NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA, 351(a)
Application Number(s)	BLA 761306/IND 119866
Priority or Standard	Standard
Submit Date(s)	September 28, 2022
Received Date(s)	September 28, 2022
PDUFA Goal Date	September 28, 2023
Division/Office	Division of Dermatology and Dentistry /Office of Immunology and Inflammation
Review Completion Date	September 28, 2023
Established/Proper Name	Lebrikizumab injection
(Proposed) Trade Name	Ebglyss
Pharmacologic Class	interleukin-13 antagonist
Code name	LY3650150
Applicant	Eli Lilly and Company
Dosage form	Prefilled Pen Prefilled Syringe with needle shield
Applicant proposed Dosing Regimen	500 mg at Week 0 and Week 2, followed by 250 mg every 2 weeks (b) (4) Week 16 or later, when adequate clinical response is achieved. The maintenance dose is mg every 4 weeks; (b) (4)
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	24079001 |Atopic dermatitis (disorder)|
Recommendation on Regulatory Action	Complete response
Recommended Indication(s)/Population(s) (if applicable)	NA
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	NA

Recommended Dosing Regimen	NA

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Lebrikizumab belongs to the pharmacological class of immunomodulators/ interleukin (IL) inhibitors. Lebrikizumab is an IgG4 monoclonal antibody that binds to IL-13 and selectively inhibits IL-13 signaling through the IL4 receptor alpha/IL-13 receptor alpha-1 pathway, thereby blocking the downstream effects of IL-13. It is a new molecular entity (NME), and the proposed proprietary name is "Ebglyss."

The proposed indication for lebrikizumab is for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Conclusions on the Substantial Evidence of Effectiveness

The substantial evidence of effectiveness was based on 2 adequate and well-controlled trials (Studies KGAB and KGAC) and 1 supportive trial (Study KGAD) that evaluated lebrikizumab for treatment of adult and adolescent subjects 12 years of age and older with moderate-to-severe atopic dermatitis whose disease was not adequately controlled with topical prescription therapies or when those therapies were not advisable. Studies KGAB and KGAC evaluated lebrikizumab as a monotherapy, and the supportive Study KGAD evaluated lebrikizumab with protocol-specified, concomitant use of topical corticosteroids (TCS). Lebrikizumab was statistically superior to placebo in Studies KGAB and KGAC in the target AD population for the primary endpoint of Investigator Global Assessment (IGA) success (defined as scoring 0 or 1 with ≥2-point reduction from Baseline) and EASI-75 (≥75% reduction from Baseline), which is one of the key secondary endpoints, at Week 16. The results from Study KGAD are supportive because the prespecified primary analysis for Study KGAD was not statistically significant for the primary endpoint of IGA success (p=0.11). After seeing the non-significant result for the primary endpoint in Study KGAD, the applicant identified implausible homogeneity of efficacy results on one investigator in which all subjects at the site were IGA responders at Week 16 on both treatment groups. After auditing the site, the applicant concluded that the data from that site was unreliable and defined a modified intent-to-treat (mITT) analysis population that excluded the subjects from this site. The mITT analysis for the primary endpoint was nominally statistically significant (p=0.01). However, because the mITT population was only identified after the unblinding and data analyses, results from Study KGAD are only supportive. In addition, a substantial proportion of subjects (60%) in Study KGAD were enrolled through investigators who also participated in either Study KGAB or KGAC. Thus, Study KGAD is not independent from Studies KGAB and KGAC.

Benefit-Risk Summary and Assessment

Lebrikizumab is an IgG4 monoclonal antibody that binds to IL-13 and selectively inhibits IL-13 signaling through the IL4 receptor alpha/IL-13 receptor alpha-1 pathway, thereby blocking the downstream effects of IL-13. It is a new molecular entity proposed for the treatment of adults and adolescent 12 years of age or older with moderate-to-severe atopic dermatitis (AD).

The substantial evidence of effectiveness was based on 2 adequate and well-controlled trials (Studies KGAB and KGAC) and 1 supportive trial (Study KGAD) that evaluated lebrikizumab in the target population. Studies KGAB and KGAC evaluated lebrikizumab as a monotherapy, and the supportive Study KGAD evaluated lebrikizumab with protocol-specified, concomitant use of topical corticosteroids (TCS). Lebrikizumab was statistically superior to placebo in Studies KGAB and KGAC in the target AD population for the primary endpoint of IGA success (defined as scoring 0 or 1 with ≥2-point reduction from Baseline) and EASI-75 (≥75% reduction from Baseline), which is one of the key secondary endpoints, at Week 16. The proportions of IGA responders in the 250 mg Q2W regimen recommended for approval were 43.1% and 33.2% in the monotherapy trials, compared with 12.7% and 10.8% in the respective placebo groups. The proportion of EASI-75 responders in the 250 mg Q2W regimen recommended for approval were 58.8% and 52.1% in the monotherapy trials, compared with 16.2% and 18.1% in the respective placebo groups. Lebrikizumab was also statistically superior to placebo for EASI-90 and pruritus NRS score (i.e., at least a 4-point reduction from Baseline in Worst Daily Pruritus NRS score), which are the key secondary endpoints, at Week 16 in the monotherapy trials.
The Applicant adequately characterized the safety profile of lebrikizumab through analyses of data from the safety database of 1756 subjects, including 382 adolescents, across 8 clinical studies. The safety profiles were similar whether lebrikizumab was administered as monotherapy or whether with concomitant topical corticosteroids. The most frequently reported adverse reactions were conjunctivitis, injection site reactions, and herpes zoster infections.

The Applicant has provided adequate evidence of safety and efficacy for the use of lebrikizumab in adults and adolescents at least 12 years of age with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Pending resolution of the CMC manufacturing site inspection issues, this reviewer recommends approval for the proposed dosing regimen of 500 mg initially, followed by 250 mg Q2W, in adults and adolescents with moderate-to-severe atopic dermatitis, with a maintenance dose of 250 mg Q4W once adequate clinical response is achieved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals. • The prevalence of AD in the United States in individuals 4-8 years of age has been reported as 10.63% and as 9.96% in those 9-12 years of age. For 10-30% of individuals with AD, it persists into the adult years. • AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is like that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and may also involve the neck, wrists, and volar aspects of the wrists. AD may be generalized. • Common comorbidities include asthma, allergic rhinitis/rhinoconjunctivitis, and food allergies.	While AD is not a life-threatening condition, it may be serious. It may significantly impact the quality of life of the patient, as well as family members. The dysfunctional skin barrier, further compromised from scratching, may predispose patients to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. Patients with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. During disease flares, approximately 80% of patients may experience disturbed sleep. The disruption in sleep could have carryover effects to impact behavior and neurocognitive functioning. Sleep disturbance in the affected individual may also disrupt the sleep of family members. Affected children may also experience depression, anxiety, social isolation, and impaired psychosocial functioning.
Current Treatment Options	• For the Applicant's target population of moderate-to-severe AD, available FDA-approved systemic treatments include dupilumab, tralokinumab, abrocitinib, upadacitinib, and corticosteroids. • Phototherapy (narrow-band ultraviolet B as the first-line) is an option for this population, but its drawbacks include a potentially time-intensive, in-office treatment schedule. Risks from	Approval of lebrikizumab would represent a useful addition to the treatment options for patients with moderate-to-severe AD that is not manageable by topical therapies; a population for whom additional approved treatment options are desirable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	phototherapy may vary according to the type of phototherapy and can include actinic damage, sunburn-like reactions, skin cancer (nonmelanoma and melanoma), and cataracts. • Due to safety concerns (e.g., increased risk of serious infections, major cardiovascular events, cancer, thrombosis, and death), JAK inhibitors (i.e., abrocitinib, upadacitinib) are reserved for the treatment of refractory, moderate-to-severe atopic dermatitis that is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. • The American Academy of Dermatology recommends that systemic corticosteroids generally be avoided because of the potential for short- and long-term adverse reactions. • Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The reported effectiveness for the products varies from "efficacious" (cyclosporine) to "inconsistent" (mycophenolate mofetil). Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. A small sampling of labeled risks includes nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil).	Lebrikizumab would be the fifth systemic product approved for treatment of moderate-to-severe AD, following the approvals of dupilumab, tralokinumab, upadacitinib, and abrocitinib, other than corticosteroids. Lebrikizumab would represent an alternative to dupilumab for systemic treatment of moderate-to-severe AD, especially in adolescents, as tralokinumab is not approved in this population, and JAK inhibitors are reserved for more refractory cases. Corticosteroids, although approved, are not generally recommended for longer term use in this indication.
Benefit	• The substantial evidence of effectiveness was based on 2 adequate and well-controlled trials (Studies KGAB and KGAC) and 1 supportive trial (Study KGAD) that evaluated lebrikizumab for treatment of adult and adolescent subjects with moderate-to-	The submitted data have met the evidentiary standard for providing substantial evidence of effectiveness. The Applicant has established that lebrikizumab is

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	severe atopic dermatitis. Two replicate studies KGAB and KGAC evaluated lebrikizumab as a monotherapy, and the third supportive study KGAD evaluated lebrikizumab with protocol-specified, concomitant use of topical corticosteroids (TCS). • Lebrikizumab was statistically superior to placebo in Studies KGAB and KGAC in the target AD population for the primary endpoint of IGA success (defined as scoring 0 or 1 with ≥2-point reduction from Baseline) and EASI-75 (≥75% reduction from Baseline), which is one of the key secondary endpoints, at Week 16. • The proportions of IGA responders in the 250 mg Q2W regimen recommended for approval were 43.1% and 33.2% in the monotherapy trials, compared with 12.7% and 10.8% in the respective placebo groups. • The proportion of EASI-75 responders in the 250 mg Q2W regimen recommended for approval were 58.8% and 52.1% in the monotherapy trials, compared with 16.2% and 18.1% in the respective placebo groups. • Lebrikizumab was also statistically superior to placebo for EASI-90 and pruritus NRS score (i.e., at least a 4-point reduction from Baseline in Worst Daily Pruritus NRS score), which are the key secondary endpoints, at Week 16 in the monotherapy trials.	effective for treatment of adult and adolescent patients with moderate-to-severe AD.
Risk and Risk Management	• The Applicant evaluated the safety and efficacy of lebrikizumab for the treatment of moderate-to-severe atopic dermatitis in subjects 12 years and above. • The safety database was adequate to assess risks and outcomes. Across the AD development program, 1756 subjects were treated with subcutaneous injections of lebrikizumab with or without concomitant TCS. A total of 903 subjects was treated with	Based on the available data, lebrikizumab has a favorable safety profile in relation to the proposed benefit. The safety database was adequate for comprehensive safety assessment of lebrikizumab for the proposed indication, patient population, dosage regimen, and duration of treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	lebrikizumab for ≥1 year. • The most frequently reported adverse reactions in the lebrikizumab 250 mg Q2W treatment groups compared to placebo were conjunctivitis, injection site reactions, and herpes zoster infections. • No deaths were reported among subjects receiving lebrikizumab during the placebo-controlled induction period. Four deaths were reported among subjects receiving lebrikizumab (1 during the maintenance escape period, 2 during the long-term extension study, and 1 during the open-label Study KGAE), though none were likely related to study drug. • The risk of immunogenicity for patients treated with lebrikizumab appears low. No clinically meaningful differences in the pharmacokinetics, safety, or efficacy of lebrikizumab were observed in patients who tested positive for anti-drug antibodies.	Safety risks have not been identified that require risk management beyond labeling and standard pharmacovigilance. A REMS is not recommended for this application.

1.2. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	8.1.2 (Pruritus NRS and Sleep-Loss Scale)
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	8.1.2 (IGA and EASI)
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Atopic dermatitis (AD), commonly known as eczema, is a chronic, relapsing inflammatory skin condition characterized by dry, pruritic skin that occurs most frequently in children but also affects many adults. It inflicts a substantial psychosocial burden on patients and their relatives and increases the risk of food allergy, asthma, allergic rhinitis, other immune-mediated inflammatory diseases, and mental health disorders.[1] Clinical features of AD include skin dryness, erythema, oozing and crusting, and lichenification. Pruritis is a hallmark of the condition and responsible for much of the disease burden for patients and their families.

AD may have different endotypes, including race, ethnicity and age, and patients with and without filaggrin mutations.[2] In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals.[3] Shaw et al. reported the prevalence of AD in the United States in individuals 4-8 years of age to be 10.63% and in those 9-12 years of age to be 9.96%.[4] For 10-30% of individuals with AD, it persists into the adult years.[5]

AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is like that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the wrists. AD may be generalized.

The pathogenesis involves a complex interplay of genetic, immunological, and environmental factors that result in abnormal skin barrier function and immune system dysfunction. Irregularities in the terminal differentiation of the epidermal epithelium lead to a faulty stratum corneum which permits the penetration of environmental allergens. The exposure to allergens may ultimately result in systemic sensitization and may predispose AD patients to other conditions, such as asthma and food allergies.[6]

Acute AD is associated with cytokines produced by T helper 2 type (Th2) cells (as well as other T-cell subsets and immune elements). These cytokines are thought to play an important role in the inflammatory response of the skin, and IL-4 and IL-13 may have distinct functional roles in Th2 inflammation.[7] IL-4 has been shown to stimulate immunoglobulin E (IgE) production from B cells.[8] IL-13 expression correlates with disease severity and flares. IL-4 mediates its biological activity via binding to IL-4Rα. IL-13 receptor alpha 1 (IL-13Rα1) may then be recruited to form a signaling complex. IL-13 mediates its biological activity via binding to IL-13Rα1 and subsequent recruitment of IL-4Rα, forming a signaling complex. [9] IL-4 and IL-13 reside on chromosome 5q23-31, among a grouping of genes related to development of allergic diseases.

[1] Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016 Mar;387(10023):1109-22
[2] Czarnowicki T, He H, Drueger J, et al. AD endotypes and implications for targeted therapeutics. J Aller Clin Immunol 2019;143:1011.
[3] Weston WL and How W. Atopic dermatitis (eczema): Pathogenesis, clinical manifestations, and diagnosis of atopic dermatitis. Dellavalle RP, Levy ML, Fowler J, eds. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed October 14, 2020).
[4] Shaw TE et al. Eczema prevalence in the United States: Data from the 2003 National Survey of Children's Health. J Invest Dermatol. (2011) 131, 67-73.
[5] Eichenfield LF, et al. Guidelines of care for the management of atopic dermatitis. Section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70:338-51.
[6] Leung DYM, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches. J Allergy Clin Immunol. 2014;134:769-79.
[7] Bao K and Reinhardt RL. The differential expression of IL-4 and IL-13 and its impact on type-2 immunity. Cytokin. 75 (2015) 25-37.
[8] May RD, Fung M. Strategies targeting the IL-4/IL-13 axes in disease. Cytokin. 2015;75:89-116.
[9] Leung DYM, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches. J Allergy Clin Immunol. 2014;134:769-79.

2.2. Analysis of Current Treatment Options

Food and Drug Administration (FDA)-approved or -licensed treatments for AD fall in the categories of corticosteroids (topical and systemic), calcineurin inhibitors (topical), phosphodiesterase-4 (PDE-4) inhibitors (topical), IL-4 receptor antagonist (dupilumab; systemic), IL-13 antagonist (tralokinumab; systemic), and JAK inhibitors (topical and systemic).

Prior to the licensure of dupilumab, corticosteroids were the only systemically administered products that were FDA-approved for treatment of an AD indication in any age group. Corticosteroids are available for treatment of AD by various routes of administration, including topical, oral, and parenteral. Although their use may result in rapid improvement, the AD commonly recurs with worse severity on discontinuation of the systemic corticosteroids (rebound). For this reason and because of the potential for adverse effects, the American Academy of Dermatology recommends that systemic steroids generally be avoided in the treatment of AD because potential risks generally outweigh the benefits.[1] Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern in children and adolescents is the risk of decreased linear growth during treatment. Labels for systemic corticosteroids do not specify any limitations on the age of indication.

Topical corticosteroids (TCS) represent the cornerstone of anti-inflammatory treatment of AD in all age groups.[1] Numerous TCS, in various dosage forms and potencies, are available for

treatment of AD, and some are specifically indicated for pediatric use. For example, fluticasone propionate lotion, 0.05%, a medium potency TCS, is indicated for relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 3 months of age and older. According to product labels, TCS may be sufficiently absorbed to lead to systemic adverse effects. Additionally, pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios. Labeled potential local adverse effects include skin atrophy, striae, telangiectasias, and hypopigmentation.

Other topical therapies indicated for AD include the topical calcineurin inhibitors, a PDE-4 inhibitor and a JAK inhibitor. The topical calcineurin inhibitors (TCI), tacrolimus ointment and pimecrolimus cream, are also indicated for treatment of AD in pediatric patients (2 years and older): tacrolimus for moderate-to-severe AD and pimecrolimus for mild-to-moderate AD. However, both are labeled for second-line, short-term use when other topical prescription treatments have failed or are inadvisable. The calcineurin inhibitors carry boxed warnings advising that the safety of their long-term use has not been established. More specifically, the boxed warnings describe that rare cases of malignancy (e.g., skin and lymphoma) have been reported in subjects treated with topical calcineurin inhibitors. Crisaborole ointment, 2%, a PDE-4 inhibitor, is approved for treatment of AD in pediatric patients (3 months of age and older). However, the product is indicated for a somewhat different AD population (mild-to-moderate AD) than the target population for dupilumab (moderate-to-severe AD). Recently a topical JAK inhibitor, ruxolitinib, was approved for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Dupilumab is an injectable IL-4 and IL-13 antagonist indicated for the treatment of moderate-to-severe atopic dermatitis in adult and pediatric patients aged 6 months and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Common adverse events include injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritis, other herpes simplex virus infection, dry eye, and eosinophilia.

Two systemic, oral, JAK inhibitors are approved for the treatment of refractory moderate-severe AD: upadacitinb and abrocitinib. Upadacitinib is indicated for adolescents and adults 12 years of age and older weighing at least 40 kg and abrocitinib is indicated for adults. The indication is restricted for patients who failed other systemic therapies including biologics and use is not recommended in combination with other immunosuppressants or biologics. While there are no approved JAK inhibitors in the age <12 years population, these products represent an alternative to having injections or systemic steroids for the treatment of moderate-severe AD. Boxed warnings for JAK inhibitors include blood clots, lymphoma and other malignancies, and serious infections. Recently the boxed warnings were updated to include the risk of cardiovascular death and stroke in high-risk patients who are aged 50 and above and are current or past smokers.

Tralokinumab is an injectable IL-13 antagonist indicated for the treatment of moderate-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Similar to dupilumab, common adverse events include upper respiratory tract infections, conjunctivitis, injection site reactions, and eosinophilia. However, tralokinumab is only indicated for adults and therefore a different target population than for dupilumab and lebrikizumab.

Nonpharmacologic care is critical to AD management and includes attention to bathing practices and the regular use of moisturizers, which are available in several delivery systems, such as creams, ointments, oils, and lotions. Moisturizers are directed at the xerosis and transepidermal water loss that are central elements of the disease. They may also relieve pruritus, lessen erythema and fissuring, and improve lichenification. Moisturizers themselves may be the principal treatment for mild disease. Although there are no standardized or universal recommendations regarding the use of moisturizers, repeated application of generous amounts is thought to be important and required, irrespective of the severity of disease. The use of moisturizers during maintenance may stave off flares and may lessen the amounts of pharmacologic agents needed to control the disease.[2]

Phototherapy (UVA and UVB) is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including children. However, phototherapy may require frequent in-office visits (e.g., several times a week) and time missed from school (and also, possibly from work for caregivers). Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions (erythema, tenderness, pruritus), skin cancer (nonmelanoma and melanoma), and cataracts. However, long-term risks from phototherapy treatment of AD in children have not been evaluated. Narrowband UVB therapy may be considered first-line because of the safety profile relative to psoralen + UVA (PUVA).

Systemic immunomodulating agents used off-label to treat AD, including in pediatric patients, include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The reported effectiveness for the products varies from “efficacious” (cyclosporine) to “inconsistent” (mycophenolate mofetil). Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. A small sampling of labeled risks includes nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil).

[1] Eichenfeld et al. Guidelines of care for the management of atopic dermatitis. Section 1. Management and treatment with topical therapies. J Am Acad Dermatol. 2014;71:116-32
[2] Ibid.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lebrikizumab is not marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Investigational new drug (IND) 119866 was submitted on December 10, 2014, for the proposed indication of the treatment of moderate-to-severe atopic dermatitis (AD). The IND-opening study was a phase 2 study entitled: "A Phase II, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Lebrikizumab in Patients with Persistent Moderate to Severe Atopic Dermatitis That Is Inadequately Controlled by Topical Corticosteroids."

An End-of-Phase 2 meeting was held on June 19, 2019, and the Applicant was given feedback on their phase 3 development program, including trial design and analysis, proposed endpoints, safety database, and the enrollment of adolescent subjects.

On October 8, 2019, the Applicant submitted a request for Fast Track Designation, which was granted by the Agency on December 6, 2019.

On November 11, 2019, the Applicant submitted an initial Pediatric Study Plan (iPSP). The Agency agreed with the proposed Pediatric Study Plan and sent notification of the Agreed iPSP to the Applicant on December 3, 2019. On March 24, 2021, the Applicant submitted an amended iPSP, which addressed plans to evaluate lebrikizumab in patients 6 months to < 12 years of age and 12 to < 18 years of age who weigh < 40 kg. On October 21, 2021, the Agency notified the Applicant of agreement with the Amended Agreed iPSP.

The protocols for the pivotal phase 3 monotherapy studies (KGAB and KGAC) were submitted to the Agency on July 18, 2019, and the protocol for the TCS combinations study (KGAD) and adolescent study (KGAE) were submitted to the Agency for review on December 20, 2019. FDA provided feedback on the pivotal monotherapy trials in an advice letter, issued on December 11, 2019, regarding various issues, including several of the proposed secondary endpoints and the handling of missing data. An additional advice letter was issued on March 27, 2020, containing additional feedback regarding several proposed secondary endpoints and the handling of missing data.

On June 13, 2022, a pre-biologics license application (BLA) meeting was held with the Applicant, and the following were discussed:

- The content and organization of the Table of Contents of the BLA
- Content of the clinical data package
- Analysis of safety data

- Proposed labeling claims
- Maintenance dosing regimens
- Plans to submit results from vaccine study

On September 28, 2022, the Applicant submitted BLA 761306 for lebrikizumab under regulatory pathway 351(a) of the Public Health Service Act, for the indication of the "treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable."

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate to support the use of this product for the proposed indication. The Division requested that the Office of Scientific Investigations (OSI) conduct clinical inspections of several domestic sites.

The sites which were selected for inspection had concerning audit findings (Dr. Carpio), high enrollment numbers (Dr. Carpio, Dr. Mendez), and absence of prior inspections (Dr. Mendez, Dr. Torkan). Dr. Wallace's site was inspected due to a previous VAI (voluntary action indicated) from a 2018 inspection with observations of not conducting investigation in accordance with the signed investigator statement, failure to prepare or maintain adequate case histories, and failure to retain investigational records for a period of two years.

OSI provided the following overall assessment of findings and recommendations:

"The inspections of Drs. Mendez, Wallace, and Torkan did not find significant concerns regarding the oversight of the clinical trial or Good Clinical Practice (GCP) or regulatory compliance, and based on the results of these inspections, data generated by these inspected clinical investigators appear acceptable in support of the proposed indication.

The inspection of Dr. Carpio yielded unreported protocol deviations and inconsistent statements that indicated his lack of command of study details and procedures, including those related to eligibility and blinding. Combined with the data anomalies identified by the sponsor (and confirmed by OSI), we recommend a sensitivity analysis excluding data from Dr. Carpio's site for Study KGAC and Study KGAD."

See Section 8.1.2 of this review for additional information regarding the exclusion of data from Dr. Carpio's site.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761306 for Ebglyss manufactured by Eli Lilly and Company. The information and data provided to support licensure are not sufficient to support a conclusion that the manufacture of Ebglyss is well-controlled and will lead to a product that is pure, potent and with consistent quality. Specifically, facility deficiencies were identified during the on-site inspection of the (b) (4) drug substance (DS) manufacturing facility and following OPMA/DBM's expedited review of (b) (4) responses to the FDA Form 483 observations, the responses were considered inadequate. Due to the unresolved facility deficiencies, a reliable interpretation of the datasets submitted to the BLA intended to support comparability between the material used in the clinical studies and commercial material, DS process validation and the DS control

strategy cannot be made. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Eli Lilly and Company to outline the deficiencies noted above and the information and data that will be required to support approval.

