatitis B surface antigen (HBsAg)	
Hepatitis B surface antibody (anti-HBs)	

Clinical Laboratory Tests	**Comments**
Immunoglobulins	Assayed by Lilly-designated laboratory.
Total immunoglobulin G (IgG)	
Total immunoglobulin A (IgA)	
Vaccine Seroresponse	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-tetanus toxoid IgG antibody	
Meningococcal Group C serum bactericidal antibodies (human complement serum bactericidal assay [hSBA])	
Pharmacokinetic Samples: lebrikizumab concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Pharmacogenetic sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Immunogenicity (ADA) Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-lebrikizumab antibodies	
Anti-lebrikizumab neutralizing antibodies	

ADA = antidrug antibody.

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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.

Events <u>NOT</u> 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 (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

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

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., 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 pre-existing 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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

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 AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE information in the eCRF and the SAE information, on a paper form.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the AE eCRF page and SAE paper form.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 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 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 sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via Paper CRF
• The primary mechanism for reporting an SAE will be a study-specific paper SAE form that will be provided to the site. • The paper SAE forms will be transmitted to the sponsor by a sponsor-designated method(s). • Site staff must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the SAE form.

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

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)
A WOCBP is defined a postmenarcheal female, who has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Women NOT of Childbearing Potential (non-WOCBP)
Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., 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.
3. 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 (e.g. oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators [SERMs], or chemotherapy that induced amenorrhea)

10.4.2. Contraception Guidance

See inclusion criterion [9] (Section 5.1) for requirements for female and male contraception.

10.4.3. 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.

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 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 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 to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

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

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. 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 drug and be withdrawn from the study.

10.5. Appendix 5: Recommended Laboratory Testing for Systemic Hypersensitivity Events

Laboratory testing should be performed at the time of a systemic hypersensitivity event. Important information about why, when, and what to test for is provided below. The management of the AE may warrant laboratory testing beyond that described below and should be performed as clinically indicated.

Laboratory testing during a systemic hypersensitivity event is not performed for diagnostic purposes. Its intent is several fold:

- To help characterize and classify systemic hypersensitivity reactions
- To meet regulatory expectations
- To improve subsequent clinical management by helping to distinguish between the various mechanistic bases of anaphylaxis

When should laboratory tests be obtained?

- In the presence of generalized urticaria or if anaphylaxis is suspected
- After the participant has been stabilized, obtain a sample within 1-2 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.
- Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

What laboratory tests should be obtained?

See the table below.

Hypersensitivity Tests	**Notes** These laboratory tests are bundled in the Clinical Laboratory Operations Hypersensitivity Lab Testing Kit. Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions.
Lebrikizumab ADAs	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Lebrikizumab concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tryptase	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. **Note:** If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine sample for N-methylhistamine testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine N-methylhistamine testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for N-methylhistamine testing at the next regularly scheduled visit or after 4 weeks, whichever is later.
Drug-specific IgE	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Basophil activation test	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. **Note:** The basophil activation test is an in vitro cell based assay that only requires a serum sample. It is a surrogate assay for drug specific IgE, but is not specific for IgE.
Complement (C3a and C5a)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Cytokine panel (IL-6, IL-1β, IL-10)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Anti-PLBL2 antibodies	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Abbreviations: ADA = anti-drug antibody; IgE = immunoglobulin E; IL = interleukin; PK = pharmacokinetic; PLBL-2 = Phospholipase B-Like 2.

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

Hepatic evaluation testing

See Section 8.2.7 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-glutamyl transferase (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 A (IgA; quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin G (IgG; quantitative)
HAV total antibody	Immunoglobulin M (IgM; quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatitis 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	Anti-smooth muscle antibody (ASMA)[a]
HBV DNA[d]	Anti-actin antibody[b]
Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[d]	EBV DNA[d]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[d]	HSV (Type 1 and 2) DNA [d]
Microbiology[c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

Abbreviation: INR = international normalized ratio.

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

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

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

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

10.7. Appendix 7: Examples of Infections That May Be Considered Opportunistic

The following are examples of infections that may be considered opportunistic in the setting of biologic therapy (adapted from Winthrop et al. [2015]). This table is provided to aid the investigator in recognizing infections that may be considered opportunistic in the context of biologic therapy. This list is not exhaustive. Infections will be categorized by Lilly as opportunistic according to *Opportunistic Infections and Biologic Therapies in Immune-Mediated Inflammatory Diseases: Consensus Recommendations for Infection Reporting during Clinical Trials and Postmarketing Surveillance* by Winthrop et al. (2015).