4.3. Clinical Microbiology

This section is not applicable for this application.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable for this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The applicant submitted an original 351(a) BLA application for Lebrikizumab Injection indicated for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Lebrikizumab-lbkz is an IgG4 monoclonal antibody (MAb) that binds with high affinity and slow off-rate to interleukin (IL)-13 and allows IL-13 to bind to IL-13Rα1 but inhibits human IL-13 signaling through the IL-4Rα/IL-13Rα1 receptor complex. IL-13 is a naturally occurring cytokine that is involved in Type 2 inflammation, which is an important component in the pathogenesis of atopic dermatitis. Lebrikizumab-lbkz inhibits IL-13-induced responses including the release of proinflammatory cytokines, chemokines and IgE. Lebrikizumab-lbkz-bound IL-13 can still bind IL-13Rα2 allowing subsequent internalization and natural clearance of IL-13.

Lebrikizumab binds with pM affinity to IL-13 of human and cynomolgus monkey, but not IL-13 of mouse or rat. Thus, cynomolgus monkeys were selected as a single pharmacologically relevant species for use in nonclinical studies with lebrikizumab. The applicant submitted a number of pharmacology studies, safety pharmacology assessment, one 6-week and one 9-month intravenous repeat dose toxicity studies, one 13-week subcutaneous bridging study, one 9-month intravenous female fertility (toxicity and cycling) study, one 13-week subcutaneous male fertility study, one 9-month intravenous female fertility study, one embryo-fetal development (EFD) study, and one prenatal and postnatal development (PPND) study in cynomolgus monkeys with lebrikizumab.

No stand-alone safety pharmacology studies were conducted with lebrikizumab. Safety pharmacology parameters were included in the 6- and 39-week intravenous and/or 13-week subcutaneous repeat-dose toxicology studies in cynomolgus monkeys. Repeated administration of lebrikizumab up to 25 mg/kg/week IV or SC had no adverse effects on the evaluated parameters for cardiovascular, respiratory or behavioral effects.

Two intravenous and one subcutaneous repeat dose toxicity studies were submitted in the BLA. The NOAEL for lebrikizumab in cynomolgus monkeys was the highest dose tested in all three studies, i.e., 22.7 mg/kg/week in the 6-week intravenous toxicology study and 25 mg/kg/week in the 9-month intravenous toxicology study and 13-week subcutaneous toxicology study. No lebrikizumab-related adverse effects (including effects on the immune system) were observed. No target organs of toxicity were identified. Lower uterine weights with no correlated histological changes were observed in the 9-month study where most of the test monkeys were sexually immature (2.5 to 4.5 years old at study start), and individual variable maturity may have contributed to the differences in uterine weights. This finding was not observed in a 9-

month study with mature female cynomolgus monkeys (4.8 to 9.3 years old at study start). There were no neoplastic or test article-related non-neoplastic proliferative lesions in the 9-month intravenous toxicology study in monkeys.

No lebrikizumab-related effects on fertility parameters such as reproductive organs, female reproductive hormones, menstrual cycle and sperm analysis were observed in sexually mature monkeys treated with lebrikizumab up to 25 mg/kg/week intravenously for 37 weeks (females) or 25 mg/kg/week subcutaneously for 13 weeks (males).

In an embryo-fetal development study in cynomolgus monkey, no malformations or embryofetal toxicity were observed in fetuses from pregnant cynomolgus monkeys administered lebrikizumab subcutaneously during organogenesis at 15, 45 or 150 mg/kg initial loading dose followed by 5, 15 or 50 mg/kg/week for 4 weeks. The NOAEL for maternal and developmental toxicity was 150/50 mg/kg/week (loading/maintenance doses). Lebrikizumab crossed the placenta in monkeys.

In a PPND study, pregnant cynomolgus monkeys received subcutaneous doses of lebrikizumab during organogenesis to parturition (gestation day {GD} 168) at 45 or 150 mg/kg initial loading dose followed by 15 or 50 mg/kg/week from GD 42 to GD 168 followed by observation of neonates until post-natal day 180. There were no test article related adverse effects on maternal, fetal, or infant parameters during the study. No embryofetal toxicity or malformations, or test article related effects on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age. The NOAEL for maternal and developmental toxicity was 150/50 mg/kg/week (loading/maintenance doses).

No genetic toxicology or carcinogenicity studies were conducted with lebrikizumab. The applicant provided an updated carcinogenicity risk assessment for lebrikizumab in this BLA submission. Weight of evidence from the literature does not raise safety concerns regarding malignancy. There was no evidence of tissue proliferation (i.e., hyperplasia, pre-neoplastic lesions) or immunosuppression in the 9-month intravenous toxicology study in cynomolgus monkeys that received lebrikizumab doses up to 25 mg/kg/week. The overall data suggest that lebrikizumab has low carcinogenic potential. Further studies to assess carcinogenic risk are considered unwarranted.

Lebrikizumab Injection does not contain any novel excipients or excipients of human or animal origin. No issues have been identified with impurities from a Pharmacology/Toxicology perspective.

This BLA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this BLA.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Lebrikizumab had a strong affinity for human IL-13 with a KD of 31 pM and prevented IL-13 from interacting with IL-4Rα, but not IL-13Rα1 and IL-13Rα2. In vitro studies showed that lebrikizumab inhibited IL-13-induced phosphorylation of signal transducer and activator of transcription 6. In an in vivo study, lebrikizumab inhibited IL-13-induced airway inflammation and reduced inflammatory cells, IL-13Rα2 expression and TGFβ1 levels. Lebrikizumab binds cynomolgus monkey IL-13 with a KD of <0.67 pM. Lebrikizumab did not cross-react with mouse or rat IL-13. Cynomolgus monkey is the pharmacologically relevant species for lebrikizumab pharmacology and toxicology evaluation.

No stand-alone safety pharmacology studies were conducted with lebrikizumab. Safety pharmacology parameters were included in the 6- and 39-week intravenous and/or 13-week subcutaneous repeat-dose toxicology studies in cynomolgus monkeys. Repeated administration of lebrikizumab up to 25 mg/kg/week IV or SC had no adverse effects on the evaluated parameters for cardiovascular, respiratory and behavioral effects. ECGs, heart rate, functional, and behavioral developments were assessed for infants in a prenatal and postnatal development study. No lebrikizumab-related effects were observed in offspring to cynomolgus monkey females treated with lebrikizumab up to 150/50 mg/kg/week (loading/maintenance doses) during pregnancy.

An in vitro study was conducted to evaluate the effect of lebrikizumab on the human ether-a-go-go related gene (hERG) ion channel current in human embryonic kidney (HEK) 293 cells transfected with hERG clone. The hERG potassium channel is responsible for the inwardly rectifying potassium current (IKr) in human ventricles. Lebrikizumab was tested at 0.2 and 6.0 mg/mL using a patch-clamp model system. No inhibitory effects on the hERG ion channel current were observed compared to vehicle control at doses up to 6.0 mg/mL in this in vitro hERG assay. An IC_{50} value could not be determined.

5.4. ADME/PK

Note: MILR1444A and TNX-650 are code names for lebrikizumab

Table 1. Summary of the PK/TK Data

Type of Study	Major Findings
Absorption	

Type of Study	Major Findings
Rat Product Comparability Study of MILR1444A Produced from CHO and NS0 Cell Lines (08-0910)	<u>Single dose of 5 mg/kg SC Rat/ CHO</u> $T_{1/2}$: 13.6 days $AUC_{(0-\infty)}$: 1340 µg·day/mL C_{max}: 61.6 µg/mL *CL or CL/F: 3.84* mL/kg/day V_d/F: 73.1 mL/kg <u>Single dose of 5 mg/kg Rat/ NS0</u> $T_{1/2}$: 14.3 days $AUC_{(0-\infty)}$: 1590 µg·day/mL C_{max}: 72.1 µg/mL *CL or CL/F: 3.27* mL/kg/day V_d/F: 64.3 mL/kg
Single Dose Intravenous Pharmacokinetics Study of TNX-650 in Cynomolgus Monkeys (04193)	<u>Female Monkey</u> $T_{1/2}$: 1 mg/kg: 17.2 days 10 mg/kg: 21.7 days 100 mg/kg: 10.4 days AUC_{0-inf}: 1 mg/kg: 400 µg·day/mL 10 mg/kg: 3880 µg·day/mL 100 mg/kg: 21300 µg·day/mL C_{max}: 1 mg/kg: 62.2 µg/mL 10 mg/kg: 216 µg/mL 100 mg/kg: 2040 µg/mL V_d: 1 mg/kg: 26.2 mL/kg 10 mg/kg: 81.3 mL/kg 100 mg/kg: 70.9 mL/kg *CL:* 1 mg/kg: 2.5 mL/day/kg 10 mg/kg: 2.7 mL/day/kg 100 mg/kg: 4.71 mL/day/kg *Dose proportionality:* After single IV administration, the C_{max} increased in a dose-proportional manner over the 100-fold dose range. The AUC_{0-inf} was also dose-proportional over the 1- to 10-mg/kg dose levels but was less than dose-proportional at the 100 mg/kg dose.

Type of Study	Major Findings
TK data from general toxicology studies 6-Week Repeated Intravenous Toxicity Study in Cynomolgus Monkeys/ 07-1510	Following a Single IV Dose Monkey *$T_{1/2}$:* 0.95 mg/kg: 16.7 days 22.57 mg/kg: 23.7 days *$AUC_{0\text{-}inf}$:* 0.95 mg/kg: 304 µg·day/mL 22.57 mg/kg: 9050 µg·day/mL *C_{max}:* 0.95 mg/kg: 23.1 µg/mL 22.57 mg/kg: 530 µg/mL *Vz:* 0.95 mg/kg: 75.1 mL/kg 22.57 mg/kg: 85.1 mL/kg *CL:* 0.95 mg/kg: 3.19 mL/day/kg 22.57 mg/kg: 2.57 mL/day/kg Mean Trough Serum Concentrations *Day 8:* 0.95 mg/kg: 10.2 µg/mL 4.90 mg/kg: 55.2 µg/mL 22.57 mg/kg: 254 µg/mL *Day 29:* 0.95 mg/kg: 31.9 µg/mL 4.90 mg/kg: 164 µg/mL 22.57 mg/kg: 753 µg/mL *Day 43:* 0.95 mg/kg: 40.6 µg/mL 4.90 mg/kg: 213 µg/mL 22.57 mg/kg: 953 µg/mL
13-Week Subcutaneous GLP Toxicity Study of TNX-650 in Monkeys/ 07-1330	Monkey *$T_{1/2}$:* 22.4 days at 5 mg/kg/week SC for 4 weeks *Dose proportionality:* Dose-dependent serum trough concentrations of lebrikizumab were observed during the 13-week dose regimen. *Anti-drug antibodies (ADA):* None
9-Month Intravenous GLP Toxicity Study of TNX-650 in Monkeys with a 3-Month Interim Sacrifice/ 07-1186	Monkey *Accumulation:* Approximately 3-fold based on peak concentrations at Month 9 vs Day 1. *Dose proportionality:* observed across the dose range of 1 to 25 mg/kg. *ADA:* 2

TK data from reproductive toxicology studies A 9-month toxicity and cycling evaluation study of MILR1444A (IV) administered by intravenous injection to sexually mature female Cynomolgus monkeys, with an 8-month recovery period/ 07-1706	<u>Female Monkey</u> *$T_{1/2}$:* 0.05 mg/kg: 19.1 days 1 mg/kg: 18.9 days 25 mg/kg: 18.9 days *AUC_{last}*: 0.05 mg/kg: 695 µg·day/mL 1 mg/kg: 19500 µg·day/mL 25 mg/kg: 438000 µg·day/mL *C_{max}:* 0.05 mg/kg: 6 µg/mL 1 mg/kg: 92.8 µg/mL 25 mg/kg: 2160 µg/mL *Dose proportionality:* Increase in AUC were proportional with increasing dose levels from 0.05 to 25 mg/kg following the last dose. *Accumulation:* Accumulation of lebrikizumab (C_{trough}) was approximately 1.5-fold after repeated administration. *ADA:* 13/30 Corresponding to the NOAEL of 25 mg/kg, a $C_{avg,ss}$ of 1640 µg/mL was calculated using the Day 57 through Day 267 concentration values at steady-state.
A study of the effect of MILR1444A, administered weekly for 13-weeks by subcutaneous injection, on male fertility in Cynomolgus monkeys (Segment I), followed by a 20-week recovery phase/ 10-2290	<u>Male Monkey (Day 84)</u> *$T_{1/2}$:* *5*mg: 15 days 25 mg: 27 days *T_{max}:* *5*mg: 87 days 25 mg: 87 days *$AUC_{84\text{-}91\ days}$* 5mg: 2660 µg·day/mL 25 mg: 9680 µg·day/mL *C_{max}:* 5mg: 1730 µg/mL 25 mg: 3010 µg/mL *Dose proportionality:* Lebrikizumab exposure (C_{max} and AUC) increased with dose in a slightly less than proportional manner and, in general, with accumulation over time. Corresponding to the NOAEL of 25 mg/kg, a $C_{avg,ss}$ of 1230 µg/mL is calculated using the Day 57 through Day 87 concentration values at steady-state.

Embryo-Fetal Development Study of MILR1444A(SC)Administered by Subcutaneous Injection to Pregnant Cynomolgus Monkeys/ 07-1269	<u>Female Monkey (GD 100)</u> *$AUC_{(48-55)}$*: 15/5 mg/kg: 10500 µg·day/mL 45/15 mg/kg: 30500 µg·day/mL 150/50 mg/kg: 100000 µg·day/mL *C_{max}:* 15/5 mg/kg: 250 µg/mL 45/15 mg/kg: 769 µg/mL 150/50 mg/kg: 2620 µg/mL *C_{last}:* 15/5 mg/kg: 18.8 mL/day/kg 45/15 mg/kg: 53.6 mL/day/kg 150/50 mg/kg: 187 mL/day/kg *Dose proportionality:* Lebrikizumab exposure (C_{max} and AUC) in the maternal animals increased in a dose proportional manner. Lebrikizumab concentrations in fetal cord blood at C-section also increased dose-proportionately. *C_{fetal}:* 15/5 mg/kg: 5.57 mL/day/kg 45/15 mg/kg: 17.7 mL/day/kg 150/50 mg/kg: 51.3 mL/day/kg *Ratio of tralokinumab concentrations in fetal and maternal serum:* 15/5 mg/kg: 0.295 45/15 mg/kg: 0.337 150/50 mg/kg: 0.322 *ADA:* Seven monkeys across the lebrikizumab treatment groups were ADA positive; however, only 2 animals, 1 in each of the low and high dose groups, had reduced serum concentrations as a consequence. Corresponding to the NOAEL of 150/50 mg/kg, a $C_{avg,ss}$ of 2041 µg/mL was calculated using all concentration values in the EFD study since there was no discernable change in the peak concentrations over time during the dosing period in the study.
A Study for Effects of MILR1444A on Embryo-Fetal and Pre- and Postnatal Development When Administered Once Weekly for up to 21-Weeks Subcutaneously to Pregnant Cynomolgus Monkeys/ 12-3655	<u>Female Monkey</u> GD: gestational day; LD: lactational day; PND: post-natal day *Mean concentrations:* *GD 42:* 45/15 mg/kg: 534 µg/mL 150/50 mg/kg: 1570 µg/mL

	GD 49: 45/15 mg/kg: 537 µg/mL 150/50 mg/kg: 1520 µg/mL *GD 98:* 45/15 mg/kg: 505 µg/mL 150/50 mg/kg: 1600 µg/mL *GD 133:* 45/15 mg/kg: 564 µg/mL 150/50 mg/kg: 1800 µg/mL *GD 168:* 45/15 mg/kg: 446 µg/mL 150/50 mg/kg: 1830 µg/mL *LD 28:* 45/15 mg/kg: 214 µg/mL 150/50 mg/kg: 585 µg/mL *LD 56:* 45/15 mg/kg: 83 µg/mL 150/50 mg/kg: 254 µg/mL *LD 84:* 45/15 mg/kg: 41.8 µg/mL 150/50 mg/kg: 112 µg/mL *LD 180:* 45/15 mg/kg: 2.19 µg/mL 150/50 mg/kg: 7.44 µg/mL <u>F1 Offspring to Dam Concentration Ratio:</u> *LD/PND 28:* 45/15 mg/kg: 1.72 150/50 mg/kg: 1.29 *LD/PND 56:* 45/15 mg/kg: 22.4 150/50 mg/kg: 32.1 *LD/PND 84:* 45/15 mg/kg: 2.81 150/50 mg/kg: 3.03 *LD/PND 180:* 45/15 mg/kg: 14.1 150/50 mg/kg: 25.8 *Dose proportionality:* Serum lebrikizumab concentrations in maternal animals indicated that exposure was maintained throughout gestation (dosing phase) in a dose-proportional manner, gradually decreased throughout lactation and was still detected in most animals on LD 180. *ADA:* Nineteen maternal animals (7 low dose, 12 high dose) had detectable ADA, and this was associated with lower serum lebrikizumab concentrations in some of these animals from LD 56 on. Mean serum lebrikizumab concentrations in the offspring were variably higher than those

Type of Study	Major Findings
	in the dams at each time point during the lactation/postnatal period (PNDs 28, 56, 84 and 180). Seven offspring, all from ADA positive dams, also had detectable ADA although without consequent impact on lebrikizumab exposure.

5.5. Toxicology

5.5.1. General Toxicology

Study 1: Study title/ number: 9-Month Intravenous GLP Toxicity Study of TNX-650 in Monkeys with a 3-Month Interim Sacrifice/ 07-1186

Key Study Findings

- No mortality or test article-related clinical or ophthalmic findings
- No test article-related effects on ECG parameters, body weight, food consumption, clinical chemistry, hematology, coagulation or urinalysis parameters, peripheral blood immunophenotype, organ weights, or tissue morphology
- The NOAEL was the high dose of 25 mg/kg/week IV.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 1, 5, or 25 mg/kg/week, once weekly
Route of administration: Intravenous injection
Formulation/Vehicle: (b) (4)
Species/Strain: Monkey/Cynomolgus
Number/Sex/Group: 4
Age: 2.5 – 4.5 years
Satellite groups/ unique design: 4/sex/group for 3-month interim sacrifice
Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No mortality during the study

Clinical Signs	No test article-related findings
Body Weights	No test article-related changings
Ophthalmoscopy	No test article-related findings
ECG	No test article-related effects
Hematology	No test article-related changings
Clinical Chemistry	No test article-related changings
Urinalysis	No test article-related changings
Gross Pathology	No test article-related findings
Organ Weights	Absolute and relative uterus weights were significantly decreased for all female treatment groups. The dose-response relationship was flat as decreased mean weights were comparable for all female treatment groups. There were no corresponding histopathological findings.
Histopathology Adequate battery: Yes	No test article-related findings. Based on the histologic characteristics of the reproductive organs, 30/32 females and 28/32 males appeared to be sexually immature. It is likely that variability in relative sexual maturity of individual monkeys may have contributed to the observed differences in uterine weights. Of note, there were no such differences in uterine weights in a subsequent 9-month IV administration study in mature female monkeys.
[Other evaluations]	No test article-related changings

General toxicology; additional studies

Study 2: Study title/ number: Single Dose Intravenous Pharmacokinetics Study of TNX-650 in Cynomolgus Monkeys/ 04193

A single-dose study was conducted to evaluate the tolerability and pharmacokinetics of lebrikizumab (Report 13-1078; non-GLP-compliant). Lebrikizumab was administered as a single IV injection at dose levels of 1, 10, or 100 mg/kg to 2 female cynomolgus monkeys/group and followed by a 42-day observation period. Assessments included mortality, clinical observations, body weight and body weight changes, clinical pathology (24-hour postdose clinical chemistry and hematology), and serum lebrikizumab pharmacokinetics and immunogenicity (ADA).

In general, lebrikizumab exposure increased in a dose-dependent manner. The mean volume of distribution approximated the blood volume. The elimination half-life ranged from 9 to 25 days. There was no mortality and no treatment-related clinical observations. Body weights of all animals remained within normal limits and clinical pathology parameters were generally within historical limits. Elevated serum aspartate aminotransferase activity was noted for 1 mid-dose animal and was considered likely of muscle origin and secondary to injection/sampling procedures. As such, a single lebrikizumab dose of up to 100 mg/kg IV was well tolerated.

Study 3: Study title/ number: 6-Week Repeated Intravenous Toxicity Study in Cynomolgus Monkeys/ 07-1510

Lebrikizumab was administered by IV injection once weekly for 6 weeks (6 doses) to male and female monkeys (3/sex/group; 1 to 2 years of age) at dose levels of 0 (vehicle control: (b) (4)

(b) (4)), 0.95, 4.9, and 22.57 mg/kg at a dose volume of 1 mL/kg (targeted dose levels were 1, 5 and 25 mg/kg and were corrected according to reported dose concentrations in the Certificate of Analysis). Necropsies were performed 1 week following the last dose. Additionally, 2 satellite groups of monkeys (2/sex/group) were given a single IV dose of 0.95 or 22.57 mg/kg to establish the toxicokinetic profile. The high dose level for this study was selected based on prior demonstration of single IV dose tolerability and exposure.

There were no deaths or test article-related adverse clinical or ophthalmic findings, and no adverse effects on ECG parameters, body weight, clinical chemistry, hematology or coagulation parameters, organ weights or tissue morphology. Weights of thyroid/parathyroid glands were statistically significantly lower in males of the mid and high dose groups compared with control group males. There were no correlating histological findings. There were no remarkable changes in peripheral blood immunophenotype (total lymphocytes, mature T cells, helper T cells, cytotoxic T cells, total B cells, natural killer cells, and monocytes). The NOAEL was the high dose of 22.57 mg/kg/week IV.

Throughout the 6-week study, serum trough concentrations of lebrikizumab showed that exposure increased in a dose-proportional manner and accumulated about 4-fold across dose levels. Several animals had low levels of anti-drug antibodies (ADA) with no appreciable impact on exposure. The mean elimination half-life ranged from approximately 17 to 24 days.

Study 4: Study title/ number: 13-Week Subcutaneous GLP Toxicity Study of TNX-650 in Monkeys/ 07-1330

Lebrikizumab was administered by SC injection once weekly for 13 weeks (13 doses) to male and female monkeys (3/sex/group; 2.4 to 3.4 years of age) at dose levels of 0 (vehicle control: (b) (4) 5, and 25 mg/kg at a dose volume of 0.04 or 0.2 mL/kg. A satellite group of monkeys (2/sex) was administered 5 mg/kg SC once weekly for 4 weeks (4 doses) and followed a 10-week administration-free period to extend toxicokinetic and immunogenicity evaluations. Dose levels were selected based on the overall results of the prior 6-week toxicology study (Report 07-1510). Monkeys were necropsied at the end of Week 13, i.e., 1 week after their 13th dose or at the end of the 10-week administration-free period.

There were no deaths, treatment-related adverse clinical signs, or other findings noted during physical or ophthalmic examinations. There were no test article-related adverse effects on ECG parameters, body weight, body weight gain, food consumption, clinical chemistry, hematology, coagulation or urinalysis parameters, organ weights, or tissue morphology. There were no remarkable changes in peripheral blood immunophenotype (total lymphocytes, mature T cells, helper T cells, cytotoxic T cells, total B cells, NK cells, monocytes).

SC injection sites were examined clinically (predose and 3 hours postdose) for the presence of erythema, edema, and other remarkable changes and scored using a modified Draize method. Further, punch biopsies of injection sites were collected for microscopic evaluation from all animals; biopsies were taken from the first and final injection sites at 24 hours postdose, and again from the first used injection site at necropsy. Dermal scores for injection sites identified no dermal irritation in any group. Microscopic evaluation of injection sites, including serial biopsies, revealed minor inflammation and hemorrhage in all dose groups, including controls; this was consistent with expected findings of injection site trauma.

The NOAEL was the high dose of 25 mg/kg/week SC.

Dose-dependent increase in systemic lebrikizumab concentrations were observed throughout the 13-week study and accumulated over time. No lebrikizumab-treated monkey had a positive ADA titer. A mean elimination half-life of about 23 days was determined for the satellite group of monkeys.

It was determined that this 13-week subcutaneous toxicity study conducted with lebrikizumab in cynomolgus monkeys provided an adequate bridge to the 6-week and 9-month intravenous toxicity studies conducted with lebrikizumab in cynomolgus monkeys due to the similar toxicity profiles noted after repeat dose subcutaneous versus intravenous administration.