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

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

Source: Adapted from Winthrop et al. (2015).

10.8. Appendix 8: American Academy of Dermatology Consensus Criteria for Chronic Atopic Dermatitis

Atopic dermatitis: Diagnosis recommendations

Patients with presumed AD should have their diagnosis based on the criteria summarized below. On occasion, skin biopsy specimens or other tests (such as serum immunoglobulin E, potassium hydroxide preparation, patch testing, and/or genetic testing) may be helpful to rule out other or associated skin conditions.

Level of Evidence: III Strength of Recommendation: C

Essential features — must be present:

- Pruritus
- Eczema (acute, subacute, chronic)
- Typical morphology and age-specific patterns*
- Chronic or relapsing history

*Patterns include:

- Facial, neck, and extensor involvement in infants and children
- Current or previous flexural lesions in any age group
- 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 (e.g., facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris/pityriasis alba/hyperlinear palms/icthyosis
- Ocular/periorbital changes
- Perifollicular accentuation/lichenification/prurigo lesions

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

- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Icthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

Adapted from Eichenfield et al. 2014.

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

Exceptional circumstances, such as pandemics or natural disasters, may cause disruptions to the conduct of the study. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations. Such changes are intended to mitigate risks of participants missing visits, allow participants to continue safely in the study, and maintain the data integrity of the study. GCP compliance and minimization of risk to study integrity are important considerations. Ensuring the safety of study participants is the prevailing consideration.

Once restrictions are lifted, the sponsor will notify sites that these provisions for changes in study conduct will be reversed and routine study conduct restored.

The following changes in study conduct captured in this Appendix will not be considered protocol deviations. Missing data will be captured as protocol deviation(s). Changes in study conduct not described in this Appendix, or not consistent with applicable local regulations, are not allowed.

Informing ethical review boards (ERBs)

Ethical review boards and regulatory bodies 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.

Remote visits

Under exceptional circumstances, some of the study visits may be conducted remotely (in addition to the remote visits already allowed by the study design). Remote visits may be conducted virtually and/or as mobile health care visits, if permitted by local laws and regulations (see below for details).

Virtual visit (telephone/telemedicine)

Telephone or technology-assisted virtual visits (telemedicine) to complete appropriate assessments are acceptable. 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 in source documents. Assessments to be completed during a virtual visit include, but are not limited to:

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

Mobile health care visit

Additional consent from the participant will be obtained for those who participate in home health care services.

If permitted by local regulations, mobile visits may be performed at locations other than the study site (e.g., participant's home) when participants cannot travel to the site due to exceptional circumstances. These will be performed by a qualified home health care service provider or trained site personnel, following sponsor written approval. Procedures performed may include, but are not limited to:

- taking blood samples
- collecting urine samples for pregnancy testing
- conducting physical assessments, depending on the qualifications of the mobile home health care provider
- administering patient-reported outcomes
- administering study intervention, and
- collecting health information.

Before administering study drug at home, participants and/or caregivers will be adequately trained on at-home study drug administration (unless they have already been trained; see also the section "Study drug and ancillary supplies" below).

Please note that requirements related to the reporting of SAEs remain unchanged. Every effort should be made for the participant to return to on-site visits as soon as reasonably possible, while ensuring the safety of the participant and investigational site staff.

Study drug and ancillary supplies

Under exceptional circumstances, the sponsor or designee will determine appropriate actions to supply/resupply participants with the study drug and ancillary supplies.

The following requirements must be met:

- sponsor approves the alternative method of delivery, taking local regulatory requirements into consideration
- participant consents verbally to alternate method of delivery
- participants or their caretakers are appropriately trained on at-home administration of the study drug (unless they have already received that training); the home health care provider will observe the participant or caregiver administer the study drug for the first time.
    - if the study drug is administered at home, participants will need to record the details about the injections in the patient diary (regardless of whether the at-home study drug administration is done by the participant him-/herself, caregiver, or mobile home health care provider). For the at-home administration information, the same electronic patient diary will be used as for recording the PROs.
- site/sponsor confirms the participant's receipt of the trial supplies
- site/sponsor confirm appropriate ethics review board notification
- alternate delivery of the study drug should be performed in a manner that does not compromise treatment blinding and ensures study drug integrity. The existing protocol requirements for product accountability remain unchanged.
- when delivering supplies to a location other than the study site (e.g., participant's home)
    - participant consent must include provision of any personal information

    - investigator/sponsor should ensure oversight of the shipping process to ensure accountability and product quality (i.e., storage conditions and intact packaging upon receipt)
- additional instructions should be provided to the participant on how to return any unused or completed trial supplies.