5.5.2. Genetic Toxicology

Genetic toxicology studies are not applicable to monoclonal antibodies and were not conducted with lebrikizumab based on ICH S6 guidance.

5.5.3. Carcinogenicity

No carcinogenicity studies were conducted with lebrikizumab in any species. The applicant provided an updated carcinogenicity risk assessment for lebrikizumab in this BLA. No significant changes have been made to the original carcinogenicity risk assessment for lebrikizumab which, with additional subsequent information provided by the applicant, was reviewed under IND (b) (4) and discussed with the Executive Carcinogenicity Assessment Committee (ECAC). Upon concurrence from the ECAC, the following comment was conveyed to the Sponsor in an EOP2 meeting dated September 6, 2011: *"We agree that a rodent carcinogenicity study or systematically following the IL-13 KO mouse for 1-2 years is not a required component of the BLA submission. Concurrence was received from the Executive Carcinogenicity Assessment Committee. Subjects in clinical trials should be assessed for potential development of tumors. Post-marketing surveillance or a registry for potential development of tumors might be required. Product labeling should inform patients of potential carcinogenic risks of anti-IL-13 therapy based upon nonclinical and clinical studies with lebrikizumab as well as information from the published scientific literature."*

Weight of evidence from the literature does not raise safety concerns regarding malignancy based on an evaluation of the available literature evidence related to IL-13 inhibition. There was no evidence of tissue proliferation (i.e., hyperplasia, pre-neoplastic lesions) or immunosuppression in the 9-month intravenous toxicology study with cynomolgus monkeys that received lebrikizumab at doses up to 25 mg/kg/week. The overall data suggest that lebrikizumab has low carcinogenic potential. Further studies to assess carcinogenic risk are considered unwarranted.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: A 9-month toxicity and cycling evaluation study of MILR1444A (IV) administered by intravenous injection to sexually mature female Cynomolgus monkeys, with an 8-month recovery period/ 07-1706

Key Study Findings

- No effects on reproductive organs, reproductive hormones or menstrual cycle length
- The NOAEL was the high dose of 25 mg/kg/week IV.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 0.05, 1, or 25 mg/kg/week, once weekly
Route of administration:	Intravenous injection
Formulation/Vehicle:	(b) (4)
Species/Strain:	Monkey/Cynomolgus; age range: 4.8-9.3 years
Number/Sex/Group:	10 female cynomolgus monkeys/group
Satellite groups:	None
Study design:	The purpose of this study was to investigate the effects of lebrikizumab on menstrual cycling and related fertility endpoints in sexually mature female monkeys during 9 months of dosing. This duration and a subsequent treatment-free period were selected given the observation of lower uterine weights in the prior 9-month repeat-dose toxicity study (Study 07-1186; see Section 5.5.1). Monkeys were 4.8 to 9.3 years of age at

	study start, and sexual maturity was confirmed by evidence of menses and ovulation, assessed by vaginal swabs, and reproductive hormone cycling within the 4 months prior to dosing. Fertility assessments included evaluation of menstrual cycle length via daily vaginal swab, ultrasound measurements of uterine area and patterns of reproductive hormones (estradiol and progesterone) during the dosing phase (Days 92 to 131 and 211 to 251) and treatment-free period (Days 448 to 487) compared to the predose phase. Additionally, the study included general toxicity endpoints, including clinical chemistry, hematology, and urinalysis parameters, and complete necropsy. Terminal evaluations focused on weights and histopathology of reproductive, endocrine, and immune system organs.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major findings**
Mortality	No mortality during the study
Clinical Signs	No test article-related findings
Body Weights	No test article-related changings
Hematology	No test article-related changings
Clinical Chemistry	No test article-related changings
Reproductive Hormones	No test article-related changings
Urinalysis	No test article-related changings
Organ Weights	No test article-related changings
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc]*	The ovaries of all animals appeared histologically normal, and all animals had a corpus luteum. No test article-related gross pathology or histopathology findings. Microscopic tissue cysts present in the uterus, cervix, parathyroid, thyroid and/or thymus were uncertain related to test article and not considered adverse as such cysts do not result in clinical signs or other detectable abnormalities when they occur incidentally in the cynomolgus monkey.

Lebrikizumab exposure (C_{max} and AUC) increased in a dose proportional manner and indicated accumulation over time. The mean elimination half-life was about 19 days. Thirteen of the 30 lebrikizumab-treated monkeys were ADA positive and, of these, reduced serum lebrikizumab concentrations were consequently observed in 4 monkeys in the low dose group and 1 monkey

in the high dose group. The NOAEL was 25 mg/kg/week based on the results from this study, which resulted in a mean AUC of 438000 µg·day/mL and a mean C_{max} of 2160 µg/mL on Day 259. A $C_{avg,ss}$ of 1640 µg/mL is calculated using the Day 57 through Day 267 concentration values at steady-state in this study.

Study title/ number: A study of the effect of MILR1444A, administered weekly for 13-weeks by subcutaneous injection, on male fertility in Cynomolgus monkeys (Segment I), followed by a 20-week recovery phase/ 10-2290

Lebrikizumab was administered subcutaneously to sexually mature male cynomolgus monkeys (6/group; age range: 4-7 years) at 0 (vehicle control; (b) (4) at pH(b) (4)), 5, or 25 mg/kg/week for 13 weeks. Four animals per group were necropsied at the end of treatment period (Day 88) and two/group at the end of a 20-week recovery period (Day 226).

All animals survived to their scheduled necropsy. No lebrikizumab related adverse effects were noted for clinical signs, physical and neurological examinations, body weight, food consumption, hematology, clinical chemistry, organ weights, macroscopic and microscopic pathology as well as male reproductive parameters (including epididymal sperm motility, flow cytometric analyzed testicular tissues, testicular size, or semen evaluation, ejaculate weight, sperm count, sperm motility, and morphology). The NOAEL was 25 mg/kg/week based on the results from this study, which resulted in a mean AUC of 9680 µg·day/mL and a mean C_{max} of 1480 µg/mL on Day 84. A $C_{avg,ss}$ of 1230 µg/mL is calculated using the Day 57 through Day 87 concentration values at steady-state in this study.

Embryo-Fetal Development

Study title/ number: Embryo-Fetal Development Study of MILR1444A(SC)Administered by Subcutaneous Injection to Pregnant Cynomolgus Monkeys/ (b) (4) 148-002

Key Study Findings

- No test article related adverse effects on maternal or embryofetal parameters.
- No embryofetal toxicity or malformations, or test article related effects on morphological or functional development were observed.
- The NOAEL for maternal and developmental toxicity was 150/50 mg/kg/week (loading/maintenance doses).

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	One subcutaneous loading dose of 0, 15, 45, or 150 mg/kg on gestation day (GD) 20 followed by 0, 5, 15 or 50 mg/kg/week, once weekly from GD 27 to GD 48.
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	(b) (4) , pH 5.7
Species/Strain:	Monkey/Cynomolgus; age range: 3.75 – 8.08 years
Number/Sex/Group:	12 pregnant cynomolgus monkeys/group
Satellite groups:	None
Study design:	Pregnancy was diagnosed by ultrasound examination on Day 18 of presumed gestation and confirmed by monkey chorionic gonadotropin (mCG) test. During gestation, the adult females (dams) were monitored for clinical signs (twice daily), changes in food consumption (once daily), body weight (at GD1, GD20 and weekly thereafter until GD 100), and pregnancy status and fetal viability, heart beat and size (via ultrasound: GDs 25, 30, 40, 51, 60, 70, 80 and 90). Blood samples from the adult females were collected at various time points throughout the study for clinical pathology, toxicokinetic (TK) and ADA analyses. Amniotic fluid from the amniotic cavity and blood from the umbilical artery of each fetus were also collected at cesarean section. All pregnant animals from each dose group underwent cesarean sectioning on GD 100 (except for No. 10310) or GD 101 (No. 10310), and the fetuses were evaluated. Fetuses removed at cesarean sectioning were assessed for viability (alive or dead) and the following examinations were conducted: external examination, sex, and body and placental weight of fetus, visceral examination of fetus, and skeletal examination of fetus.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No test article related effects
Clinical Signs	No test article related effects
Body Weights	No test article related effects
Necropsy findings Cesarean Section Data	No test article related effects
Necropsy findings Offspring	No test article related effects

Lebrikizumab exposure (C_{max} and AUC) in the maternal animals increased in a dose proportional manner. Seven monkeys across the lebrikizumab treatment groups were ADA Positive; however, only 2 animals, 1 in each of the low and high dose groups, had reduced serum concentrations as a consequence. Lebrikizumab concentrations in fetal cord blood at C-section also increased dose-proportionately, and mean fetal-to-maternal concentration ratios were approximately 0.3 across the groups. The NOAEL was 150/50 mg/kg/week based on the results from this study, which resulted in a mean maternal AUC of 100000 µg·day/mL and a mean maternal C_{max} of 2620 µg/mL on gestation day 100. A maternal $C_{avg,ss}$ of 2041 µg/mL is calculated using all concentration values in the EFD study since there was no discernable change in the peak concentrations over time during the dosing period in the study.

Prenatal and Postnatal Development

Study title/ number: A Study for Effects of MILR1444A on Embryo-Fetal and Pre- and Postnatal Development When Administered Once Weekly for up to 21-Weeks Subcutaneously to Pregnant Cynomolgus Monkeys/ 12-3655

Key Study Findings

- No test article related adverse effects on maternal, fetal, or infant parameters.
- No embryofetal toxicity or malformations, or test article related effects on morphological, functional, or immunological development were observed in the offspring from birth through 6 months of age.
- The NOAEL for maternal and developmental toxicity was 150/50 mg/kg/week (loading/maintenance doses).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	One subcutaneous loading dose of 0, 45, or 150 mg/kg on gestation day (GD) 35 followed by 0, 15 or 50 mg/kg/week, once weekly from GD 42 until parturition (approximately GD 168).
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	(b) (4) , pH 5.7
Species/Strain:	Monkey/Cynomolgus; age range: 4 – 7 years
Number/Sex/Group:	16 pregnant cynomolgus monkeys
Satellite groups:	None
Study design:	Pregnancy was determined by ultrasound examination on Day 32 of presumed gestation. During gestation, the adult females (dams) were monitored for clinical signs (twice daily), physical examination (body temperature/ pulse oximetry) (GD 32), changes in food consumption (once daily), body weight (at GD1, GD32 and weekly thereafter until PND 180), and pregnancy status including embryo-fetal development status (via ultrasound, Crown-rump: GDs 32, 39 and 46; Head width: GDs 46, 60, 74, 88, 102, 116, and 130; Femoral length: GDs 74, 88, 102, 116, and 130; Heart rate: GDs 60, 74, 88, 102, 116, 130, 144, 158, and 172). Blood samples from the adult females were collected at various time points throughout the study for clinical pathology, toxicokinetic (TK) and ADA analyses. The pregnant females were allowed to deliver their offsprings by natural birth. For approximately 6 months postpartum/postnatal, the adult females and offsprings were evaluated for changes in clinical signs, body weight, and/or other parameters. Offsprings underwent skeletal examination (PND 7), morphological development assessments (PNDs 28, 91 and 175), functional development assessment (PND 35), behavioral development assessment (PNDs 28 and 175), fundoscopic examination (once between PNDs 168 and 174), and electrocardiography (once between PNDs 168 and 174). Blood samples from the offsprings were collected at various time points throughout

	the study for clinical pathology, toxicokinetics and ADA formation analyses. Postnatal immunological assessments were conducted, including peripheral blood immunophenotyping (PNDs 70 and 180) and T-cell dependent antibody response to KLH (PND 147). The offsprings were euthanized on approximately PND 180. An external and visceral exam and full necropsy were conducted on all infants, including macroscopic tissue examinations and bone marrow examinations. A subset of organs/tissues were collected, weighed, and preserved, and selected tissues were evaluated for histopathology. Offspring were maintained with their mothers for the entire postnatal period, and the mothers were released from the study once their offspring was no longer on study.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F0 Dams	No mortality. No test article-related changes were observed in clinical signs, gestation length, body weight, food consumption, body temperature, pulse oximetry, urinalysis, hematology, or serum chemistry in dams during the gestation or lactation period. No test article-related changes were observed in fetal growth or fetal heart rate. No test article-related abortion, embryo/fetal death, or stillbirth occurred.
F1 Generation	The numbers of live offspring in the lebrikizumab groups were comparable to that in the control group. No test article-related changes were noted in clinical signs including mortality, body weight, external or skeletal findings, morphological development, hematology, serum chemistry, peripheral blood immunophenotyping, immunocompetence (response to KLH), functional development, observation of dam-offspring interaction, ophthalmology, electrocardiography, bone marrow examination, gross pathology, organ weights, or histopathology.
F2 Generation	Not evaluated.

Juvenile Animal Toxicity Study

The PPND study conducted in cynomolgus monkeys to assess the effects of lebrikizumab on pre- and postnatal embryo-fetal and infant development revealed no test article-related effects in infant monkeys up to six months of age (see above). Lebrikizumab was detected in the milk of lactating cynomolgus monkeys. In addition, the adolescent phase was covered by the repeat dose studies in cynomolgus monkeys with approximate ages at start: 1-2 years in 6-week intravenous study; 2.4-3.4 years in 13-week subcutaneous study and 2.5-4.5 years in 9-month intravenous study. Based on animal age and study findings in the repeat dose toxicity studies and the PPND study in monkeys, it has been determined that no additional juvenile animal toxicology studies are needed for this product.

5.5.5. Other Toxicology Studies

Ex Vivo Tissue Cross-Reactivity

The tissue binding specificity of lebrikizumab was evaluated in a comprehensive panel of human and cynomolgus monkey tissues in separate studies.

In each study, lebrikizumab was applied to tissue cryosections (3 human and 2 monkey donors/tissue, where available) at concentrations of 5 µg/mL (optimal concentration) or 40 µg/mL, based on prior method development. Lebrikizumab binding was assessed immunohistochemically using biotinylated lebrikizumab and a direct avidin-biotin complex immunoperoxidase staining procedure. Appropriate controls were included in each study to validate the adequacy of tissue sections for immunohistochemistry and to assist in the determination of specificity of lebrikizumab binding.

No specific lebrikizumab staining was observed in any human or cynomolgus monkey tissues. This result is consistent with the expected outcome for an antibody that cross-reacts with a soluble antigen.

Excipients and Impurities

Lebrikizumab Injection does not contain any novel excipients or excipients of human or animal origin.

None of the impurities in the biologic product cause safety concerns.

Toxicology studies in cynomolgus monkeys were conducted using either Chinese hamster ovary (CHO) cell-derived toxicology lots that were characterized using contemporary analytical methods (13-week male fertility and PPND), similar to CHO cell-derived clinical and commercial lots, or using murine myeloma (NS0) cell-derived toxicology lots that were characterized using older methods. Despite these differences, drug substance purity and impurity levels appeared overall to be similar across toxicology lots made from either cell line based on the data provided by the applicant and, as noted above, lebrikizumab exposures in monkeys were generally similar across studies. Furthermore, in rats, PK parameters were comparable following a single dose of lebrikizumab derived from each cell line (See Section 5.4).

On this basis, purity and impurity acceptance criteria (specifications) for lebrikizumab drug substance and drug product are justified by the overall nonclinical toxicity profile established for lebrikizumab toxicology lots derived from either cell line.

Extractables/Leachables

Description of Container Closure System for Drug Substance

Lebrikizumab bulk drug substance is (b) (4)

Safety: Extractables Study

An extractables study of the drug substance container closure system (CCS) was designed to detect, identify and semi-quantitate chemical entities under exaggerated conditions to establish a comprehensive extractables profile and to understand which leachables may have the potential to migrate into the drug substance under typical-use conditions for human health risk assessment. The container and (b) (4) were directly examined for volatile organic compounds (VOCs) using Headspace Gas Chromatography-Mass Spectrometry (headspace GC-MS). After extraction, the samples were analyzed for semi-volatile organic compounds (SVOCs) using Direct Injection Gas Chromatography-Mass Spectrometry (GC-MS), non-volatile organic chemical entities (NVOCs) using High Performance Liquid Chromatography-Photodiode Array-Mass Spectrometry (HPLC-PDA-MS) and elemental impurities using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) or Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES). The container and the (b) (4) were evaluated for extractables including those recommended for risk assessment in ICH Q3D (R1). Three of the aqueous (b) (4) container extracts were analyzed for elemental extractables by ICP-MS. For the (b) (4) ICP-OES data from the supplier's study ((b) (4)) was included in the assessment.

Analytical Evaluation Threshold

The analytical evaluation threshold (AET) is defined as the concentration above which peaks (leachables) need to be identified, quantitated and toxicologically assessed. The AET is derived from the safety concern threshold (SCT) which is the threshold at or below which a leachable would have a dose so low as to present negligible safety concerns for carcinogenic and noncarcinogenic toxic effects. The applicant proposed a SCT of (b) (4) µg/dose. The recommended clinical dose is an initial dose of 500 mg at Week 0 and Week 2, followed by 250 mg once every two weeks. Therefore, the proposed SCT of (b) (4) µg/dose is acceptable from a Pharmacology/ Toxicology perspective based on the proposed dosage regimen and ICH M7 (R1): *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.* The AET for lebrikizumab DS is therefore (b) (4) µg/mL based on a SCT of (b) (4) µg/dose and the maximum recommended human dose of 500 mg (4.0 mL). For risk assessment of the extractables, the AET is divided by the potential leachable concentration to determine

the margin of safety (MOS). A MOS >1 is considered acceptable.

Volatile Organic Chemical Extractable Results

Several VOCs were reported from the container and the (b) (4) Under the conservative assumptions set by the applicant, all concentrations for these VOC extractables are well-below the lebrikizumab AET ((b) (4) µg/mL). None of the extractable VOC are of toxicological concern as potential leachables in lebrikizumab drug substance.

The SVOC and NVOC extractables Results

The SVOC and NVOC extractables reported ≥ (b) (4) µg/mL in the aqueous buffers or product simulant solutions included in the lebrikizumab drug substance human health safety assessment are summarized in the following table. None of the extractable SVOC and NVOC are of toxicological concern as potential leachables in lebrikizumab drug substance.

Table 2. Margin of Safety for (b) (4) SVOC, NVOC Potential Leachables

Component (extract)	Extractables	Extractable Concentration (µg/mL)	Potential Leachable Concentration (µg/mL)	AET[a] (µg/mL)	MOS[b]
(b) (4) (water)	(b) (4)				35[f]
(b) (4) (simulant 2)					55
(b) (4) (citrate buffer)					230
					2200
					1100
					3200
					3700

[a] Analytical Evaluation Threshold (AET) was derived by a toxicologist.
[b] MOS = Margin of Safety = AET (µg/mL)/Potential Leachable (µg/mL); MOS are rounded down to be conservatively protective.

(b) (4)

[f] MOS is underestimated for this Q2W to Q4W dosing regimen because the AET is derived from an ADI that is protective for chronic, daily exposure.

Source: BLA 761306, Section 3.2.S.6 Container Closure System.

Elemental Impurities

Container and (b) (4) extracts were analyzed by ICP-MS for elemental impurities including those necessary for risk assessment for parenteral products per ICH Q3D. All reported elements are assessed relative to their permitted daily intake (PDE) limits that were either established by a toxicologist or published in ICH Q3D. No elements were reported > (b) (4) ng/mL in the extracts of the container. The calculated margins of safety for the reported elements were all significantly greater than one, as summarized in the following table.

Table 3. Assessment of (b) (4) Elemental Extractables

Potentially Leachable Element	Reported Extractable (µg/cm²)	Potential Leachable Concentration[a] (µg/mL)	Potential Exposure as Leachable[b] (µg)	Parenteral PDE[c] (µg)	MOS[d]
(b) (4)					1900
					300,000
					2,500,000
					350,000
					170,000
					720
					200,000
(b) (4)					

[b] Potential Exposure = Potential Leachable concentration multiplied by the maximum lebrikizumab DS dose, 4 mL.

[c] Permitted Daily Intake limits were provided by a toxicologist. These limits are considered conservative comparators for intermittent (weekly) exposure. Since upper tolerable parenteral limits are difficult to discern for (b) (4) mcg/day is used as default.

[d] MOS = Margin of Safety = PDE (µg/day)/Potential Leachable (µg/day); Margins of Safety were rounded down to be conservative.

Source: BLA 761306, Section 3.2.S.6 Container Closure System.

Safety: Leachables Stability Study

A leachables study for two lots of lebrikizumab drug substance is being conducted concurrently with the process validation stability studies. Exposure to organic potential leachables at a concentration at or less than (b) (4) µg/mL would not be of toxicological concern for human health. The reporting limits for the leachables study chromatographic methods were

conservatively set at (b) (4) µg/mL (b) (4) the AET.

For the leachables stability study, the drug substance samples are stored for up to (b) (4) months at the long-term (b) (4) °C). For accelerated leachables stability testing, additional samples are stored inverted and upright for up to (b) (4) months at (b) (4) °C prior to analysis.

Leachables Study Results – VOC, SVOC and NVOC

The long-term study of samples stored in the (b) (4) condition is on-going. No leachables have been reported by any of the analytical methods in either drug substance batch for 0, 1 and 3 months.

In the on-going accelerated leachables study, no leachables have been reported in either drug substance batch for 1 and 3 months.

Elemental Analysis

Inductively coupled plasma methods with optical emission spectrometry and mass spectrometry detectors were developed for lebrikizumab to evaluate the drug substance for many leachable elements that may arise from the CCS and other elements recommended for risk assessment of parenteral products per ICH Q3D. The elements permitted concentrations for lebrikizumab and the reporting limits are summarized in the following table.

Table 4. ICP Methods for Elemental Analysis of Lebrikizumab Drug Substance

Method	Element	ICH Q3D Classification	PDE[a] (µg/day)	Permitted Concentration[b] (µg/g)	Reporting Limit[c](µg/g)
ICP-OES	(b) (4)	1			(b) (4)
		1			
		2A			
		2A			
		2B			
		3			
		3			
		1			
		1			
		2A			
		2B			
		3			
		3			
		3			
		NA			
		3			
		3			
		NA			
		2B			
		NA			
		NA			

Method	Element	ICH Q3D Classification	PDE[a] (µg/day)	Permitted Concentration[b] (µg/g)	Reporting Limit[c](µg/g)
ICP-OES	(b) (4)	NA			(b) (4)
		NA			
		NA			
		NA			
ICP-MS		NA			

Abbreviations: ICP-OES = inductively coupled plasma-optical emission spectrometry; ICP-MS = inductively coupled plasma-mass spectrometry; NA = not applicable.

[a] Permitted Daily Exposure (PDE) limits for most elements are provided in ICH Q3D or by Lilly Toxicologists.

[b] Permitted Concentration = PDE (b) (4) g maximum dose. The maximum dose of 4 mL is multiplied by the DS density to determine the mass of the maximum dose (4 mL * (b) (4) g/mL = (b) (4) g). Permitted concentrations are rounded down to be conservatively protective.

[c] The ICP-OES method reporting limit units are µg/g; The ICP-MS reporting units are µg/mL.

Source: BLA 761306, Section 3.2.S.6 Container Closure System.

The elemental analysis results for the two PV batches of lebrikizumab stored in the (b) (4) are summarized in the following two tables.

Table 5. ICP Results Lebrikizumab Drug Substance in (b) (4) Batch S3137160

Elements	Reporting Limit[a]	Time Point (Months)						
		0	2	12	24	36	48	60
(b) (4)				--	--	--	--	--
				--	--	--	--	--
				--	--	--	--	--
				--	--	--	--	--
				--	--	--	--	--
				--	--	--	--	--
				--	--	--	--	--

Abbreviations: "- -" = per study protocol, not yet tested; <RL = none detected above the reporting limit.

[a] The ICP-OES method reporting limit units are µg/g; The ICP-MS reporting units are µg/mL.

Source: BLA 761306, Section 3.2.S.6 Container Closure System.

Table 6. ICP Results Lebrikizumab Drug Substance in (b) (4) Batch S3137161

Elements	Reporting Limit[a]	Time Point (Months)					
		2	12	24	36	48	60
(b) (4)			--	--	--	--	--
			--	--	--	--	--
			--	--	--	--	--
			--	--	--	--	--
			--	--	--	--	--
			--	--	--	--	--
			--	--	--	--	--
			--	--	--	--	--

Abbreviations: "- -" = per study protocol, not yet tested; <RL = none detected above the reporting limit.
[a] The ICP-OES method reporting limit units are µg/g; The ICP-MS reporting limit units are µg/mL.

Source: BLA 761306, Section 3.2.S.6 Container Closure System.

(b) (4) were reported in both batches of lebrikizumab stored in the (b) (4) at levels that are of no toxicologic concern.

Elemental Leachables Safety Assessment

All reported elements are assessed relative to the permitted daily exposure (PDE) limits, which are acceptable from a Pharmacology/Toxicology perspective based on available data, the recommended human dosing regimen and ICH Q3D guidance document. The potential exposure for the reported elements is conservatively based on the assumption that the leachables concentration in the (b) (4) would be present at the same concentration in the (b) (4). Results reported in terms of the lebrikizumab drug substance mass were multiplied by the density ((b) (4) g/mL). Then the potential exposure (µg/dose) was determined by multiplying the leachable concentrations (µg/mL) by the maximum DS dose volume (4 mL). For human health risk characterization, each PDE is divided by the estimated potential exposure to determine the margin of safety (MOS). A MOS >1 is considered acceptable.

The maximum results for the lebrikizumab samples stored in the (b) (4) are assessed for Safety of the three elements in the following table.

Table 7. Lebrikizumab (b) (4) Elemental Leachables – Human Health Risk Assessment

Batch	Time Point	Leachable Element	Maximum Result	Patient Exposure[a] (µg)	Parenteral PDE[b] (µg)	MOS[c]
S3137160, S3137161	2 months	(b) (4)				110
S3137160	2 months					790
S3137160	2 months					130

[a] The reported concentrations of (b) (4) were multiplied by the DS density ((b) (4) g/mL). Then the concentrations (µg/mL) of each element were multiplied by the maximum lebrikizumab 4 mL dose volume to calculate the patient exposure.
[b] Permitted Daily Intake (PDE) values are considered conservative comparators for intermittent exposure. Parenteral PDE values provided by Toxicologists.
[c] Margins of Safety (MOS) were calculated by dividing the PDE by the Patient Exposure and were rounded down to be conservatively protective.
(b) (4)

Source: BLA 761306, Section 3.2.S.6 Container Closure System.

The assessment of these results confirm the safety of the leachable elements for the lebrikizumab drug substance stored in the (b) (4).

Leachables Study Conclusion

No VOC, SVOC, or NVOC leachables have been reported through three months of storage in the accelerated and (b) (4) study conditions. No leachable elements of toxicological concern have been reported in the first two months of the study. The leachables study results, together with the results from the corresponding routine stability studies, demonstrate the safety and compatibility of the (b) (4) CCS for the lebrikizumab drug substance.

The same approaches for drug substance were used for the container closure system (CCS) for the drug product which include a pre-filled syringe with needle safety device (PFS-NSD) or an autoinjector (AI). The proposed safety concern threshold (SCT), analytical evaluation threshold (AET) and permitted daily intake (PDE) limits are the same as used for drug substance. There are no safety concerns with the identified extractables and leachables for the PFS-NSD or the AI from a Pharmacology/Toxicology perspective based on the results from the extractables and leachables studies for the PFS-NSD and the AI and safety assessments of the identified extractables and leachables.

6 Clinical Pharmacology

6.1. Executive Summary

The applicant is seeking the approval of EBGLYSS [generic name: Lebrikizumab (LY3650150)] for the treatment of adults and adolescents 12 years of age or older with moderate-to-severe atopic dermatitis (AD). The clinical pharmacology of Lebrikizumab has been evaluated in a total of 13 clinical studies (six phase 1, three phase 2, and 4 phase 3 trials), and efficacy and safety were evaluated in 3 pivotal phase 3 trials. The phase 3 AD studies included adults and adolescents (aged 12 to less than 18 years who weigh at least 40 kg), while the phase 1 and 2 studies included adults only. There were data from 304 adolescents in the population pharmacokinetics (PopPK) analysis.

Lebrikizumab has dose-proportional pharmacokinetics (PK) with dose -proportional increase in exposure across IV doses of 0.1 to 5.0 mg/kg and SC doses of 37.5 to 500 mg in patients with AD or in healthy volunteers. No target-mediated drug disposition was observed. Following the 500 mg loading doses at Week 0 and Week 2, steady-state serum concentrations were achieved with the first 250 mg Q2W dose at Week 4. Based on a population PK analysis, the values of ($C_{max,ss}$), ($C_{avg,ss}$), and ($C_{trough,ss}$) following the 250 mg Q2W subcutaneous (SC), dose in patients with AD were 108 µg/mL, 100 µg/mL, and 87 µg/mL, respectively. The $C_{max,ss,}$ the $C_{avg,ss,}$ and the $C_{trough,ss}$ following the 250 mg Q4W SC dose in patients with AD were 63 µg/mL, 51 µg/mL, and 36 µg/mL, respectively. Following a single SC 250 mg dose of lebrikizumab, T_{max} was approximately 7 to 8 days post dose. The absolute bioavailability for a subcutaneous dose was around 86%. Based on a population PK analysis, the total volume of distribution at steady-state was around 5.14 L, clearance was 0.154 L/day and was independent of dose. The mean elimination half-life was around 24.5 days.

Age, sex, race, injection site location, disease state (AD versus healthy), and markers of renal function (eGFR) did not have a significant effect on the PK of lebrikizumab. Body weight was identified as a significant covariate on lebrikizumab PK. Lebrikizumab trough concentrations were slightly lower (C_{avg} 26%) in subjects with higher body weight. Mean lebrikizumab concentrations were 17% to 21% higher for adolescents compared with adults, when administered with the same dosing regimen. Exposure-response data suggests that no dose adjustment is needed based on body weight.

No clinical studies evaluating the drug interaction potential of lebrikizumab were conducted.

No apparent dose-response with EASI outcomes was observed among the 2 doses (250 mg Q2W and Q4W) assessed in studies KGAB and KGAC. Based on the phase 2b dose ranging study, similar efficacy (efficacy appears to reach at plateau) across dose groups was observed. Among the dose groups, lebrikizumab dose of 250 mg Q2W and 250 mg Q4W appeared to achieve the

most favorable benefit-risk profile and these doses were selected to be further evaluated in the phase 3 trials.

The results from the phase 3 studies (Study KGAB, Study KGAC and Study KGAD) demonstrated that treatment with lebrikizumab 250 mg Q2W through Week 16, followed by Q2W and Q4W maintenance dosing regimens provided improvements compared to placebo across numerous clinically relevant measures of efficacy in the treatment of moderate-to-severe atopic dermatitis patients. There were no meaningful efficacy differences between Q2W and Q4W maintenance dosing regimens. See section 8.1 and 8.2 for detailed assessment of efficacy and safety.

Treatment emergent antibodies to lebrikizumab developed in 4/145 (2.8%) of subjects treated with lebrikizumab 250 mg every 2 weeks followed by 250 mg every four weeks during the 12-month treatment period in lebrikizumab studies. All of these antibodies were neutralizing and of low titer. Overall, the small number of subjects who were positive for antibodies to lebrikizumab (total n=4) limits a definitive conclusion of the effect of immunogenicity on lebrikizumab PK, efficacy and safety.

Recommendations
The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology information submitted under BLA 761306 and finds the BLA approvable, pending resolution of the CMC manufacturing site inspection issues in a subsequent review cycle. The applicant proposed maintenance dose of (b) (4) (refer to section 6.3.2 for more information).

Post marketing requirement/Post marketing commitment

The Pediatric Research Equity Act (PREA) PMR studies need to be completed. Please refer to section 10 for more details.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Lebrikizumab steady-state exposure following either a subcutaneous dose of 250 mg every 2 weeks or every 4 weeks in patients with atopic dermatitis are presented in Table 6.2.1.1. Lebrikizumab exposure increases dose-proportionally over a subcutaneous dose range of 37.5 to 500 mg. Lebrikizumab steady state is achieved at week 4 following administration of the loading doses of 500 mg at Week 0 and Week 2.

Table 8. Lebrikizumab-lbkz Steady-State Exposure Following Subcutaneous Administration in Patients with Atopic Dermatitis

Lebrikizumab-lbkz Dosage[a]	C_{max}	C_{avg}	C_{trough}
250 mg every 2 weeks	108 mcg/mL	100 mcg/mL	87 mcg/mL
250 mg every 4 weeks	63 mcg/mL	51 mcg/mL	36 mcg/mL

C_{max} = Maximum concentration, C_{avg} = Average concentration, C_{trough} = Trough concentration
a Following approved recommended loading doses

Absorption
Following a single subcutaneous 250 mg dose of lebrikizumab, peak serum concentrations were achieved approximately 7 to 8 days post dose. The absolute bioavailability for a subcutaneous dose was approximately 86%.

Injection site locations did not influence the absorption of lebrikizumab-lbkz.

Distribution
The lebrikizumab steady-state volume of distribution is 5.14 L.

Metabolism/Elimination
Lebrikizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

The lebrikizumab half-life was 24.5 days and clearance was 0.154 L/day. Lebrikizumab exhibits linear elimination that is independent of dose.

Specific Populations
Age, Sex, Race
Age, sex, or race did not have a significant effect on the pharmacokinetics of lebrikizumab.

Weight
Lebrikizumab trough concentrations were lower in subjects with higher body weight.

Patients with Renal or Hepatic Impairment
Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the pharmacokinetics of lebrikizumab have not been conducted. Lebrikizumab is a monoclonal antibody and it is not expected to undergo significant hepatic or renal elimination. No clinically significant differences in the pharmacokinetics of lebrikizumab were observed in patients with mild or moderate renal impairment.

Drug Interaction Studies
An effect of lebrikizumab on the PK of co-administered medications has not been studied.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosage of EBGLYSS is 500 mg (two 250 mg injections) at Week 0 and Week 2, followed by 250 mg (one injection) every 2 weeks (b) (4) Week 16 or later, when adequate clinical response is achieved. The maintenance dose is EBGLYSS 250 mg every 4 weeks.

Therapeutic Individualization

Intrinsic factors were not found to have a clinically meaningful effect on lebrikizumab PK in moderate-to-severe atopic dermatitis patients. Therefore, no dose adjustment is necessary for these factors.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Review Issues	**Recommendations and Comments**
Mechanism of Action	Lebrikizumab is an IgG4 monoclonal antibody (MAb) that binds to interleukin (IL)-13. Lebrikizumab inhibits IL-13-induced responses including the release of proinflammatory cytokines, chemokines and IgE. Lebrikizumab-bound IL-13 can still bind IL-13Rα2 allowing subsequent internalization and natural clearance of IL-13.
Active Moieties	Lebrikizumab is an IgG4 monoclonal antibody (MAb) and it is the active moiety.
General Information	
Bioanalysis	Lebrikizumab serum concentrations were measured using validated enzyme-linked immunosorbent assay (ELISA).
Healthy Volunteers vs. Patients	No significant effects of disease state [AD (N=1326) versus healthy (N=281)] were identified in the PopPK analysis.
Drug exposure at steady state following the therapeutic dosing regimen	Following the 500-mg loading doses at Week 0 and Week 2, steady-state serum concentrations were achieved with the first 250 mg Q2W dose at Week 4. For participants who switch from 250 mg Q2W to 250 mg Q4W at some point during treatment, the new lower steady-state concentrations are expected to be reached after 3 doses, or 12 weeks on Q4W dosing.
Maximal tolerated dose or	In clinical pharmacology studies under this BLA, the PK of

exposure	lebrikizumab was assessed at following dose range: • IV doses over a range of 0.1 to 5 mg/kg, and • SC doses over a range of 37.5 to 375 mg.
Dose Proportionality	Lebrikizumab exposure was dose proportional over a dose range of 0.1 to 5 mg/kg when administered via IV route in the single-ascending dose Study KGBB. In the PopPK analysis that included SC data over a dose range of 37.5 to 500 mg, a PK model with linear clearance best described the data. Therefore, the exposure of lebrikizumab is dose proportional and the clearance is linear with no target-mediated drug disposition nor any change in clearance over time.
Absorption	
Bioavailability	The absolute bioavailability for a subcutaneous dose was approximately 86%.
t_{max}	The median t_{max} was 7 to 8 days after a single SC dose.
Site of injection	Similar PK exposure parameters across injection sites and device type [Autoinjector (AI) versus Pre-Filled Syringe with Needle Safety Device (PFS-NSD)]
Distribution	
Volume of Distribution	The central and peripheral volume of distribution estimates were 3.86 L and 1.28 L, respectively, in the PopPK analysis.This indicates a total volume of distribution at steady state of 5.14 L.
Metabolism	
Primary metabolic pathway(s)	Lebrikizumab is a mAb and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs.
Elimination	
Mean Terminal Elimination half-life	The mean half-life of lebrikizumab was approximately 24.5 days in the PopPK analysis.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The 3 pivotal trials consist of 2 monotherapy Studies, KGAB (ADvocate 1) and KGAC (ADvocate 2), and 1 combination study with low-to-mid potency TCS, Study KGAD (ADhere). All three trials assessed the primary endpoint, the proportion of subjects who achieved an IGA score of 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline at Week 16. Other evaluated outcomes at Week 16 included the proportion of subjects with EASI-75 and EASI-90, and improvement in itch severity as defined by a reduction of at least 4 points on an 11-point Pruritus NRS. ADvocate 1 and ADvocate 2 also evaluated the maintenance and durability of response through Week 52.

These clinical trials met their primary endpoint and demonstrated efficacy compared to placebo (43% vs 13% for IGA 0 or 1 (ADvocate 1), 33% vs 11% for IGA 0 or 1 (ADvocate 2), and 41% vs

22% for IGA 0 or 1 (ADhere); and 59% vs 16% for EASI-75 (ADvocate 1), 52% vs 18% for EASI-75 (ADvocate 2), and 70% vs 42% for EASI-75 (ADhere). Safety for lebrikizumab was based on the adverse event profiles in these clinical trials, and the main concern was conjunctivitis. Most cases of conjunctivitis and keratitis were mild or moderate in severity and recovered or resolved without treatment interruption or discontinuation. Injection site reactions were reported by 2.6% of the EBGLYSS group and 1.5% of the placebo group in the first 16 weeks of the monotherapy trials. Incidence of injection site reactions declined with continued treatment. Please refer to the section 8.1 and 8.2 for more details on efficacy and safety.

The results from these phase 3 studies (Study KGAB, and Study KGAC) demonstrated that treatment with lebrikizumab 250 mg Q2W through Week 16, followed by Q2W and Q4W maintenance dosing regimens provided improvements compared to placebo across numerous clinically relevant measures of efficacy in the treatment of moderate-to-severe atopic dermatitis patients. There were no meaningful efficacy differences between Q2W and Q4W maintenance dosing regimens. An acceptable safety profile was also observed with no meaningful differences between the Q2W and Q4W maintenance dosing regimens.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dose "500 mg (two 250 mg injections) at Week 0 and Week 2, followed by 250 mg (one injection) every 2 weeks (b) (4) Week 16 or later, when adequate clinical response is achieved. The maintenance dose is EBGLYSS 250 mg every 4 weeks" based on the data obtained from phase 3 trials is acceptable.

The dose selection was informed by the phase 2 study KGAF.
This study showed a clear dose response for all primary and key secondary efficacy endpoints (Table 9). Therefore, lebrikizumab 500 mg at Week 0 and Week 2 followed by 250 mg Q2W was selected as the loading and induction dose for phase 3 to enable a rapid response. The best response for all endpoints was observed with the highest lebrikizumab dose (lebrikizumab 250 mg Q2W), although the next highest dose, lebrikizumab 250 mg Q4W, also induced significant improvement in key endpoints. These results provided the basis for dose selection for the pivotal phase 3 trials. As adult and adolescent patients with AD have similar disease characteristics and have similar efficacy outcomes in response to therapies same dose of lebrikizumab was used in adolescent participants (those aged 12 to less than 18 years and weighing at least 40 kg) as adults. The lowest dose of 125 mg Q4W did show efficacy, however clinical significance was not established across all endpoints. Hence, this dose was not further assessed in the phase 3 trials.

Table 9. Summary of Primary and Select Secondary Endpoints for Study KGAF at Week 16

	PBO	LEB 125mg Q4W	LEB 250mg Q4W	LEB 250mg Q2W

	N = 52	N = 73	N = 80	N = 75
Loading dose		250mg W0	500mg W0	500mg W0 + W2
Primary Endpoint: EASI percentage change from Baseline at Week 16				
LS Mean (LSSD)[a, b]	-41.1 (56.5)	-62.3 (37.3)	-69.2 (38.3)	-72.1 (37.2)
p-Value vs. placebo[a]		0.0165	0.0022	0.0005
Proportion of participants with IGA 0,1 and ≥2-point reduction from Baseline to Week 16				
Participants with response (%)[b]	15.3	26.6	33.7	44.6
p-Value vs. placebo[c]		0.1917	0.0392	0.0023
Proportion of participants with EASI 75 at Week 16				
Participants with response (%)[b]	24.3	43.3	56.1	60.6
p-Value vs. placebo[c]		0.061	0.0021	0.0005
Proportion of participants with EASI 90 at Week 16				
Participants with response (%)[b]	11.4	26.1	36.1	44.0
p-Value vs. placebo[c]		0.0800	0.0062	0.0006
Proportion of participants with Pruritus NRS 4-point or greater improvement from Baseline to Week 16				
Participants with n/N (%)[b]	6/22 (27.3)	23/55 (41.8)	27/57 (47.4)	35/50 (70.0)
p-Value vs. placebo[c]		0.2371	0.1067	0.0008

Abbreviations: ANCOVA = analysis of covariance; EASI = Eczema Area and Severity Index; EASI 75 = 75% reduction from Baseline in EASI; EASI 90 = 90% reduction from Baseline in EASI; IGA = Investigator's Global Assessment; IGA 0,1 = IGA score of 0 or 1, with a 2-point or greater reduction from Baseline; LEB = lebrikizumab; LS = least square; LSSD = least square standard deviation; MCMC = Markov Chain Monte Carlo; N = number of participants in the analysis population; n = number of participants in the specified category; NRS = numeric rating scale; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.

a. LS mean, SD, contrast p-values from an ANCOVA with a factor of treatment group and corresponding baseline EASI as a covariate. Values were adjusted for multiple imputation.
b. Missing values were imputed using MCMC multiple imputation. For categorical endpoints, participants with a missing baseline value were not included in the analyses.
c. p-Value from pairwise Cochran-Mantel-Haenszel tests. Values were adjusted for multiple imputations.
d. p-Value from pairwise Cochran-Mantel-Haenszel tests. No imputations were made for missing data.

(Source: Clinical Study Report (Study KGAF), Tables 14.2.1.1.1, 14.2.1.2.1 and 14.2.2.1.1, Pages. 177, 178, 220.)

Induction Regimen:

The induction dosing regimen in the phase 3 trials was 500-mg doses at Weeks 0 and 2, followed by 250 mg Q2W from Weeks 4 to 16. This phase 3 dosing regimen was selected based on the phase 2b data (Study KGAF), which demonstrated a clear dose-response over the range of doses tested and had an acceptable safety profile. The best efficacy results were observed with the 250 mg Q2W dose regimen (which included loading doses of 500 mg at Weeks 0 and 2).

Study KGAB

- 43.1% achieved IGA 0,1 with lebrikizumab compared to 12.7% with placebo (PBO)
- 58.8% achieved EASI 75 with lebrikizumab compared to 16.2% with placebo (PBO)

Study KGAC

- 33.2% achieved IGA 0,1 with lebrikizumab compared to 10.8% with placebo (PBO)

- 52.1% achieved EASI 75 with lebrikizumab compared to 18.1% with placebo (PBO)

Similarly, results from Study KGAD demonstrated that the use of lebrikizumab combined with TCS, as needed, offers significant improvement compared to TCS alone.

Study KGAD

- 41.2% achieved IGA 0,1 with lebrikizumab+TCS compared to 22.1% with PBO+TCS
- 69.5% achieved EASI 75 with lebrikizumab+TCS compared to 42.2% with PBO+TCS

PK simulations using the PopPK model demonstrate that administration of 500 mg loading doses at Week 0 and Week 2 achieved steady-state concentrations by Week 4, while administration of lebrikizumab 250 mg Q2W without loading doses would achieve steady-state concentrations at approximately Week 12. Therefore, use of the loading doses at Weeks 0 and 2 allows patients to reach steady-state concentrations quickly, which may provide more rapid onset of efficacy in the induction period. Safety data from lebrikizumab-treated patients during the first 16 weeks indicated an acceptable safety profile.

Maintenance Regimen

The maintenance dosing regimens evaluated in the phase 3 trials were 250 mg Q2W or 250 mg Q4W starting at Week 16 for responders based on EASI 75 or IGA 0,1. Non-responders in phase 3 at Week 16 were dosed with 250 mg Q2W in the maintenance period.

In the pooled analysis at Week 52:

- 77% of lebrikizumab 250 mg Q4W and 71% of lebrikizumab 250 mg Q2W-treated participants maintained an IGA 0,1 response at Week 52, compared to 48% of placebo treated (lebrikizumab withdrawal) participants, and
- 82% of lebrikizumab 250 mg Q4W and 78% of lebrikizumab 250 mg Q2W-treated participants maintained an EASI 75 response at Week 52, compared to 66% of placebo-treated (lebrikizumab withdrawal) participants.

For responders at Week 16, the simulations of EASI percentage change from baseline were comparable for the 250 mg Q2W and Q4W, suggesting both would maintain a high level of EASI response (-89% and -85%) as a maintenance dosing regimen. The EASI 75 response rates were at a high level for both Q2W and Q4W (88% and 80%). EASI 90 response rates were also at a high level for both Q2W and Q4W regimens (60% and 48%). There was overlap in the 95% CI for the various EASI metrics for Q2W and Q4W, suggesting that they would be expected to perform similarly in a clinical setting. The phase 3 data also suggested that the efficacy was near E_{max} in this dose range and that response was similar between 250 mg Q2W and Q4W in the maintenance period.

For non-responders at Week 16, the simulations of EASI percentage change from baseline showed -66% for Q2W and -57% for Q4W at Week 52. While this group had not reached EASI 75 at Week 16, they had marked improvement in EASI with lebrikizumab treatment. This non-

responder category should actually be considered a “partial responder” group, because their EASI has moderately improved with lebrikizumab treatment, as shown in the simulation. The EASI 75 response rates in maintenance phase were numerically higher for Q2W versus Q4W (41% versus 26%), but with overlap in the 95% CI for EASI 75. The EASI 90 response rates in maintenance were fairly low for this partial responder group for both Q2W and Q4W (8% versus 5%) with overlap in the 95% CI. There is no phase 3 data to directly inform this group’s dosing recommendation; however, the simulations based on the established E-R relationship can help to predict the expected Week 52 response rates for the non-responder group.

Reviewer’s Comments:
The findings from phase 3 studies, demonstrate that the 250 mg Q4W maintenance dose maintains a high level of EASI response and is the recommended maintenance regimen, after adequate clinical response is achieved. In general, the safety profile was consistent and similar between lebrikizumab 250 mg Q2W and Q4W during the maintenance period. Overall, the frequency of participants that reported TEAEs was similar across treatment groups. Because lebrikizumab 250 mg Q2W and Q4W both maintained clinical response equally well with a similar immunogenicity and safety profile, the less-frequent dose 250 mg Q4W is recommended for maintenance. Switching patients who have responded to this regimen will lower the burden of injections and offer a convenient dosing frequency.

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Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Based on the evaluation of the influence of intrinsic and extrinsic factors on lebrikizumab PK, no significant effects of the following covariates were identified for age (12 to 93), sex, race, injection site location, disease state, and markers of renal function. Body weight (BW) was the only factor identified as a significant covariate on lebrikizumab PK; however, based on the exposure-response data, no dose adjustments are needed based on BW. BW based allometric exponents of 0.8 and 1.0 were included on clearance parameters and volume of distribution parameters, respectively, in the PopPK model. Please refer to pharmacometrics review in appendix 19.4.2 for more information.

AD disease state
The PK in subjects with AD were similar to the PK in healthy subjects in the Population PK analysis.