Local laboratory option

In exceptional circumstances, to ensure participant safety and with the sponsor's prior written approval, local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for the following:

- Vaccine-specific antibody titer levels:
    - Anti-tetanus toxoid IgG antibody, and
    - Meningococcal Group C serum bactericidal antibodies (hSBA)
- PK samples
- Immunogenicity (ADA) samples
- Pharmacogenetics sample

The local laboratory must be qualified in accordance with local regulations. Clinically significant laboratory findings will be reported as an AE in the AE eCRF.

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.

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.

Increasing visit window(s) for the key endpoint visits

Participants should complete the vaccine administration visit (Visit 8/Week 12) and the final study endpoint visit (Visit 10/Week 16) as per original SoA whenever possible and deemed safe to do so by the investigator. However, in order to maximize the ability for such on-site visits, minimize missing data, and preserve the intended conduct of the study, the visit windows may be adjusted as follows, upon specific guidance from the sponsor:

- For Visit 8 (Week 12), to +7/-3 days
- For all dosing visits and Visit 10 (Week 16), to +7 days

Whenever possible, the visit intervals should be adjusted to allow 4 weeks between Visit 8 (Week 12) and Visit 10 (Week 16), to allow for the highest level of vaccine response to be seen.

Documentation

Changes to study conduct

Changes to study conduct will be documented as the following:

- Sites will need to identify and document the details of how participants, visit types, and activities conducted were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.
- The site should document the participant's verbal consent for having remote visits and remote dispensing of study drug, ancillaries and diaries, prior to implementation of these activities.
- Source document(s) that are 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.

Missing data and other protocol deviations

The study site should capture specific explanation for any missing data and other protocol deviations in source documents. This information will also be captured by the monitors in the monitoring system. While protocol deviations may be unavoidable in an exceptional circumstance, documentation of protocol deviations and missing data will be important for data analysis and reporting.

10.10. Appendix 10: Abbreviations

Term	Definition
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BCG	Bacillus Calmette-Guerin
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. 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
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatinine 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.
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form

Term	Definition
CTA	Clinical Trial Agreement
DMC	data monitoring committee
DSMB	Data Safety Monitoring Board
EASI	Eczema Area and Severity Index
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
eCRF	electronic case report form
EDC	electronic data capture system
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ERCP	endoscopic retrograde cholangiopancreatography
ET	early termination
FLG	filaggrin
FSH	follicle stimulating hormone
GCP	good clinical practice
cGMP	current Good Manufacturing Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus

Term	Definition
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
hSBA	human complement serum bactericidal assay
huIgG4	humanized monoclonal immunoglobulin G4 antibody
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IgA	immunoglobulin A
IGA	Investigator Global Assessment
IgE	immunoglobulin E
IgG	immunoglobulin G
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
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Boards
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IUD	intrauterine device

Term	Definition
IUS	intrauterine hormone-releasing system
IWRS	interactive web-response system
LLOQ	lower limit of quantitation
LOR	loricrin
LTBI	latent tuberculosis infection
MCMC	Markov Chain Monte Carlo
MCV	Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline)
MRCP	magnetic resonance cholangiopancreatography
non-WOCBP	women of nonchildbearing potential
NRS	Numeric Rating Scale
Participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PFS-NSD	prefilled syringe with needle safety device
PK	pharmacokinetics
POEM	Patient-Oriented Eczema Measure
PP	per protocol
PRO	patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PT-INR	prothrombin time international normalized ratio
PUVA	phototherapy and photochemotherapy
Q2W	once every 2 weeks
SAE	serious adverse event
SAP	Statistical Analysis Plan
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SERM	selective estrogen receptor modulator

Term	Definition
SoA	Schedule of Activities
TBL	total bilirubin level
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
Tdap	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi)
TE-ADA	treatment-emergent antidrug 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.
TSLP	thymic stromal lymphopoietin
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	women of childbearing potential

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Leo Document ID = 30577e5c-a4fb-44d4-9b5a-8a926d6547fc

Approver: PPD

Approval Date & Time: 05-Aug-2020 20:50:21 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 05-Aug-2020 21:26:22 GMT

Signature meaning: Approved