Body weight
Body weight was identified as a significant covariate on lebrikizumab PK, and was included on clearance and volume parameters in the population PK model (weight range of 39.6 kg to 192.1 kg). Higher weight resulted in lower overall lebrikizumab concentrations.
Graphical E-R analyses at Week 16 and Week 52 showed similar efficacy over the PK exposure range. Additionally, model-based efficacy simulations were performed using the final E-R model, and showed similar efficacy across body weight quartiles. The simulated efficacy response at 52 weeks in each body weight quartile for lebrikizumab 250 mg Q2W was 89%

(EASI 75). For lebrikizumab 250 mg Q4W, the simulated efficacy response ranged from 78% in the highest weight quartile to 82% in the lowest weight quartile (EASI 75). Therefore, the E-R model suggests the effect of body weight on PK is not clinically relevant in this dose range.

Table 10. Maintenance Period EASI Simulations for Body Weight Quartiles in an Adult Population Using the Final E-R Model

	Week 16 Responders at 52 Weeks				
	Model Simulations				
Maintenance Dosing Regimen	**Mean Weight of each Quartile (kg)**	**Range of each Weight Quartile (kg)**	**Mean EASI Change from Baseline %**	**EASI 75 %**	**EASI 90 %**
250 mg Q2W	57	45.9 to <63.9	-89	89	60
	70	63.9 to <75.4	-89	89	60
	82	75.4 to <89.8	-89	89	60
	106	89.8 to 178.7	-89	89	58
250 mg Q4W	57	45.9 to <63.9	-86	82	50
	70	63.9 to <75.4	-85	81	48
	82	75.4 to <89.8	-85	81	48
	106	89.8 to 178.7	-84	78	45

Abbreviations: EASI = Eczema Area Severity Index; E-R = exposure-response; Q2W = every 2 weeks; Q4W = every 4 weeks.
Notes: Simulation methods: Final E-R model was used. Virtual population of adult participants was generated by random sampling of body weights from adults in Studies KGAB and KGAC. Simulations used the phase 3 induction dosing regimen up to Week 16, followed by 250 mg Q2W or 250 mg Q4W from Weeks 16 to 52. Simulations created virtual populations of 125 participants per dose arm, with 500 replicates performed. Median across the 500 simulations for each EASI parameter is reported. The subgroup of Week 16 responders in each simulation is shown.
(Source: Summary of Clinical Pharmacology Table 2.7.2.19, Page 65.)

Hence, no dose adjustment on the basis of body weight is needed for the adolescent (weight at least 40 kg) and adult population in the AD indication.

Reviewer's Comments:
In Studies KGAB and KGAC, the efficacy response (EASI 75) at 52 Weeks was evaluated in the following weight categories: <60 kg, ≥60 kg to <100 kg, and ≥100 kg. For participants who received lebrikizumab 250 mg Q2W or Q4W up to 52 weeks, the efficacy response in the <60 kg and ≥60 kg to <100 kg weight categories was similar. The efficacy response in participants in the ≥100 kg weight category who received lebrikizumab 250 mg Q2W or Q4W up to 52 weeks was numerically lower compared to the other two weight categories.
The following percentages of subjects receiving lebrikizumab 250 mg Q2W up to 52 Weeks achieved EASI 75 in each weight category:

- *89% for <60 kg, n=26*
- *77% for ≥60 kg to <100 kg, n=74*
- *63% for ≥100 kg, n=12*

The following percentages of subjects receiving lebrikizumab 250 mg Q4W up to 52 Weeks achieved EASI 75 in each weight category:

- *87% for <60 kg, n=26*
- *86% for ≥60 kg to <100 kg, n=78*
- *43% for ≥100 kg, n=11*

However, the interpretation of the trend for subjects in the highest weight category to experience a lower treatment effect is limited due to the small sample size for both Q2W and Q4W.

Age

The effect of age on lebrikizumab PK was investigated in the Population PK analysis and was not a significant covariate. In the Population PK dataset, the range of ages was 12 to 93 years, with 77 subjects over the age of 65 years and 16 participants over the age of 75 years. The Population PK dataset also included data from 304 adolescent participants (12 to less than 18 years, at least 40 kg).

Lebrikizumab concentrations were slightly higher for adolescents compared to adults in the Population PK analysis, due to the lower body weight distribution for adolescents (mean of 66 kg versus 79 kg in adults) in the phase 3 trials. The PK exposure for adolescents was 17% to 21% higher than adults, as a result of their lower mean body weight. The adolescents and adults were dosed with the same dosing regimen in the phase 3 studies, and no dose adjustment on the basis of age is needed based on the phase 3 data.

Sex

No significant effects of sex (49% male and 51% female) on PK of lebrikizumab were identified in the Population PK analysis.

Race

No significant effects of race on PK of lebrikizumab were identified in the Population PK analysis. The races tested were Caucasian (64%), Asian (16%), African descent (15%), and all others (6%).

Renal and hepatic impairment

Lebrikizumab is a monoclonal antibody and expected to be eliminated via proteolytic degradation to amino acids and is not anticipated to be eliminated intact in the urine. Population PK analysis showed that markers of renal function [estimated glomerular filtration rate, (eGFR)] did not affect the PK of lebrikizumab.

Specific clinical pharmacology studies to evaluate the effects of renal or hepatic impairment on the PK of lebrikizumab have not been conducted.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

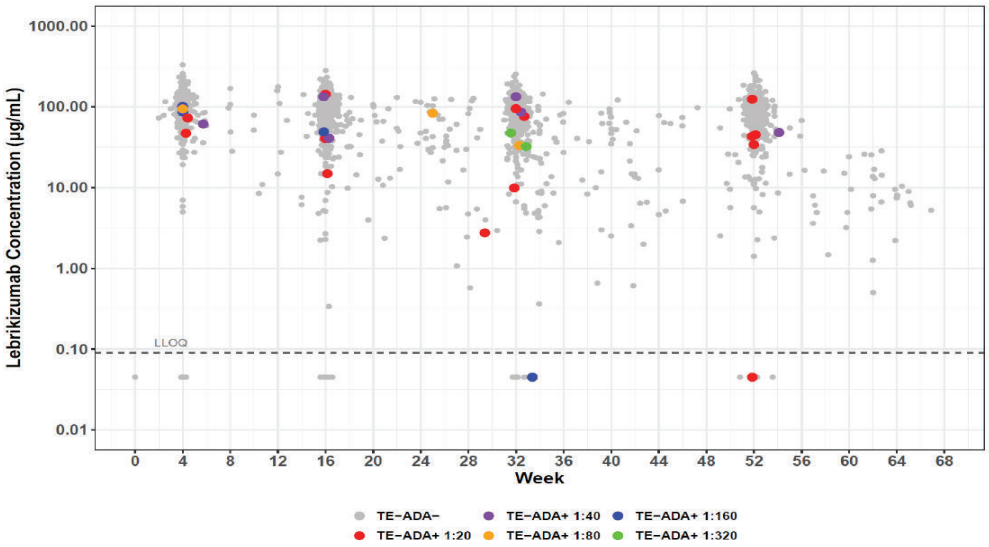
No Pharmacokinetic (PK) drug interactions are expected based on the characteristics of lebrikizumab. No drug interaction studies were conducted. Food-drug interactions are not applicable for SC administration.

What was the Impact of Immunogenicity on Lebrikizumab Exposure?

During the 12-month treatment period, 4/145 (2.8%) of subjects treated with 250 mg Q2W followed by 250 mg Q4W developed antibodies to lebrikizumab, most of which were neutralizing and of low titer.

Graphical evaluations of TE ADA and lebrikizumab exposure demonstrate that participants who were TE ADA positive had lebrikizumab concentrations largely consistent with the patients who were TE ADA negative (Figure2 below) .

Figure 2. Observed lebrikizumab serum concentrations following SC dosing of lebrikizumab 250 mg Q2W during Weeks 0-52 (induction and maintenance and open-label escape arm) in Studies KGAB, KGAC, KGAD, and KGAE by TE ADA status and titer



Abbreviations: LLOQ = lower limit of quantitation of the lebrikizumab bioanalytical assay; PK = pharmacokinetics; Q2W = every 2 weeks; SC = subcutaneous; TE ADA = treatment-emergent anti-drug antibodies.
Note: Individual dots represent individual PK samples. The horizontal dashed line represents the LLOQ value (0.09 µg/mL) reported from bioanalytical results.
(Source: Integrated Summary of Immunogeniciy, Figure ISI.8.1, Page. 96.)

Effects of Immunogenicity on Efficacy

The effects of immunogenicity on the clinical outcomes of IGA 0,1 and EASI 75 were assessed at Week 52 for lebrikizumab responders who were definitively TE ADA positive or TE ADA negative. For each treatment group, estimated response rates for various titer thresholds of TE ADA positivity were tabulated, to assess whether higher titer may be impactful.

The proportion of participants who were TE ADA positive at any time during induction or maintenance was low across all maintenance treatment regimens, and consequently the number of observed participants with higher titer was small. When examined by titer category, within each maintenance treatment there was no suggestion from available data that TE ADA positivity or titer magnitude led to diminished response of either EASI 75 or IGA 0,1.

The small number of TE ADA positive participants limits robust conclusions about impact of higher titer on efficacy response. Nonetheless, the risk of immunogenicity for participants treated with lebrikizumab is low, and therefore, the chance of diminished efficacy due to ADA is expected to be low.

Effect of Immunogenicity on Safety
No clinically meaningful differences in the frequency of hypersensitivity events were observed in TE ADA positive participants compared with TE ADA negative participants in any treatment group. The frequency of Injection site reactions (ISRs) was higher in participants in the lebrikizumab 250 mg Q2W only group, who were TE ADA positive (3/28, 10.7%) compared to those who were TE ADA negative (23/792, 2.9%). Although the frequency of ISRs was higher in participants who were TE ADA positive treated with lebrikizumab 250 mg Q2W compared to placebo, few events of ISRs were reported in TE ADA positive lebrikizumab-treated participants, and there was no temporal association with ISRs and development of TE ADA.

Overall, the risk of immunogenicity for patients treated with lebrikizumab is low, and therefore, the likelihood for ADA to impact efficacy, exposure, or safety is also expected to be low.

Reviewer Comment:
While no association between TE ADA (including titer magnitude) and treatment effect could be established, the number of TE ADA positive participants was too small, which limits robust conclusions about impact of immunogenicity on PK, efficacy and safety.

Overall, the risk of immunogenicity for subjects treated with lebrikizumab is low and is unlikely to impact the clinical benefit-risk profile.

Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Yes. The proposed commercial presentations to enable SC dosing are a Pre-Filled Syringe with Needle Safety Device (PFS-NSD) and an Autoinjector (AI), each containing 2 mL of the 125

mg/mL commercial formulation of lebrikizumab. The commercial formulation was used in all phase 3 AD studies. Therefore, no bridging studies to previous formulations were required.

A bioequivalence study (Study KGBG) of lebrikizumab using a PFS-NSD and an investigational AI was conducted in Healthy Participants (N=240). Inferential statistical analysis demonstrated 2-mL (125 mg/mL) lebrikizumab autoinjector (test) was bioequivalent to 2-mL (125 mg/mL) lebrikizumab PFS-NSD (reference) as the 90% confidence intervals (CIs) of the geometric least squares means ratios for lebrikizumab $AUC_{(0\text{-}tlast)}$, $AUC_{(0\text{-}\infty)}$, and C_{max} were all contained within the pre-specified confidence limits of 0.80 and 1.25.

Bioequivalence was established between the AI and the PFS-NSD in Study KGBG.

Table 11. Statistical Analysis of the Pharmacokinetic Parameters of Lebrikizumab for Study KGBG

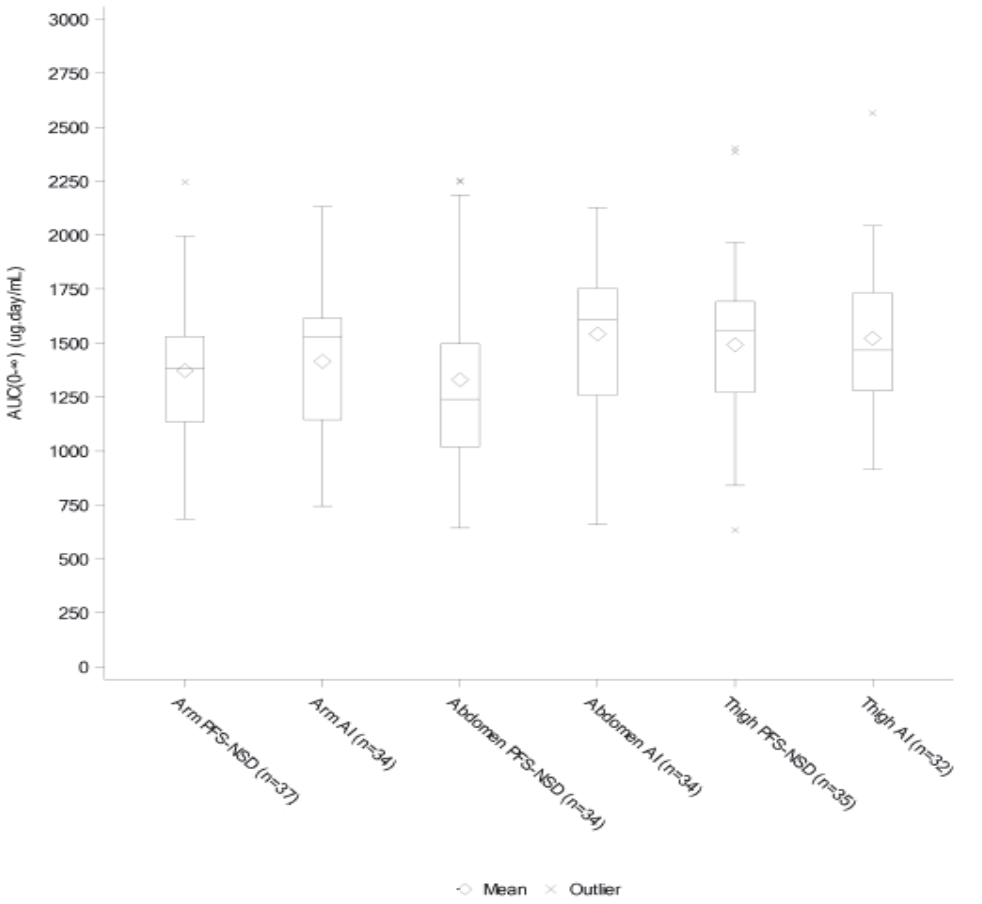
Parameter	Treatment	N	Geometric Least Squares Mean	Ratio of Geometric Least Squares Mean (Test:Reference) (90% CI)
$AUC_{(0\text{-}tlast)}$ (µg.day/mL)	2-mL (125 mg/mL) lebrikizumab PFS-NSD (Reference)	117	1262	
	2-mL (125 mg/mL) lebrikizumab AI (Test)	117	1370	1.09 (1.03, 1.14)
$AUC_{(0\text{-}\infty)}$ (µg.day/mL)	2-mL (125 mg/mL) lebrikizumab PFS-NSD (Reference)	106	1357	
	2-mL (125 mg/mL) lebrikizumab AI (Test)	100	1458	1.07 (1.02, 1.14)
Cmax (µg/mL)	2-mL (125 mg/mL) lebrikizumab PFS-NSD (Reference)	120	38.6	
	2-mL (125 mg/mL) lebrikizumab AI (Test)	118	42.2	1.09 (1.03, 1.16)

Abbreviations: AI = autoinjector; $AUC_{(0\text{-}\infty)}$ = area under the concentration–time curve from time zero to infinity; $AUC_{(0\text{-}tlast)}$ = area under the concentration–time curve from time zero to time t, where t is the last time point with a measurable concentration; CI = confidence interval; C_{max} = maximum observed drug concentration; n = number of observations; PFS-NSD = prefilled syringe with needle safety device.

(Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2.7.1.6, Page 23.)

The effect of administration site (arm, abdomen, or thigh) on the PK after a single SC dose with both devices was also studied in Study KGBG and similar PK was observed across the arm, abdomen, and thigh (Figure 3 below).

Figure 3. Box plots of systemic exposure to lebrikizumab after single SC administration of 2-mL (125 mg/mL) lebrikizumab via AI (test) or PFS-NSD (reference), stratified by injection site



Abbreviations: AI=Autoinjector; IQR= interquartile range; PFS-NSD= pre-filled syringe with needle safety device, SC=subcutaneous. The middle line in each boc plot represents the median; the top and bottom margins of the box represent the 75th and 25th percentailes; the whiskers extend to 1.5 x IQR; data beyond 1.5 x IQR are plotted individually as outliers.
(Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Figure 2.7.1.1, Page 25.)

Office of Study Integrity and Surveillance (OSIS) Inspection for Bioanalytical Sites:
An inspection of the (b) (4) and (b) (4) sites was not able to be completed, however OSIS's inspection history for the sites is provided below. OSIS conducted an inspection of the (b) (4), site in (b) (4). The inspection was conducted under the following submission: BLA NON-RESPONSIVE. OSIS concluded that data from the reviewed studies was reliable. Similarly, OSIS conducted an inspection of the (b) (4), site in (b) (4). The inspection was conducted under the following submission: NDA NON-RESPONSIVE. After review of the observation and the site's response, OSIS recommended that the data from the audited study be accepted for review with the exception of one run.

Are the bioanalytical methods properly validated to measure PK and PD in plasma samples?

Validated ELISA assays were used to determine concentrations of lebrikizumab in human serum in clinical studies. The assay was initially developed and validated at Tanox, Inc. (Houston, TX; acquired by Genentech, Inc.). The ELISA was subsequently validated at Genentech, Inc. (Method 4.AIL13.4.AVR_0; South San Francisco, CA) and (b) (4) The Genentech- or (b) (4)-validated assays were used to support all clinical studies conducted beyond Study KGBB. The bioanalytical reports describe the assay performance and sample assay results. The additional details of bioanalytical methods are provided in Appendix 19.4 (section19.4.1).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table **12**. Listing of Clinical Trials Relevant to this BLA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
Study KGAB (ADvocate 1)	Randomized, double-blind, placebo-controlled, parallel-group study designed to confirm the safety and efficacy of lebrikizumab in adults and adolescents	Induction (0-16 w): PBO Q2W LEB 250mg Q2W Maintenance (16-52w): PBO (LEB Withdrawal) LEB 250mg Q2W[a] LEB 250mg Q4W[a] Escape arm[b]	The primary efficacy endpoint included the percentage of subjects with an IGA score of 0 or 1 and a ≥ 2-point reduction from Baseline at Week 16	16-week induction period 36-week maintenance period	424	Adult and adolescent (≥12 to <18 years and weigh at least 40kg) patients with moderate-to-severe AD	89 centers in Australia, Canada, Estonia, France, Latvia, Lithuania, Poland, South Korea, Spain, and United States
Study KGAC (ADvocate 2)	Randomized, double-blind, placebo-controlled, parallel-group study designed to confirm the safety and efficacy of lebrikizumab in adults and adolescents	Induction (0-16 w): PBO Q2W LEB 250mg Q2W Maintenance (16-52w): PBO (LEB Withdrawal) LEB 250mg Q2W[a] LEB 250mg Q4W[a] Escape arm[b]	Same as Study KGAB	16-week induction period 36-week maintenance period	445	Adult and adolescent (≥12 to <18 years and weigh at least 40kg) patients with moderate-to-severe AD	82 centers in Bulgaria, Canada, Germany, Mexico, Singapore, Taiwan, Ukraine, and the US
Study KGAD (ADhere)	Randomized, double-blind, placebo-controlled, parallel-group study designed	Induction (0-16w): PBO Q2W + TCS LEB 250mg Q2W[c] + TCS	Same as Studies KGAB and KGAC	16-week treatment period	228	Adult and adolescent (≥12 to <18 years and weigh	54 centers in Canada, Germany,

	to evaluate the safety and efficacy of lebrikizumab when used in combination with TCS treatment in adults and adolescents					at least 40kg) patients with moderate-to-severe AD	Poland, and the United States.
Uncontrolled Clinical Studies to Support Efficacy and Safety							
Study KGAE (ADore)	Open-label, single group safety study in adolescents	Open label (0-52 w): LEB 250mg Q2W	The primary endpoint was the proportion of subjects discontinued from study treatment due to adverse events through the last treatment visit Secondary endpoints included the percentage of subjects with an IGA score of 0 or 1 and a ≥ 2-point reduction from Baseline and the percentage of subjects achieving EASI 75	52-week treatment period	206	Adolescent patients (≥12 to <18 years and weigh at least 40kg) with moderate-to-severe AD.	55 centers in Australia, Canada, Poland, and the United States.

Study KGAA (Adjoin)	A LTE study in adult and adolescent participants who either met the inclusion criteria or who completed a parent study (KGAB, KGAC, KGAD, KGAE, KGAK)	Open label or Blinded[d], 0-100 w LEB 250mg Q2W[e] LEB 250mg Q4W	The primary endpoint was the proportion of subjects discontinued from study treatment due to adverse events through the last treatment visit Secondary endpoints included the proportion of subjects with a response of IGA 0,1 at each visit and the proportion of participants achieving response of EASI 75 from baseline of parent study at each visit	100 weeks	979	Adult and adolescent (≥12 to <18 years and weigh at least 40kg) patients with moderate-to-severe AD	199 centers in Australia, Bulgaria, Canada, Estonia, France, Germany, Latvia, Lithuania, Mexico, Poland, Singapore, South Korea, Spain, Taiwan, Ukraine, and the United States.
Studies to Support Safety							
Study KGAG	A phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety	Group 1: LEB 250 mg SC single dose (Day 1) followed by 2 placebo doses (Weeks 4 and 8) for	The primary efficacy endpoint was the percentage of subjects	12-week treatment period	212 Group 1: 53	Adult patients with persistent moderate to severe AD, present for at least 1 year,	62 centers in Australia, Canada, Czech Republic,

	and efficacy of Lebrikizumab in patients with persistent moderate to severe atopic dermatitis that is inadequately controlled by topical corticosteroids	a total of 3 doses + TCS Group 2: LEB 125 mg SC single dose (Day 1) followed by 2 placebo doses (Weeks 4 and 8) for a total of 3 doses + TCS Group 3: LEB 125 mg SC Q4W for a total of 3 doses + TCS Group 4: Placebo SC Q4W for a total of 3 doses + TCS	achieving EASI 50 at Week 12		Group 2: 53 Group 3: 52 Group 4: 54	who were inadequately controlled by TCS	Finland, France, Germany, Netherlands, Poland, South Korea, Spain, Switzerland, Taiwan, UK, and USA
Study KGAH	A phase 2, randomized, open-label, multi-center Phase 2 study to evaluate the safety of Lebrikizumab comparted to topical corticosteroids (TCS) in adult patients with persistent moderate to severe atopic dermatitis (AD)	LEB 125 mg: 3 SC doses administered Q4W during 12-week treatment period to subjects in lebrikizumab arm TCS creams: Hydrocortisone 2.5% Triamcinolone acetonide 0.1%	The primary safety outcome measure was the incidence of treatment-emergent adverse events (TEAEs) at Week 12	12-week treatment period	55	Adult patients (18-75 years of age) with persistent moderate to severe AD, inadequately controlled by TCS	19 centers in the USA and Canada

Study KGAF	A phase 2b, randomized, double-blind, placebo-controlled, dose-ranging trial to evaluate the efficacy and safety of Lebrikizumab in patients with moderate-to-severe atopic dermatitis	Group 1: Baseline loading dose of LEB 250 mg, followed by LEB 125 mg Q4W Group 2: Baseline loading dose of LEB 500 mg, followed by LEB 250 mg Q4W Group 3: Baseline and Week 2 loading doses of LEB 500 mg, followed by LEB 250 mg Q2W Group 4: Placebo Q2W	The primary endpoint was the percent change from baseline to Week 16 in EASI score	16-week treatment period	280	Adult patients with chronic AD, present for at least 1 year	56 centers in the United States

a: Participants who received PBO during the first 16 weeks of the study and who were re-randomized to lebrikizumab treatment received a loading dose of 500 mg at Weeks 16 and 18 if randomized to the LEB 250 mg Q2W arm, or at only Week 16 if randomized to the 250 mg Q4W arm.
B: If participants did not meet protocol-defined response criteria at Week 16 or received rescue therapy, they were moved to the escape arm and received open-label lebrikizumab 250 mg Q2W up to 52 weeks.
C: Participants randomly assigned to lebrikizumab 250 mg Q2W at Baseline received 500-mg loading doses at Week 0 and Week 2.
D: Depending on the participant's parent study, he or she was reassigned to either an open-label or blinded treatment arm.
E: Participants who completed a parent study receiving PBO who were randomized to LEB 250 mg Q2W received a loading dose of 500 mg LEB at Weeks 0 and 2.

7.2. Review Strategy

The Applicant conducted 2 replicate, randomized, plabebo-controlled phase 3 studies (ADvocate 1 [KGAB] and ADvocate 2 [KGAC]) that evaluated use of lebrikizumab as monotherapy. Additionally, the Applicant conducted one study (ADhere [KGAD]) that required protocol-specified use of concomitant TCS. These 3 pivotal studies will represent the main clinical evaluation for safety and efficacy. The safety database will focus on common adverse events and adverse events of special interest. See Section 8.2 for a more detailed description of the safety database.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Studies KGAB (ADvocate 1), KGAC (ADvocate 2), and KGAD (ADhere)

Trial Design

The evaluation of the efficacy of lebrikizumab for the treatment of adults and adolescent patients with moderate-to-severe atopic dermatitis (AD) was based on 2 adequate and well-controlled Studies KGAB and KGAC and 1 supportive Study KGAD.

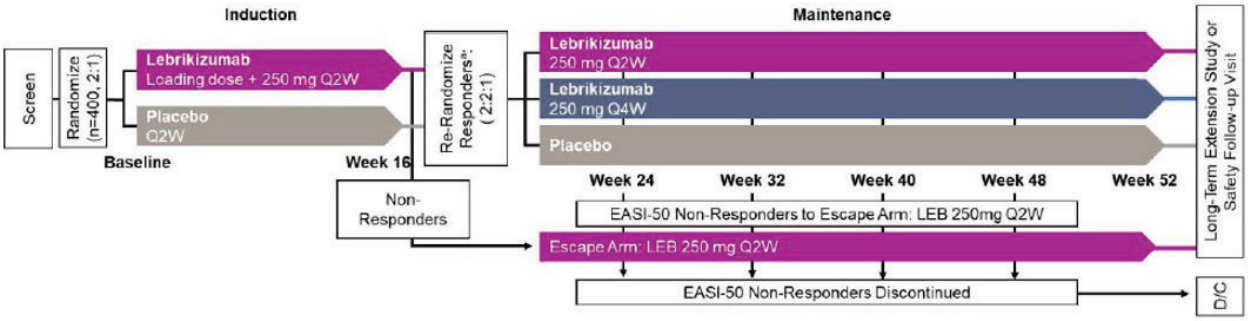
Studies KGAB and KGAC were two phase 3 randomized, double-blind, placebo-controlled, and parallel group studies sharing an identical study design. The studies were designed to evaluate the efficacy and safety of lebrikizumab as a monotherapy for moderate-to-severe AD, utilizing a 16-week induction treatment period followed by a 36-week long-term maintenance treatment period corresponding to 52 weeks of total treatment. The study design is presented in Figure 4.

The primary endpoint for the clinical studies for the FDA submission is the percentage of responders to the treatment, defined as having an investigator's global assessment (IGA) score of 0 or 1 and a reduction of $\geq$2 points from baseline to week 16. As detailed below, the clinical studies evaluated several other endpoints including a reduction of at least 75% in EASI (EASI 75%) from baseline to Week 16, which is considered as a key secondary endpoint for the FDA submission and a co-primary endpoint, along with response on the IGA, for the European Medicines Agency (EMA) submission.

For maintenance treatment period, subjects who were considered to have responded to the treatment were defined as having an investigator's global assessment (IGA) score of 0 or 1, or at least 75% reduction in EASI (EASI 75%) from baseline to Week 16, and not receiving any rescue treatment during the 16-week induction period. After completing of the Week 16 visit, subjects who responded to the lebrikizumab treatment were randomly reassigned in a 2:2:1 ratio to one of the following groups: lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, or placebo Q2W.

Subjects who did not achieve an IGA score of 0 or 1 nor EASI 75 at Week 16 or who received topical or systemic rescue therapy between baseline to Week 16 were assigned to an Escape Arm and received open-label lebrikizumab 250 mg Q2W through Week 52. Following re-randomization at Week 16, subjects not maintaining an EASI 50 response at Weeks 24, 32, 40, or 48 were assigned to an Escape Arm and received open-label lebrikizumab 250 mg Q2W through Week 52. Subjects who did not achieve an EASI 50 response in the Escape Arm after 8 weeks of treatment were terminated from the study.

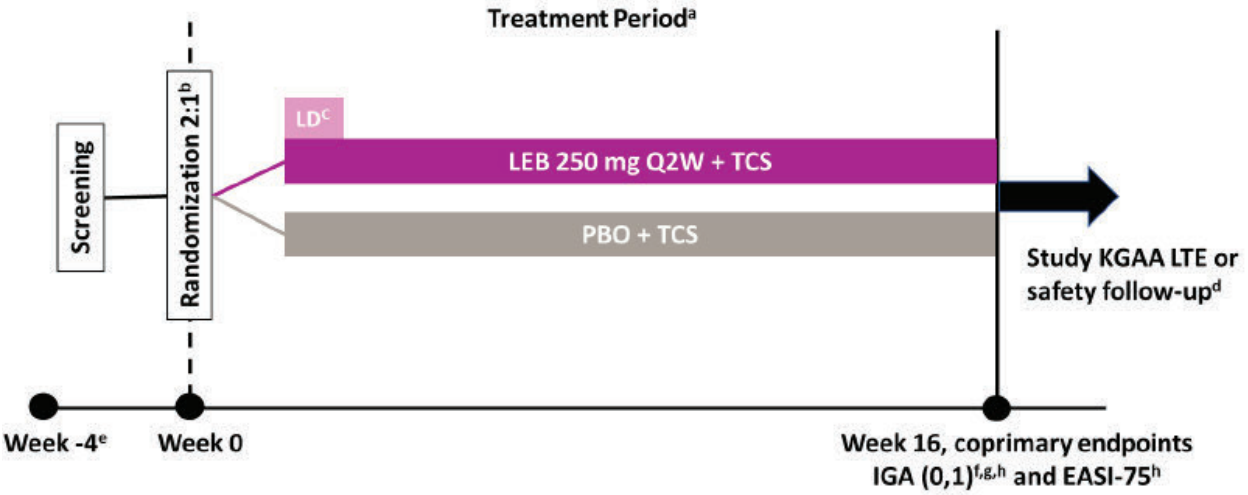
Figure 4. Study design for Studies KGAB and KGAC



Abbreviations: D/C = discontinue; EASI = Eczema Area and Severity Index; EASI 50 = 50% reduction in EASI; KGAB = J2T-DM-KGAB; KGAC = J2T-DM-KGAC; LEB = lebrikizumab; n = number of subjects; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: page 33 of KGAB. Clinical Study Report; page 32 of KGAC. Clinical Study Report

Study KGAD was a 16-week, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the safety and efficacy of lebrikizumab when used in combination with topical corticosteroid (TCS) treatment compared with placebo in combination with TCS for moderate-to-severe AD. The study design is presented in Figure 5.

Figure 5. Study design for Study KGAD



Abbreviations: EASI= Eczema Area and Severity Index; EASI 75 = 75% reduction in EASI; IGA = Investigator's Global Assessment; KGAD = J2T-DM-KGAD; LD = loading dose ; LEB = lebrikizumab; LTE = long-term extension; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroid.
Source: page 29 of KGAD. Clinical Study Report

Study Endpoints

The primary endpoint for all three studies is percentage of subjects with the investigator's global assessment (IGA) score of 0 or 1 and a reduction of ≥2 points from baseline to week 16. The IGA is a static and numeric 5-point scale ranging from 0 (clear) to 4 (severe) intended to assess the participant's overall severity of AD at a certain visit. Table 13 provides description of the categories of the IGA scale.

Table 13. Investigator Global Assessment

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

Source: page 41 of KGAB. Clinical Study Report

In addition to the primary endpoint, each of the monotherapy studies (Studies KGAB and KGAC) lists 8 major secondary endpoints and the combination study (Study KGAD) lists 4 major secondary endpoints.

The secondary endpoints for Studies KGAB and KGAC are listed below:

1) Percentage of participants achieving EASI 75 (≥ 75% reduction from baseline in EASI) at Week 16
2) Percentage of participants achieving EASI 90 (≥ 90% reduction from baseline in EASI) at Week 16
3) Percentage of participants with a Pruritus NRS score of ≥ 4 points at baseline who achieve a ≥ 4-point reduction from baseline to Week 16
4) Percentage of participants with an IGA score 0 or 1 and a reduction of ≥2 points at Week 16 in adults
5) Percentage of participants with an IGA score 0 or 1 and a reduction of ≥2 points at Week 4
6) Percentage of participants with a Pruritus NRS score of ≥ 4 points at baseline who achieve a ≥ 4-point reduction from baseline to Week 4
7) Percentage of participants with a Sleep-Loss Scale score of ≥ 2 points at baseline who achieve a ≥ 2-point reduction from baseline to Week 16
8) Percentage of participants with a Pruritus NRS score of ≥ 4 points at baseline who achieve a ≥ 4-point reduction from baseline to Week 2

The secondary endpoints for Study KGAD are:

1) Percentage of participants achieving EASI 75 (≥ 75% reduction from baseline in EASI) at Week 16
2) Percentage of participants with a Pruritus NRS score of ≥ 4 points at baseline who achieve a ≥ 4-point reduction from baseline to Week 16
3) Percentage of participants with a Pruritus NRS score of ≥4 points at baseline who achieve both EASI 75 and a ≥4-point reduction in Pruritus NRS score from baseline to Week 16

4) Percentage of participants achieving EASI 90 (≥ 90% reduction from baseline in EASI) at Week 16

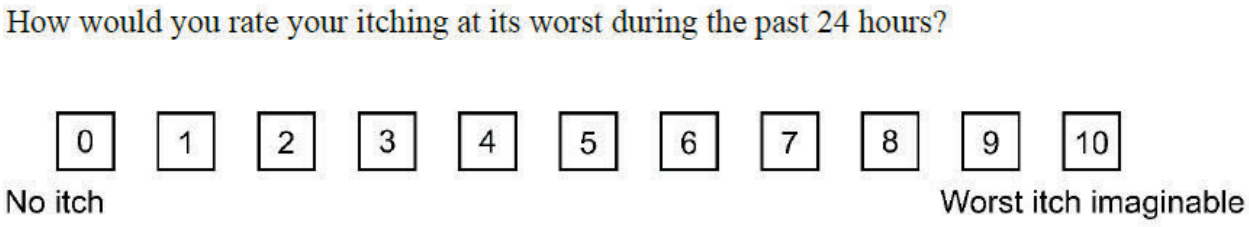
The EASI assesses the extent of disease at 4 body regions and measures 4 clinical signs at the visit, each on a scale of 0 to 3:

- erythema
- edema or papulation
- excoriation, and
- lichenification

The EASI confers a maximum score of 72, with higher values indicating more severe disease, extensive disease, or both. The EASI evaluates 2 dimensions of AD: disease extent and clinical signs[1]. Assessors were trained and certified by the sponsor prior to conducting this assessment.

The Pruritus NRS is an 11-point scale used by subjects to rate their worst itch severity over the past 24 hours, with 0 indicating "No itch" and 10 indicating "Worst itch imaginable." Pruritus NRS daily question is presented in Figure 6.

Figure 6. Pruritus NRS Daily Question

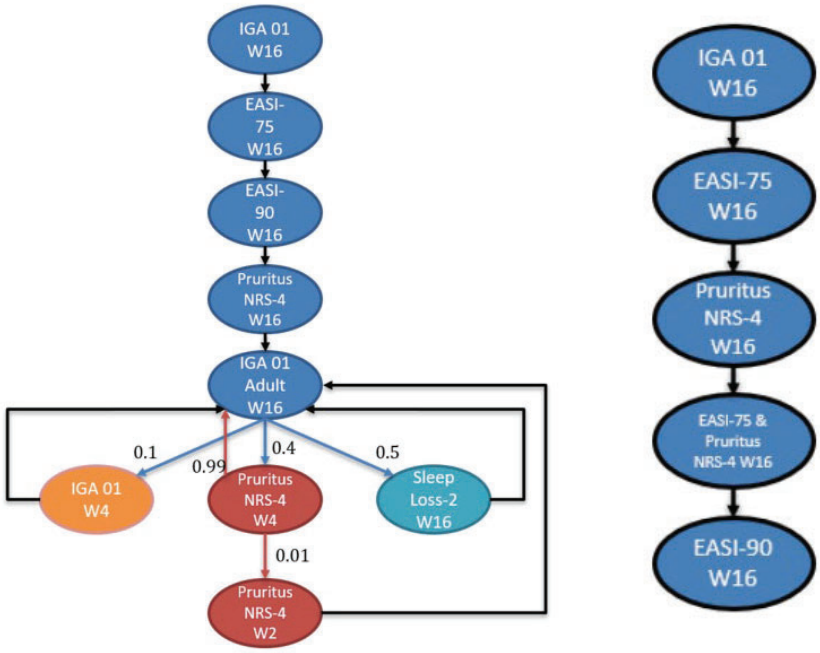


Source: page 70 of KGAB. Protocol

The protocol / statistical analysis plan (SAP) prespecified using the graphical multiple testing approach to control the overall Type I error rate at two-sided alpha of 0.05, for all primary and major secondary endpoints for the induction period (through Week 16) in each of the pivotal studies. Figure 7 describes the graphical testing scheme.

[1] Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8. doi: 10.1034/j.1600-0625.2001.100102.x. PMID: 11168575.

Figure 7. Graphical approach to control type 1 error rate for Studies KGAB and KGAC (left) and KGAD (right)



Source: page 50 of KGAB. Statistical Analysis Plan; page 58 of KGAC. Statistical Analysis Plan; page 33 of KGAD. Statistical Analysis Plan

Statistical Reviewers' Comment:
It should be noted that left Figure 7 does not display appropriately the recycling of the alpha level among the last 4 endpoints in the figure and some of arrows are incorrectly directed toward the "IGA 01 adult W16" endpoint. It appears likely that the intention is to pass unused alpha among the four endpoints at the bottom of the hierarchy. However, because the exact procedure is unclear, we consider splitting the alpha level for testing the "IGA 01 adult W16" endpoint among the 3 endpoints shown in the figure with their assigned weights and ignore recycling the alpha level among these 3 endpoints; then we consider a sequential approach for passing the alpha level for testing "Pruritus NRS-4 W4" to "Pruritus NRS-4 W2".

Statistical Analysis Plan

Three types of estimands were used for the efficacy analysis in the induction period. The primary estimand was used for primary and all major secondary endpoints. Two secondary estimands were also used, one for all categorical endpoints and one for all continuous endpoints. Table 14 summarizes the primary and supportive estimands for the induction period.

The primary estimand used composite and hypothetical strategies for handling intercurrent events for the primary and key secondary endpoint analyses. Subjects who received topical or systemic rescue medication, or discontinued the treatment due to lack of efficacy, had values

set to their baseline values subsequent to this time through Week 16 (composite); data after treatment discontinuation due to any other reasons were treated as missing (hypothetical). After the handling of intercurrent events, the missing data were imputed with the Markov Chain Monte Carlo Multiple Imputation (MCMC-MI) method.

The supportive estimand used a composite strategy for handling intercurrent events for the primary and secondary categorical endpoints analyses. Subjects who received topical or systemic rescue medication or discontinued treatment were considered nonresponders. After the handling of intercurrent events, any remaining missing data were imputed with nonresponder imputation (NRI).

For the secondary continuous endpoints analyses conducted relative to the supportive estimand (hypothetical), data after the use of rescue medication or treatment discontinuation were treated as missing and missing data was handle with mixed-effects model of repeated measures (MMRM) or last observation carried forward (LOCF).

Table 14. Description of Primary and Supportive Estimands for the Induction Period

Estimand	Analysis Strategy for Intercurrent Events			Missing Data Imputation Method
	Rescue Medication[a]	Treatment Discontinuation		
		Due to Lack of Efficacy	Due to Any Other Reasons	
Primary Estimand (Hybrid)	Composite: set to Baseline	Composite: set to Baseline	Hypothetical: set to missing	Primary analysis: MCMC-MI sensitivity analysis: tipping point analysis
Supportive Estimand for Categorical Endpoints (Composite)	Composite: set to nonresponder	Composite: set to nonresponder	Composite: set to nonresponder	NRI
Supportive Estimand for Continuous Endpoints (Hypothetical)	Hypothetical: set to missing	Hypothetical: set to missing	Hypothetical: set to missing	MMRM, LOCF

Abbreviations: LOCF = last observation carried forward; MCMC-MI = Markov chain Monte Carlo multiple imputation; MMRM = mixed-model repeated measures; NRI = nonresponder imputation.
[a] Rescue medication during induction was defined as any topical or systemic medication.
Source: page 4 of KGAB. Clinical Study Report

8.1.2. Study Results

Compliance with Good Clinical Practices

Site exclusion

For Studies KGAC and KGAD, following the primary outcome database lock, the applicant identified implausible homogeneity of efficacy results on one investigator (Dr. Carpio) who participated in two studies (Site 5042 in Study KGAC and 6006 in Study KGAD). The investigator at Site 5042 in Study KGAC enrolled 18 subjects (14 on lebrikizumab and 4 on placebo) and

nearly all subjects were recorded as having identical IGA scores at baseline, Week 2, 4, 6, and 8. Similarly, the same investigator at Site 6006 in Study KGAD, enrolled 17 subjects (8 on lebrikizumab and 9 on placebo) and nearly all subjects were recorded as having identical IGA scores at Week 4, 6, 12, and 16, and all 17 subjects (on both treatment groups) had an IGA score of 1 (i.e, responders) at Week 16. Refer to Section 4.1 for discussion of OSI findings from the inspection of Dr. Carpio's site (Site 5042 in Study KGAC and 6006 in Study KGAD), which identified unreported protocol deviations and inconsistent statements that indicated his lack of command of study details and procedures, including those related to eligibility and blinding.

As a result of the findings of the site audit, the applicant defined a modified intent to treat (mITT) population that excluded the 18 subjects in Study KGAC, specifically 14 subjects from the lebrikizumab treatment group and 4 subjects from the placebo group, and 17 subjects in Study KGAD, specifically 8 subjects from the lebrikizumab treatment group and 9 subjects from the placebo group, from efficacy and safety analyses. The mITT population became the primary efficacy analysis population.

In Study KGAC, the overall efficacy results in the mITT and ITT populations were consistent across primary and key secondary endpoints. However, in Study KGAD, inclusion of the data from the site causes IGA endpoint to no longer be statistically significant because the site had 100% response rates in both groups. We also note that there were 32 investigators who participated in Study KGAD with either Study KGAB or Study KGAC, and one investigator participated in all three studies. Table 15 lists the common sites and the number of randomized subjects in each study under each investigator. Although unique subjects were enrolled in each study, a substantial proportion (60.1%) of the investigators who participated in Study KGAD also participated in one of the other two trials. Thus, Study KGAD is not fully independent from Study KGAB and KGAC due to the potential impact of site or investigator-specific factors. To minimize the impact of the common investigators, we consider Study KGAD to be supportive. Further, as Howard Sofen enrolled 19 subjects in Study KGAB and 1 subject in Study KGAC, we concluded that having one subject enrolled in another study would not have meaningful impact on judging the independence of the two Studies KGAB and KGAC and consequently the efficacy results.

Table 15. List of Investigators Participating in Multiple Studies

	No. of Subjects Randomized in Study KGAB	No. of Subjects Randomized in Study KGAC	No. of Subjects Randomized in Study KGAD	Total No. of Subjects Randomized
Abel Jarell	6		6	12
Adam Reich	9		2	11
Andreas Pinter		3	1	4
Andrew Blauvelt	15		11	26
Angela Moore		9	8	17
Bernadetta Majorek-Olechowska	4		2	6

Bruce Torkan		15	7	22
Chih-Ho Hong		20	2	22
David Greenstein		2	2	4
Francis Averill	2		1	3
Howard Sofen	19	1	6	26
Irena Walecka-Herniczek	5		2	7
Isaiah Day	4		2	6
Jamie Weisman		5	1	6
Jeffrey Crowley		4	2	6
Jose Carpio		18	17	35
Jose Mendez		19	13	32
Kamila Padlewska	2		2	4
Kristian Reich		3	5	8
Melinda Gooderham	2		1	3
Melody Stone	5		1	6
Mirwais Saifi	6		2	8
Neil Sadick	4		3	7
Paul Wallace	16		4	20
Rosalyn George		7	2	9
Scott Guenthner	9		8	17
Seth Forman	18		10	28
Sunil Dhawan		4	2	6
Thomas Wildfeuer		1	1	2
Todd Schlesinger		4	2	6
Vivian Laquer	5		5	10
Walter Nahm		6	2	8
Wendy McFalda		2	2	4
n/N (%)	131/424 (30.9)	123/445 (27.6)	137/228 (60.1)	391/1097 (35.6)

Abbreviations: n = number of randomized subjects in each study under each investigator participating multiple studies; N = number of subjects in the analysis population
Source: reviewer analysis; adsl.xpt and clinsite.xpt

On October 18, 2021, after unblinding, the applicant informed FDA of a study site closure for Jose Carpio (Site 5042 in Study KGAC and 6006 in Study KGAD) due to Good Clinical Practice (GCP) noncompliance. On March 23, 2022, the applicant submitted an amended SAP and modified the primary analysis population to remove the site. Consequently, modified intent-to-treat (mITT) population became primary population of interest for efficacy and safety analyses. In this review, both ITT and mITT analyses results are summarized, and recommendations regarding the appropriateness of each population for interpreting the results will be discussed for the individual endpoints.

Re-randomization Errors

In Studies KGAB and KGAC, the following re-randomization errors had occurred in maintenance period due to incorrect answers on rescue medication use questions, errors in the electronic data capture (EDC) system, or an investigator's missing assessment the use of TCS. Table 16 shows the description of analysis populations.

- Four subjects in Study KGAB and 3 subjects in Study KGAC were treated with

lebrikizumab in the induction period, achieved IGA 0,1 responder status or EASI 75 at Week 16 but used rescue medication prior to Week 16 were incorrectly randomly assigned to the Maintenance Primary Population (MPP).

- Three subjects in Study KGAB did not meet IGA 0,1 responder status or EASI 75 at Week 16 and did not use rescue medication from baseline to Week 16 were incorrectly randomly assigned to the Maintenance Secondary Population (MSP).
- Six subjects in Study KGAB and 14 subjects in Study KGAC met IGA 0,1 responder status or EASI 75 at Week 16 and did not use rescue medication prior to Week 16 were incorrectly assigned to the Week 16 Maintenance Escape Population (MEP).

Table 16. Analysis Populations

Population	Description
All Entered Participants	All participants who signed informed consent. Participant flow will be summarized.
Intent-to-Treat (ITT) Population	All randomly assigned participants, even if the participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Participants were analyzed according to the treatment to which they were assigned.
Modified ITT (mITT) Population	ITT Population excluding all participants from a specific site due to critical audit finding. Participants were analyzed according to the treatment to which they were assigned.
Safety Population	All randomly assigned participants who received at least 1 dose of study treatment during the Induction Period.
Maintenance Primary Population (MPP)	All participants who were randomly assigned to lebrikizumab 250 mg Q2W at baseline visit and randomly reassigned to lebrikizumab 250mg Q2W, lebrikizumab 250 mg Q4W, or placebo at Week 16 and received at least 1 dose of the study treatment during the Maintenance Period. Participants were analyzed according to the treatment to which they were randomly reassigned. Only information prior to escape is presented.
Maintenance Secondary Population (MSP)	Includes participants who were randomly assigned to placebo at Baseline visit and randomly reassigned to lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, or placebo at Week 16, and received at least 1 dose of study treatment during the Maintenance Period. Selective efficacy analyses for the Maintenance Period were conducted on the Maintenance Secondary Population. Participants were analyzed according to the treatment to which they were randomly reassigned. Only information prior to escape is presented.
W16 Maintenance Escape Population (MEP)	Includes participants who were NOT randomly reassigned to lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, or placebo but were assigned to the Escape Arm at Week 16 and received at least 1 dose of study treatment during the Maintenance Period.

Abbreviations: Q2W = every 2 weeks; Q4W = every 4 weeks; W16 = Week 16
Source: page 57 of KGAB. Statistical Analysis Plan; page 57 of KGAC. Statistical Analysis Plan.

The applicant clarified that 7 subjects who were incorrectly assigned to the MPP were not included in the analysis population for the key maintenance period endpoints and performed post hoc sensitivity analysis. They stated that there are no or minimal changes in the IGA 0,1, EASI 75, and Pruritis NRS 4-point response rates, suggesting the incorrectly assigned subjects to the MPP did not have any impact on efficacy results.

The applicant provided additional comments that 16 out of 20 subjects who were incorrectly

assigned to the MEP treated with lebrikizumab in the induction period but the efficacy analysis with these subjects included in the MPP is not warranted because they were treated with open-label lebrikizumab in the Escape Arm as opposed to blinded treatment in the MPP.

Statistical Reviewers' Comment: As the re-randomization errors had occurred after Week 16, we agree that there is no impact on efficacy analyses for the induction periods of Studies KGAB and KGAC.

Financial Disclosure

The Applicant submitted FDA Form 3454 certifying that investigators were in compliance with 21 CFR part 54. The Applicant disclosed financial interests for 24 clinical investigators across the three clinical trials (KGAB, KGAC and KGAD). There do not appear to be any concerns regarding any conflicts of interest related to financial payments to the investigators. See Section 19.2.

Patient Disposition

Study KGAB randomized 424 subjects, 283 to lebrikizumab and 141 to placebo. Study KGAC randomized 445 subjects, 295 to lebrikizumab and 150 to placebo. Study KGAD randomized 228 subjects, 153 to lebrikizumab and 75 to placebo. In total, the three studies randomized 1,097 subjects, 731 to lebrikizumab and 366 to placebo. ITT population for the three studies is identical to randomized population. Due to critical audit finding of unreliable data at a specific site, discussed in Compliance with Good clinical Practices, data from 18 subjects from Study KGAC and 17 subjects from Study KGAD at the site were excluded, creating an mITT population with a total of 1062 subjects. About 50% and 55% of subjects who were randomly assigned to lebrikizumab at baseline visit in Studies KGAC and KGAD, respectively, were maintenance primary population. Table 17 shows details about ITT, mITT, safety, and maintenance primary population for each study.

Table 17. Population

	J2T-DM-KGAB			J2T-DM-KGAC			J2T-DM-KGAD		
Randomized Population	PBO N=141	LEB 250mg Q2W N=283	Total N=424	PBO N=150	LEB 250mg Q2W N=295	Total N=445	PBO + TCS N=75	LEB 250mg Q2W + TCS N=153	Total N=228
ITT Population, n (%)									
Yes	141 (100.0)	283 (100.0)	424 (100.0)	150 (100.0)	295 (100.0)	445 (100.0)	75 (100.0)	153 (100.0)	228 (100.0)
mITT Population, n (%)									

Yes	141 (100.0)	283 (100.0)	424 (100.0)	146 (97.3)	281 (95.3)	427 (96.0)	66 (88.0)	145 (94.8)	211 (92.5)
No	0	0	0	4 (2.7)	14 (4.7)	18 (4.0)	9 (12.0)	8 (5.2)	17 (7.5)
Safety Population, n (%)									
Yes	141 (100.0)	282 (99.6)	423 (99.8)	149 (99.3)	295 (100.0)	444 (99.8)	75 (100.0)	153 (100.0)	228 (100.0)
No	0	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)	0	0	0
Maintenance Primary Population, n (%)									
Yes	0	157 (55.5)	157 (37.0)	0	148 (50.2)	148 (33.3)	-	-	-
No	141 (100.0)	126 (44.5)	267 (63.0)	150 (100.0)	147 (49.8)	297 (66.7)	-	-	-

Abbreviations: ITT = intent to treat; LEB = lebrikizumab; n = number of subjects in the specified category; N = number of subjects in the analysis population; mITT = modified intent to treat; PBO = placebo; Q2W = every 2 weeks.
Note: Analysis populations is described in table 16.
Source: reviewer analysis; adsl.xpt.

For Study KGAB, a total of 383 out of 424 randomized subjects completed the week 16 induction period, including 85.1% of subjects receiving placebo and 92.9% of subjects in the lebrikizumab treatment group. The frequently reported reasons for treatment discontinuation in the placebo group were lack of efficacy and withdrawal by subject. The frequently reported reason for treatment discontinuation in the lebrikizumab treatment group were protocol deviation and lost to follow-up. See table 18.

Table 18. Treatment Disposition for Induction Period with ITT Population in Study KGAB

	PBO N=141	**LEB 250mg Q2W N=283**	**Total N=424**
Treatment Disposition, n (%)			
Completed	120 (85.1)	263 (92.9)	383 (90.3)
Discontinued	21 (14.9)	20 (7.1)	41 (9.7)
Reasons for Treatment Discontinuation, n (%)			
Protocol deviation	5 (3.5)	6 (2.1)	11 (2.6)
Lack of efficacy	7 (5.0)	2 (0.7)	9 (2.1)
Withdrawal by subject	6 (4.3)	3 (1.1)	9 (2.1)
Lost to follow-up	1 (0.7)	4 (1.4)	5 (1.2)
Adverse event	1 (0.7)	2 (0.7)	3 (0.7)
Due to epidemic/pandemic	1 (0.7)	2 (0.7)	3 (0.7)
Other	0	1 (0.4)	1 (0.2)

Abbreviations: ITT = intent to treat; LEB = lebrikizumab; n = number of subjects in the specified category; N = number of subjects in the analysis population; PBO = placebo; Q2W = every 2 weeks.
Source: reviewer analysis; adsl.xpt and adds.xpt.

For Study KGAC, a total of 389 subjects completed the week 16 induction period, including

89.0% of subjects receiving placebo and 92.2% of subjects in the lebrikizumab treatment group. The frequently reported reasons for treatment discontinuation in the placebo group were withdrawal by subject, adverse event, and lack of efficacy. The frequently reported reasons for treatment discontinuation in the lebrikizumab treatment group were adverse event and protocol deviation. Overall, the reasons for treatment discontinuation were similar for the two treatment arms, with higher rates of discontinuation due to adverse events and lack of efficacy on the placebo arm. See table 19.

Table 19. Treatment Disposition for Induction Period with mITT Population in Study KGAC

	PBO N=146	LEB 250mg Q2W N=281	Total N=427
Treatment Disposition, n (%)			
Completed	130 (89.0)	259 (92.2)	389 (91.1)
Discontinued	16 (11.0)	22 (7.8)	38 (8.9)
Reasons for Treatment Discontinuation, n (%)			
Adverse event	4 (2.7)	6 (2.1)	10 (2.3)
Withdrawal by subject	5 (3.4)	4 (1.4)	9 (2.1)
Protocol deviation	0	6 (2.1)	6 (1.4)
Lack of efficacy	4 (2.7)	1 (0.4)	5 (1.2)
Due to epidemic/pandemic	1 (0.7)	4 (1.4)	5 (1.2)
Lost to follow-up	2 (1.4)	0	2 (0.5)
Other	0	1 (0.4)	1 (0.2)

Abbreviations: LEB = lebrikizumab; mITT = modified intent to treat; n = number of subjects in the specified category; N = number of subjects in the analysis population; PBO = placebo; Q2W = every 2 weeks.
Source: reviewer analysis; adsl.xpt and adds.xpt.

For Study KGAD, a total of 192 subjects completed the week 16, including 87.9% of subjects receiving placebo and 92.4% of subjects in the lebrikizumab treatment group. The frequently reported reason for treatment discontinuation in both groups was withdrawal by subject. Overall, the reasons for treatment discontinuation were similar for the two treatment arms, with higher rates of discontinuation due to adverse events and protocol deviation on the placebo arm. See table 20.

Table 20. Treatment Disposition for Double-Blinded Treatment Period with mITT Population in KGAD

	PBO + TCS N=66	LEB 250mg Q2W + TCS N=145	Total N=211
Treatment Disposition, n (%)			
Completed	58 (87.9)	134 (92.4)	192 (91.0)
Discontinued	8 (12.1)	11 (7.6)	19 (9.0)
Reasons for Treatment Discontinuation, n (%)			
Withdrawal by subject	4 (6.1)	3 (2.1)	7 (3.3)
Protocol deviation	2 (3.0)	2 (1.4)	4 (1.9)
Lack of efficacy	1 (1.5)	3 (2.1)	4 (1.9)
Adverse event	0	3 (2.1)	3 (1.4)
Physician decision	1 (1.5)	0	1 (0.5)

Abbreviations: LEB = lebrikizumab; mITT = modified intent to treat; n = number of subjects in the specified category; N = number of subjects in the analysis population; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.
Source: reviewer analysis; adsl.xpt and adds.xpt.

Protocol Violations/Deviations

In Study KGAB, as shown in Table 21, a total of 69 subjects, equal to 16.3% of the total ITT population, were identified to have at least 1 important protocol deviation. The most frequent important protocol deviation, identified for 25 subjects (5.9%), was inclusion or exclusion criteria. The subjects with this violation either failed to complete electronic diary entries for pruritus and sleep-loss for a minimum of 4 of 7 days preceding randomization, or they had uncontrolled chronic disease that might require bursts of oral corticosteroids. The types of important protocol deviations were generally consistent across the two arms.

Table 21. Important Protocol Deviations by Category Before Maintenance Period with ITT Population in Study KGAB

	PBO N=141 n (%)	LEB 250mg Q2W N=283 n (%)	Total N=424 n (%)
Subjects with 1 or more important protocol deviation	24 (17.0)	45 (15.9)	69 (16.3)
Inclusion / exclusion	9 (6.4)	16 (5.7)	25 (5.9)
Study procedure / missed procedures	5 (3.5)	10 (3.5)	15 (3.5)
Study procedure / site staff authorization, delegation, training	4 (2.8)	9 (3.2)	13 (3.1)
Study procedure / missing safety assessments	5 (3.5)	4 (1.4)	9 (2.1)
Informed consent form / other	3 (2.1)	5 (1.8)	8 (1.9)
Concomitant medication[a]	2 (1.4)	1 (0.4)	3 (0.7)
SAE reported late	0	3 (1.1)	3 (0.7)
IP / IP dosing[b]	0	2 (0.7)	2 (0.5)
Randomization/treated but not randomized[c]	0	2 (0.7)	2 (0.5)
IP[a]	0	1 (0.4)	1 (0.2)

Abbreviations: ITT = intent to treat; IP = investigational product; LEB = lebrikizumab; n = number of subjects in the specified category; N = number of subjects in the analysis population; PBO = placebo; Q2W = every 2 weeks; ROW = rest of world; SAE = serious adverse event; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.
[a] Subjects received treatment prohibited by the protocol.
[b] Incorrect IP kit given to the subject.
[c] One subject was incorrectly stratified to ROW instead of US at baseline; 1 subject was incorrectly entered into the maintenance period due to an error recording TCS/TCI use.
Source: reviewer analysis; page 55 of KGAB. Clinical Study Report; adsl.xpt and addv.xpt.

In Study KGAC, as shown in Table 22, a total of 69 subjects, equal to 15.5% of the total ITT Population, were identified to have at least 1 important protocol deviation. The most frequent important protocol deviation, identified for 32 subjects (7.2%), was inclusion or exclusion criteria. The 18 subjects who were excluded due to a critical finding at a site audit are included in the inclusion or exclusion criteria of protocol deviations. The rest of subjects with this violation either failed to complete electronic diary entries for pruritus and sleep-loss for a minimum of 4 of 7 days preceding randomization, or they used prior or concomitant therapy. The types of important protocol deviations were generally consistent across the two arms.

Table 22. Important Protocol Deviations by Category Before Maintenance Period with ITT Population in Study KGAC

	PBO N=150 n (%)	LEB 250mg Q2W N=295 n (%)	Total N=445 n (%)
Subjects with 1 or more important protocol deviation	21 (14.0)	48 (16.3)	69 (15.5)
Inclusion / exclusion[a]	9 (6.0)	23 (7.8)	32 (7.2)
Study procedure / site staff authorization, delegation, training	7 (4.7)	7 (2.4)	14 (3.1)
Study procedure / missed procedures	4 (2.7)	6 (2.0)	10 (2.2)
Informed consent form / other	3 (2.0)	4 (1.4)	7 (1.6)
IP / IP dosing[b]	1 (0.7)	6 (2.0)	7 (1.6)
Study procedure / missing safety assessments	0	6 (2.0)	6 (1.3)
Concomitant medication[c]	1 (0.7)	2 (0.7)	3 (0.7)

Abbreviations: ITT = intent to treat; IP = investigational product; LEB = lebrikizumab; n = number of subjects in the specified category; N = number of subjects in the analysis population; PBO = placebo; Q2W = every 2 weeks.
[a] 18 subjects who were excluded due to a critical finding at a site audit are included in the Inclusion/exclusion category of protocol deviations.
[b] Incorrect IP kit given to subject.
[c] Subjects received treatment prohibited by the protocol.
Source: reviewer analysis; page 54 of KGAC. Clinical Study Report; adsl.xpt and addv.xpt.

In Study KGAD, as shown in Table 23, a total of 120 subjects, equal to 52.6% of the total ITT Population, were identified to have at least 1 important protocol deviation. The 17 subjects who were excluded due to a critical finding at a site audit are included in the Inclusion/exclusion category of protocol deviations. The impact of subjects who were excluded due to the critical audit finding are further discussed below in the efficacy results section for Study KGAD. The most frequent important protocol deviation, identified for 73 subjects (32.0%), was study procedure/missing safety assessments. The subjects with this violation either missed baseline, at least 1 postbaseline patient-reported outcome PROMIS measure, or lab value for chemistry or hematology. The deviation occurred at comparable rates for both groups. A higher proportion of subjects on the placebo + TCS arm had inclusion/exclusion violations, and a higher proportion of subjects on the lebrikizumab arm had study procedure/ site staff authorization, delegation, and training violations.

Table 23. Important Protocol Deviations by Category Before Maintenance Period with ITT Population in KGAD

	PBO + TCS N=75 n (%)	LEB 250mg Q2W + TCS N=153 n (%)	Total N=228 n (%)
Subjects with 1 or more important protocol deviation	41 (54.7)	79 (51.6)	120 (52.6)
Study procedure / missing safety assessments	23 (30.7)	50 (32.7)	73 (32.0)
Inclusion / exclusion[a]	12 (16.0)	16 (10.5)	28 (12.3)
Study procedure / site staff authorization, delegation, training	3 (4.0)	15 (9.8)	18 (7.9)
Informed consent form / other	3 (4.0)	7 (4.6)	10 (4.4)

Study procedure / missed procedures	2 (2.7)	7 (4.6)	9 (3.9)
IP / IP dosing	2 (2.7)	1 (0.7)	3 (1.3)
Study procedure / missing efficacy assessments	0	1 (0.7)	1 (0.4)

Abbreviations: ITT = intent to treat; IP = investigational product; LEB = lebrikizumab; n = number of subjects in the specified category; N = number of subjects in the analysis population; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.
[a] 17 subjects who were excluded due to a critical finding at a site audit are included in the Inclusion/exclusion category of protocol deviations.
Source: reviewer analysis; page 47 of KGAD. Clinical Study Report; adsl.xpt and addv.xpt.

Demographic Characteristics

Table 24 presents the demographic characteristics for subjects randomized in Study KGAB. The result of this table shows the demographic characteristics were generally well-balanced across the treatment groups at baseline. The mean age of subjects as 35.5 years, with 13.0% of the population made up of adolescents aged 12 years to less than 18 years. Similar percentages of females and males were randomized, and the majority of subjects were White (68.2%), followed by Asian (16.5%) and Black or African American (11.6%). The majority of subjects (44.8%) were from the United States, followed by subjects from Poland (19.1%). The mean duration of time since AD onset was 22.6 years.

Table 24. Summary of Baseline Characteristics for Induction Period with ITT Population in Study KGAB

	PBO N=141	LEB 250mg Q2W N=283	Total N=424
Age, years			
Mean (SD)	34.2 (16.4)	36.1 (17.8)	35.5 (17.3)
Median	30.0	31.0	31.0
Min, Max	12, 82	12, 93	12, 93
Age Group, n (%)			
12 to <18	18 (12.8)	37 (13.1)	55 (13.0)
18 to <65	113 (80.1)	225 (79.5)	338 (79.7)
65+	10 (7.1)	21 (7.4)	31 (7.3)
Sex, n (%)			
Female	73 (51.8)	141 (49.8)	214 (50.5)
Male	68 (48.2)	142 (50.2)	210 (49.5)
Race, n (%)			
American Indian or Alaska Native	0	7 (2.5)	7 (1.7)
Asian	31 (22.0)	39 (13.8)	70 (16.5)
Black or African American	16 (11.3)	33 (11.7)	49 (11.6)
Multiple	1 (<1)	4 (1.4)	5 (1.2)
Native Hawaiian or Other Pacific Islander	0	2 (<1)	2 (<1)
Not Reported	0	1 (<1)	1 (<1)
White	93 (66.0)	196 (69.3)	289 (68.2)
Other	0	1 (<1)	1 (<1)
Country, n (%)			
Australia	13 (9.2)	26 (9.2)	39 (9.2)
Canada	7 (5.0)	16 (5.7)	23 (5.4)

Estonia	4 (2.8)	4 (1.4)	8 (1.9)
France	0	7 (2.5)	7 (1.7)
Latvia	6 (4.3)	5 (1.8)	11 (2.6)
Lithuania	7 (5.0)	11 (3.9)	18 (4.2)
Poland	25 (17.7)	56 (19.8)	81 (19.1)
Spain	4 (2.8)	9 (3.2)	13 (3.1)
South Korea	13 (9.2)	21 (7.4)	34 (8.0)
United States	62 (44.0)	128 (45.2)	190 (44.8)
Duration since AD onset, years			
Mean (SD)	23.8 (15.4)	22.0 (14.8)	22.6 (15.0)
Median	21.0	20.0	20.0
Min, Max	1, 81	1, 73	1, 81

Abbreviations: AD = atopic dermatitis; ITT = intent to treat; LEB = lebrikizumab; MAX = maximum; MIN = minimum; n = number of participants in the specified category; N = number of participants in the analysis population; PBO = placebo; Q2W = every 2 weeks; SD = standard deviation.
Source: reviewer analysis; adsl.xpt.

Table 25 presents that the demographic characteristics in Study KGAC were well balanced across the treatment groups at baseline. The mean age of subjects as 36.2 years, with 11.0% of the population made up of adolescents aged 12 years to less than 18 years. Similar percentages of females and males were randomized, and the majority of subjects were White (59.3%), followed by Asian (28.6%) and Black or African American (8.2%). The majority of subjects (39.1%) were from the United States, followed by subjects from Germany (19.0%). The mean duration of time since AD onset was 20.5 years.

Table 25. Summary of Baseline Characteristics for Induction Period with mITT Population in Study KGAC

	PBO N=146	**LEB 250mg Q2W N=281**	**Total N=427**
Age, years			
Mean (SD)	35.3 (17.2)	36.6 (16.8)	36.2 (16.9)
Median	30.0	32.0	32.0
Min, Max	14, 85	12, 77	12, 85
Age Group, n (%)			
12 to <18	17 (11.6)	30 (10.7)	47 (11.0)
18 to <65	119 (81.5)	228 (81.1)	347 (81.3)
65+	10 (6.8)	23 (8.2)	33 (7.7)
Sex, n (%)			
Female	75 (51.4)	136 (48.4)	211 (49.4)
Male	71 (48.6)	145 (51.6)	216 (50.6)
Race, n (%)			
American Indian or Alaska Native	2 (1.4)	3 (1.1)	5 (1.2)
Asian	44 (30.1)	78 (27.8)	122 (28.6)
Black or African American	10 (6.8)	25 (8.9)	35 (8.2)
Multiple	3 (2.1)	4 (1.4)	7 (1.6)
Native Hawaiian or Other Pacific Islander	1 (<1)	2 (<1)	3 (<1)
White	85 (58.2)	168 (59.8)	253 (59.3)

Other	1 (<1)	1 (<1)	2 (<1)
Country, n (%)			
Bulgaria	7 (4.8)	15 (5.3)	22 (5.2)
Canada	16 (11.0)	42 (14.9)	58 (13.6)
Germany	28 (19.2)	53 (18.9)	81 (19.0)
Mexico	3 (2.1)	6 (2.1)	9 (2.1)
Singapore	8 (5.5)	11 (3.9)	19 (4.4)
Taiwan	21 (14.4)	39 (13.9)	60 (14.1)
Ukraine	3 (2.1)	8 (2.8)	11 (2.6)
United States	60 (41.1)	107 (38.1)	167 (39.1)
Duration since AD onset, years			
Mean (SD)	20.1 (14.1)	20.8 (15.2)	20.5 (14.8)
Median	18.0	19.0	19.0
Min, Max	1, 76	1, 68	1, 76

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; MAX = maximum; MIN = minimum; mITT = modified intent-to-treat; n = number of participants in the specified category; N = number of participants in the analysis population; PBO = placebo; Q2W = every 2 weeks; SD = standard deviation.
Source: reviewer analysis; adsl.xpt.

Table 26 presents that the demographic characteristics in Study KGAD were well balanced across the treatment groups at baseline. The mean age of subjects as 37.2 years, with 21.8% of the population made up of adolescents aged 12 years to less than 18 years. Similar percentages of females and males were included, and the majority of subjects were White (61.6%), followed by Asian (14.7%) and Black or African American (13.3%). The majority of subjects (71.6%) were from the United States, followed by subjects from Poland (12.8%). The mean duration of time since AD onset was 21.1 years.

Table 26. Summary of Baseline Characteristics with mITT Population in Study KGAD

	PBO + TCS N=66	**LEB 250mg Q2W + TCS N=145**	**Total N=211**
Age, years			
Mean (SD)	36.7 (17.9)	37.5 (19.9)	37.2 (19.2)
Median	32.0	33.0	33.0
Min, Max	13, 72	12, 82	12, 82
Age Group, n (%)			
12 to <18	14 (21.2)	32 (22.1)	46 (21.8)
18 to <65	47 (71.2)	98 (67.6)	145 (68.7)
65+	5 (7.6)	15 (10.3)	20 (9.5)
Sex, n (%)			
Female	33 (50.0)	70 (48.3)	103 (48.8)
Male	33 (50.0)	75 (51.7)	108 (51.2)
Race, n (%)			
American Indian or Alaska Native	2 (3.0)	5 (3.4)	7 (3.3)
Asian	13 (19.7)	18 (12.4)	31 (14.7)
Black or African American	9 (13.6)	19 (13.1)	28 (13.3)
Multiple	1 (1.5)	8 (5.5)	9 (4.3)
Native Hawaiian or Other Pacific Islander	0	3 (2.1)	3 (1.4)
White	40 (60.6)	90 (62.1)	130 (61.6)

Other	1 (1.5)	2 (1.4)	3 (1.4)
Country, n (%)			
Canada	8 (12.1)	14 (9.7)	22 (10.4)
Germany	2 (3.0)	9 (6.2)	11 (5.2)
Poland	8 (12.1)	19 (13.1)	27 (12.8)
United States	48 (72.7)	103 (71.0)	151 (71.6)
Duration since AD onset, years			
Mean (SD)	21.2 (13.9)	21.0 (17.4)	21.1 (16.3)
Median	19.8	15.4	16.4
Min, Max	1, 56	0, 72	0, 72

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; MAX = maximum; MIN = minimum; mITT = modified intent-to-treat; n = number of participants in the specified category; N = number of participants in the analysis population; PBO = placebo; Q2W = every 2 weeks; SD = standard deviation; TCS = topical corticosteroids.
Source: reviewer analysis; adsl.xpt.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 27 presents baseline IGA, EASI, and Pruritus NRS disease characteristics for the three studies. The baseline disease characteristics were generally balanced across the two treatment arms in each study. For Study KGAB, at baseline, 40.3% of subjects had severe AD, based on their IGA score, and the rest of the subjects had moderate AD at baseline. The mean EASI of 29.6 was in the severe range, and the mean Pruritus NRS score was 7.2 on a scale of 0 to 10.

For Study KGAC, at baseline, 36.8% of subjects had severe AD, based on their IGA score, and the rest of the subjects had moderate AD. The mean EASI of 29.7 was in the severe range, and the mean Pruritus NRS score was 7.1 on a scale of 0 to 10.

For Study KGAD, at baseline, 30.8% of subjects had severe AD, based on their IGA score, and the rest of the subjects had moderate AD. The mean EASI of 27.3 was in the severe range, and the mean Pruritus NRS score was 7.1 on a scale of 0 to 10.

Table 27. Summary of Baseline Disease Characteristics with mITT Population

	J2T-DM-KGAB			J2T-DM-KGAC			J2T-DM-KGAD		
	PBO N=141	LEB 250 mg Q2W N=283	Total N=424	PBO N=146	LEB 250 mg Q2W N=281	Total N=427	PBO + TCS N=66	LEB 250 mg Q2W + TCS N=145	Total N=211
IGA, n (%)									
3, moderate	83 (58.9)	170 (60.1)	253 (59.7)	95 (65.1)	175 (62.3)	270 (63.2)	48 (72.7)	98 (67.6)	146 (69.2)
4, severe	58 (41.1)	113 (39.9)	171 (40.3)	51 (34.9)	106 (37.7)	157 (36.8)	18 (27.3)	47 (32.4)	65 (30.8)
EASI									
Mean (SD)	31.0 (12.9)	28.8 (11.3)	29.6 (11.9)	29.6 (10.8)	29.7 (12.0)	29.7 (11.6)	26.4 (10.6)	27.7 (11.1)	27.3 (10.9)
Median	26.7	25.7	26.1	27.6	26.0	26.7	23.7	25.1	24.7
Min, Max	16, 67	16, 72	16, 72	16, 65	16, 70	16, 70	16, 66	16, 72	16, 72

Pruritus NRS									
Mean (SD)	7.3 (1.7)	7.2 (1.9)	7.2 (1.8)	7.2 (1.9)	7.1 (1.9)	7.1 (1.9)	6.8 (2.0)	7.3 (1.8)	7.1 (1.9)
Median	7.2	7.5	7.4	7.6	7.3	7.4	7.0	7.5	7.4
Min, Max	2, 10	0, 10	0, 10	1, 10	0, 10	0, 10	1, 10	2, 10	1, 10
Missing	5	6	11	3	12	15	3	6	9
Pruritus NRS, n (%)									
Score < 4	6 (4.3)	14 (4.9)	20 (4.7)	9 (6.2)	16 (5.7)	25 (5.9)	6 (9.1)	9 (6.2)	15 (7.1)
Score ≥ 4	130 (92.2)	263 (92.9)	393 (92.7)	134 (91.8)	253 (90.0)	387 (90.6)	57 (86.4)	130 (89.7)	187 (88.6)
Missing	5 (3.5)	6 (2.1)	11 (2.6)	3 (2.1)	12 (4.3)	15 (3.5)	3 (4.5)	6 (4.1)	9 (4.3)

Abbreviations: EASI = Eczema Area and Severity Index; IGA = Investigator Global Assessment; LEB = lebrikizumab; MAX = maximum; MIN = minimum; mITT = modified intent-to-treat; n = number of subjects in the specified category; N = number of subjects in the analysis population; NRS = numeric rating scale; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; TCS = topical corticosteroids.
Source: reviewer analysis; adsl.xpt.

Efficacy Results – Primary Endpoint

Table 28 presents the statistical reviewer's analysis results, which are consistent with the applicant's results, for primary endpoint for Studies KGAB, KGAC, and KGAD using primary estimand MCMC-MI with mITT population. The primary endpoint of percentage of subjects achieving IGA 0 or 1 and a 2-point or greater improvement from baseline at Week 16 of induction period was met. A significantly greater percentage of subjects achieved IGA 0 or 1, with a 2-point or more reduction at Week 16 in the lebrikizumab-treated group compared with the placebo-treated group across the three studies.

- Study KGAB: placebo-treated group, 12.7%; lebrikizumab-treated group, 43.1%; p<0.001
- Study KGAC: placebo-treated group, 10.8%; lebrikizumab-treated group, 33.2%; p<0.001
- Study KGAD: placebo-treated group, 22.1%; lebrikizumab-treated group, 41.2%; p=0.01

Table 28. Percentage of Subjects with an IGA score of 0 or 1 and a ≥ 2-point reduction from Baseline at Week 16, Markov Chain Monte Carlo Multiple Imputation (MCMC-MI), mITT Population

	J2T-DM-KGAB		J2T-DM-KGAC		J2T-DM-KGAD	
	PBO N=141	LEB250 Q2W N=283	PBO N=146	LEB250 Q2W N=281	PBO + TCS N=66	LEB250 Q2W + TCS N=145
Response, n (%)[1]	18 (12.7)	122 (43.1)	16 (10.8)	93 (33.2)	15 (22.1)	60 (41.2)
95% CI[1]	(6.9, 18.5)	(37.1, 49.0)	(5.7, 16.0)	(27.4, 38.9)	(11.5, 32.7)	(32.9, 49.4)
Difference (95% CI)[2]	-	29.7 (21.6, 37.8)	-	21.9 (14.2, 29.6)	-	18.3 (5.1, 31.5)
Odds Ratio (95% CI)[2]	-	5.69 (3.08, 10.53)	-	3.94 (2.19, 7.11)	-	2.49 (1.20, 5.16)
p-value[2]	-	<0.0001	-	<0.0001	-	0.01

Abbreviations: CI = confidence interval; IGA = Investigator Global Assessment; LEB = Lebrikizumab; mITT = modified intent to treat; n = number of patients in the specified category; N = number of patients in the analysis population; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.

Note: patients who received topical or systemic rescue medication, or discontinued treatment due to lack of efficacy, had values set to their baseline value subsequent to this time through Week 16; MCMC-MI was used to handle the remaining missing data. The analysis results were combined across all multiply imputed datasets using SAS PROC MIANALYZE. Percentage is calculated after MCMC-MI is used to handle the missing data.

The common risk difference is the difference in proportions adjusted for the stratification factor(s): geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 versus adults >=18 years) and disease severity (IGA 3 versus 4), where the confidence intervals are calculated using Mantel-Haenszel-Sato method. The relative risk and odds ratio are also adjusted for the same stratification factor(s).

[1] Unadjusted response rate and confidence interval.
[2] Cochran-Mantel-Haenszel (CMH) test adjusted by geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 versus adults ≥ 18 years) and disease severity (IGA 3 versus 4).
Source: reviewer analysis; adsl.xpt and adigamc.xpt

To evaluate the impact of the site exclusion in Studies KGAC and KGAD, discussed in Compliance with Good Clinical Practices, reviewer conducted for primary endpoint analysis using primary estimand MCMC-MI with ITT population, which includes all subjects from the audited site. Table 29 presents the statistical reviewer's analysis results. For Study KGAC, theoverall efficacy results in the mITT and ITT populations were consistent across primary endpoint. However, for Study KGAD, the primary endpoint is no longer statistically significant because the high placebo response rate from subjects enrolled at Site 6006 that contributes to a higher-than-expected overall placebo response rate. The site exclusion is detailed in Compliance with Good Clinical Practices.

- Study KGAC: placebo-treated group, 12.7%; lebrikizumab-treated group, 34.7%; p<0.001
- Study KGAD: placebo-treated group, 32.1%; lebrikizumab-treated group, 44.3%; p=0.11

Table 29. Percentage of Subjects with an IGA score of 0 or 1 and a ≥ 2-point reduction from Baseline at Week 16, Markov Chain Monte Carlo Multiple Imputation (MCMC-MI), ITT Population

	J2T-DM-KGAB		J2T-DM-KGAC		J2T-DM-KGAD	
	PBO N=141	LEB250 Q2W N=283	PBO N=150	LEB250 Q2W N=295	PBO + TCS N=75	LEB250 Q2W + TCS N=153
Response, n (%)[1]	18 (12.7)	122 (43.1)	19 (12.7)	102 (34.7)	24 (32.1)	68 (44.3)
95% CI[1]	(6.9, 18.5)	(37.1, 49.0)	(7.3, 18.1)	(29.0, 40.4)	(20.9, 43.3)	(36.2, 52.3)
Difference	-	29.7	-	21.6	-	11.3
(95% CI)[2]		(21.6, 37.8)		(13.8, 29.4)		(-2.4, 25.0)
Odds Ratio	-	5.69	-	3.68	-	1.64
(95% CI)[2]		(3.08, 10.53)		(2.10, 6.46)		(0.88, 3.04)
p-value[2]	-	<0.0001	-	<0.0001	-	0.11

Abbreviations: CI = confidence interval; IGA = Investigator Global Assessment; ITT = intent to treat; LEB = Lebrikizumab; n = number of patients in the specified category; N = number of patients in the analysis population; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.

Note: patients who received topical or systemic rescue medication, or discontinued treatment due to lack of efficacy, had values set to their baseline value subsequent to this time through Week 16; MCMC-MI was used to handle the remaining missing data. The analysis results were combined across all multiply imputed datasets using SAS PROC MIANALYZE. Percentage is calculated after MCMC-MI is used to handle the missing data.

The common risk difference is the difference in proportions adjusted for the stratification factor(s): geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 versus adults >=18 years) and disease severity (IGA 3 versus 4), where the confidence intervals are calculated using Mantel-Haenszel-Sato method. The relative risk and odds ratio are also adjusted for the same stratification factor(s).

[1] Unadjusted response rate and confidence interval.
[2] Cochran-Mantel-Haenszel (CMH) test adjusted by geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 versus adults ≥ 18 years) and disease severity (IGA 3 versus 4).
Source: reviewer analysis; adsl.xpt and adigamc.xpt

Statistical Reviewers' Comment: The applicant did not identify the concerns with the data from the audited site until after the results from Studies KGAC and KGAD were analyzed. Thus, all decisions related to the removal of the data from the audited site are post hoc. For Study KGAC, despite this issue, the conclusions and treatment effect estimates are consistent under both analysis populations (prespecified and post hoc), and Study KGAC supports the efficacy of lebrikizumab and the results can be included in labeling. (b) (4), for Study KGAD, the conclusions on the primary endpoint in Study KGAD differ depending upon whether the data from the audited site are included or excluded. In addition to that, there were dependence issues described in detail in Compliance with Good Clinical Practices. Thus, the results from Study KGAD are not sufficiently reliable (b) (4).

Table 30 presents the statistical reviewer's analysis results, which are consistent with the applicant's results, for primary endpoint using supportive estimand NRI with mITT population. The NRI analysis yields results similar to the MCMC-MI method with mITT population in each study, and the conclusions are not impacted by the two ways of handling missing data.

- Study KGAB: placebo-treated group, 11.3%; lebrikizumab-treated group, 41.0%; p<0.001
- Study KGAC: placebo-treated group, 9.6%; lebrikizumab-treated group, 31.3%; p<0.001
- Study KGAD: placebo-treated group, 19.7%; lebrikizumab-treated group, 39.3%; p=0.01

Table 30. Percentage of Subjects with an IGA score of 0 or 1 and a ≥ 2-point reduction from Baseline at Week 16, Non-Responder Imputation (NRI), mITT Population

	J2T-DM-KGAB		J2T-DM-KGAC		J2T-DM-KGAD	
	PBO N=141	LEB250 Q2W N=283	PBO N=146	LEB250 Q2W N=281	PBO + TCS N=66	LEB250 Q2W + TCS N=145
Response, n (%)[1]	16 (11.3)	116 (41.0)	14 (9.6)	88 (31.3)	13 (19.7)	57 (39.3)
95% CI[1]	(6.1, 16.6)	(35.3, 46.7)	(4.8, 14.4)	(25.9, 36.7)	(10.1, 29.3)	(31.4, 47.3)
Difference (95% CI)[2]	-	29.0 (21.5, 36.5)	-	21.3 (13.9, 28.6)	-	18.8 (6.7, 30.9)
Odds Ratio (95% CI)[2]	-	6.08 (3.29, 11.26)	-	4.05 (2.22, 7.39)	-	2.71 (1.32, 5.59)
p-value[2]	-	<0.0001	-	<0.0001	-	0.01

Abbreviations: CI = confidence interval; IGA = Investigator Global Assessment; ITT = intent to treat; LEB = Lebrikizumab; n = number of patients in the specified category; N = number of patients in the analysis population; NRI = nonresponder imputation; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.

Note: patients who received topical or systemic rescue medication, discontinued treatment due to any reasons were set to non-response subsequent to this time through Week 16; intermittent missing values were also set to non-response.

The common risk difference is the difference in proportions adjusted for the stratification factor(s): geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 versus adults >=18 years) and disease severity (IGA 3 versus 4), where the confidence intervals are calculated using Mantel-Haenszel-Sato method. The relative risk and odds ratio are also adjusted for the same stratification factor(s).

[1] Unadjusted response rate and confidence interval.
[2] Cochran-Mantel-Haenszel (CMH) test adjusted by geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 versus adults ≥ 18 years) and disease severity (IGA 3 versus 4).
Source: reviewer analysis; adsl.xpt and adigaad.xpt

Data Quality and Integrity

See Compliance with Good Clinical Practices above.

Efficacy Results – Secondary and other relevant endpoints

For Studies KGAB and KGAC, the secondary endpoints were supportive of the findings for the primary endpoint. See Table 31 and 32. For these two studies, lebrikizumab 250mg Q2W treatment results in a statistically significant improvement compared with placebo in all major secondary endpoints except pruritus NRS at week 2 endpoint for Study KGAC.

Table 31. Major Secondary Endpoints with Markov Chain Monte Carlo Multiple Imputation (MCMC-MI) and ITT Population in Study KGAB

	PBO N=141 n (%)	LEB250Q2W N=283 n (%)	Difference (95% CI)[1]	p-value[1]
EASI 75 at Week 16	23 (16.2)	166 (58.8)	42.0 (33.3, 50.6)	<0.0001
EASI 90 at Week 16	13 (9.0)	108 (38.3)	28.8 (21.3, 36.3)	<0.0001
Pruritus NRS[2] at Week 16	17 (13.0)	121 (45.9)	32.9 (24.6, 41.3)	<0.0001
IGA at Week 16 in Adults	14 (11.3)	104 (42.2)	30.8 (22.1, 39.4)	<0.0001
IGA at Week 4	1 (0.8)	30 (10.6)	9.6 (5.7, 13.6)	0.0005
Pruritus NRS[2] at Week 4	3 (2.3)	56 (21.5)	19.3 (13.7, 25.0)	<0.0001
Sleep-loss scale score at Week 16	4 (4.7)	76 (39.0)	34.6 (26.2, 43.0)	<0.0001
Pruritus NRS[2] at Week 2	1 (0.9)	16 (6.1)	5.3 (1.9, 8.6)	0.02

Abbreviations: CI = confidence interval; IGA = Investigator Global Assessment score 0 (clear) or 1 (almost clear) and a reduction ≥ 2 points from Baseline; EASI = Eczema Area and Severity Index; EASI75 = greater than or equal to 75% Improvement in EASI score from baseline; EASI90 = greater than or equal to 90% Improvement in EASI score from baseline; ITT = intent to treat; LEB = Lebrikizumab; n = number of patients in the specified category; N = number of patients in the analysis population; NRS = numeric rating scale; PBO = placebo; Q2W = every 2 weeks.

Percentage is calculated after MCMC-MI is used to handle the missing data.

[1] Cochran-Mantel-Haenszel (CMH) test adjusted by geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 versus adults ≥ 18 years) and disease severity (IGA 3 versus 4).

[2] Baseline weekly Pruritus NRS were calculated by averaging the daily scores up to 7 days before the first injection with at least 4 non-missing values. Post-baseline weekly Pruritus NRS were calculated by averaging the daily scores from the previous 7 days with at least 1 non-missing values.
Source: reviewer analysis; adsl.xpt, adeasimc.xpt, adigamc.xpt, and adpnprmc.xpt

Table 32. Major Secondary Endpoints with Markov Chain Monte Carlo Multiple Imputation (MCMC-MI) and mITT Population in Study KGAC

	PBO N=146 n (%)	LEB250Q2W N=281 n (%)	Difference (95% CI)[1]	p-value[1]
EASI 75 at Week 16	26 (18.1)	146 (52.1)	33.3 (24.4, 42.2)	<0.0001
EASI 90 at Week 16	14 (9.5)	86 (30.7)	20.7 (13.3, 28.1)	<0.0001
Pruritus NRS[2] at Week 16	15 (11.5)	101 (39.8)	28.3 (20.0, 36.5)	<0.0001
IGA at Week 16 in Adults	15 (11.5)	80 (31.8)	20.4 (12.3, 28.6)	<0.0001
IGA at Week 4	2 (1.4)	25 (9.0)	8.1 (4.1, 12.0)	0.002
Pruritus NRS[2] at Week 4	4 (3.0)	42 (16.8)	13.2 (7.7, 18.7)	0.0002
Sleep-loss scale score at Week 16	8 (8.2)	45 (28.0)	18.9 (9.6, 28.1)	0.0006
Pruritus NRS[2] at Week 2	1 (0.7)	9 (3.6)	2.7 (-0.1, 5.4)	0.11

Abbreviations: CI = confidence interval; IGA = Investigator Global Assessment score 0 (clear) or 1 (almost clear) and a reduction ≥ 2 points from Baseline; EASI = Eczema Area and Severity Index; EASI75 = greater than or equal to 75% Improvement in EASI score from baseline; EASI90 = greater than or equal to 90% Improvement in EASI score from baseline; LEB = Lebrikizumab; mITT = modified intent to treat; n = number of patients in the specified category; N = number of patients in the analysis population; NRS = numeric rating scale; PBO = placebo; Q2W = every 2 weeks.

Percentage is calculated after MCMC-MI is used to handle the missing data.

[1] Cochran-Mantel-Haenszel (CMH) test adjusted by geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 versus adults ≥ 18 years) and disease severity (IGA 3 versus 4).

[2] Baseline weekly Pruritus NRS were calculated by averaging the daily scores up to 7 days before the first injection with at least 4 non-missing values. Post-baseline weekly Pruritus NRS were calculated by averaging the daily scores from the previous 7 days with at least 1 non-missing values.
Source: reviewer analysis; adsl.xpt, adeasimc.xpt, adigamc.xpt, and adpnprmc.xpt

For Study KGAD, the secondary endpoint results are supportive of the primary endpoint results for the mITT population. See Table 33. However, as noted with the discussion of the primary endpoint results for Study KGAD, the decision to exclude the data from the audited site following the planned analysis using all subjects, also makes it difficult to interpret the secondary endpoint results in Study KGAD.

Table 33. Major Secondary Endpoints with Markov Chain Monte Carlo Multiple Imputation (MCMC-MI) and mITT Population in Study KGAD

	PBO + TCS N=66 n (%)	LEB250Q2W + TCS N=145 n (%)	Difference (95% CI)[1]	p-value[1]
EASI 75 at Week 16	28 (42.2)	101 (69.5)	26.4 (12.1, 40.8)	0.0004
Pruritus NRS[2] at Week 16	18 (31.9)	66 (50.6)	19.2 (4.3, 34.1)	0.02
Pruritus NRS[2] & *EASI 75* at Week 16[3]	10 (16.8)	50 (38.3)	21.6 (8.3, 35.0)	0.005
EASI 90 at Week 16	14 (21.7)	60 (41.2)	18.9 (6.1, 31.7)	0.01

Abbreviations: CI = confidence interval; EASI = Eczema Area and Severity Index; EASI75 = greater than or equal to 75% Improvement in EASI score from baseline; EASI90 = greater than or equal to 90% Improvement in EASI score from baseline; LEB = Lebrikizumab; mITT = modified intent to treat; n = number of patients in the specified category; N = number of patients in the analysis population; NRS = Numeric Rating Scale; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.

Percentage is calculated after MCMC-MI is used to handle the missing data.

[1] Cochran-Mantel-Haenszel (CMH) test adjusted by geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 versus adults ≥ 18 years) and disease severity (IGA 3 versus 4).

[2] Baseline weekly Pruritus NRS were calculated by averaging the daily scores up to 7 days before the first injection with at least 4 non-missing values. Post-baseline weekly Pruritus NRS were calculated by averaging the daily scores from the previous 7 days with at least 1 non-missing values.

[3] For this endpoint, N for Placebo is 57 and N for combination of lebrikizumab in combination with TCS is 130.
Source: reviewer analysis; adsl.xpt, adeasimc.xpt, adigamc.xpt, and adpnprmc.xpt

Dose/Dose Response

See Clinical Pharmacology section 6.3.2.

Durability of Response

In Studies KGAB and KGAC, the efficacy of lebrikizumab for maintenance therapy was evaluated in subjects who were randomly assigned to lebrikizumab at baseline and had an IGA score of 0 or 1, or at least 75% reduction in EASI to lebrikizumab induction therapy at Week 16. During the maintenance period, those responding subjects were randomly reassigned at Week 16 to placebo or lebrikizumab 250 mg Q4W or lebrikizumab 250mg Q2W.

In Studies KGAB and KGAC, lebrikizumab responders who were randomly reassigned to the

treatment with lebrikizumab maintained IGA 0 or 1 and 2-point or greater improvement from baseline and EASI 75 from Week 16 through Week 52 at numerically higher rates compared with responders who were randomly reassigned to placebo. See Tables 34 and 35. The percentage of subjects originally treated with lebrikizumab who were randomly reassigned to placebo (lebrikizumab withdrawal) during the maintenance period and maintained IGA response through Week 52 was relatively high (46.5% in KGAB and 49.8% in KGAC). A higher percentage of responding subjects who continued treatment with lebrikizumab maintained IGA response than those who were randomized to treatment withdrawal, however, there was no clear dose response for a maintenance regimen of lebrikizumab Q2W versus Q4W. Subjects in Study KGAB randomized to maintenance treatment with lebrikizumab Q2W and Q4W had similar responses at Week 52 (74.2% vs. 75.8% for Q4W and Q2W, respectively), while in Study KGAC, subjects randomized to less frequent dosing (Q4W) had a higher level of response at Week 52 than subjects randomized to more frequent dosing (Q2W): 80.6% vs. 64.6%. See Figures 8, 9, 10, and 11.

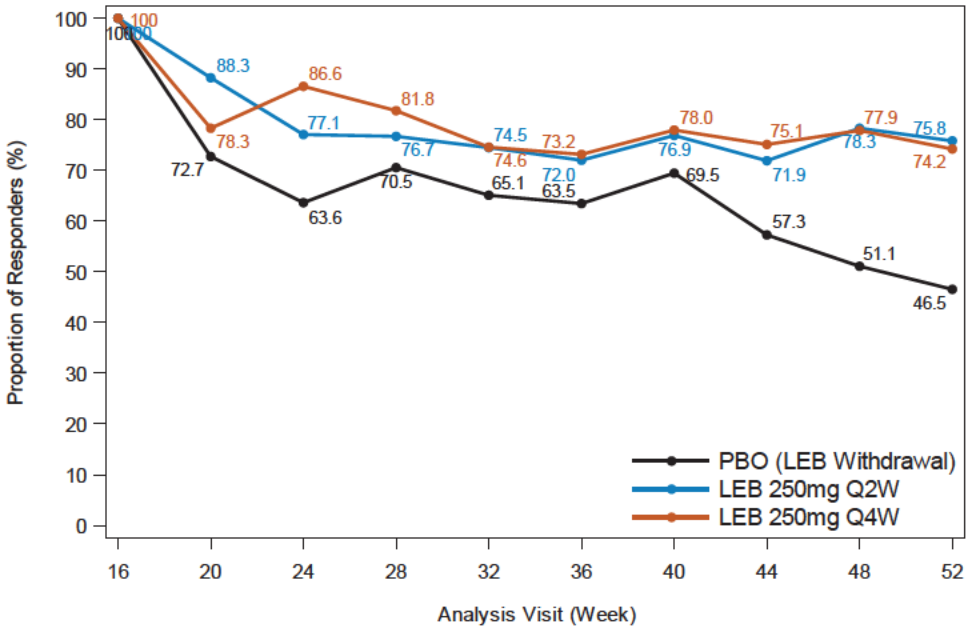
Table 34. Major Secondary Endpoints for Maintenance Period in Lebrikizumab Responder at Week 16 in Study KGAB

	PBO	LEB250Q4W			LEB250Q2W		
	n / N (%)	n / N (%)	Difference (95% CI)[1]	p-value[1]	n / N (%)	Difference (95% CI)[1]	p-value[1]
IGA at Week 52	10 / 22 (46.5)	33 / 45 (74.2)	28.0 (2.8, 53.2)	0.03	34 / 45 (75.8)	29.0 (4.6, 53.3)	0.02
EASI 75 at Week 16	18 / 30 (61.3)	49 / 62 (79.2)	17.9 (-2.3, 38.1)	0.07	48 / 61 (79.2)	17.5 (-4.5, 39.5)	0.11

Abbreviations: CI = confidence interval; IGA = Investigator Global Assessment score 0 (clear) or 1 (almost clear) with 2-point improvement; EASI = Eczema Area and Severity Index; EASI75 = greater than or equal to 75% Improvement in EASI score from baseline; LEB = Lebrikizumab; n = number of patients in the specified category; N = number of patients in the analysis population; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.

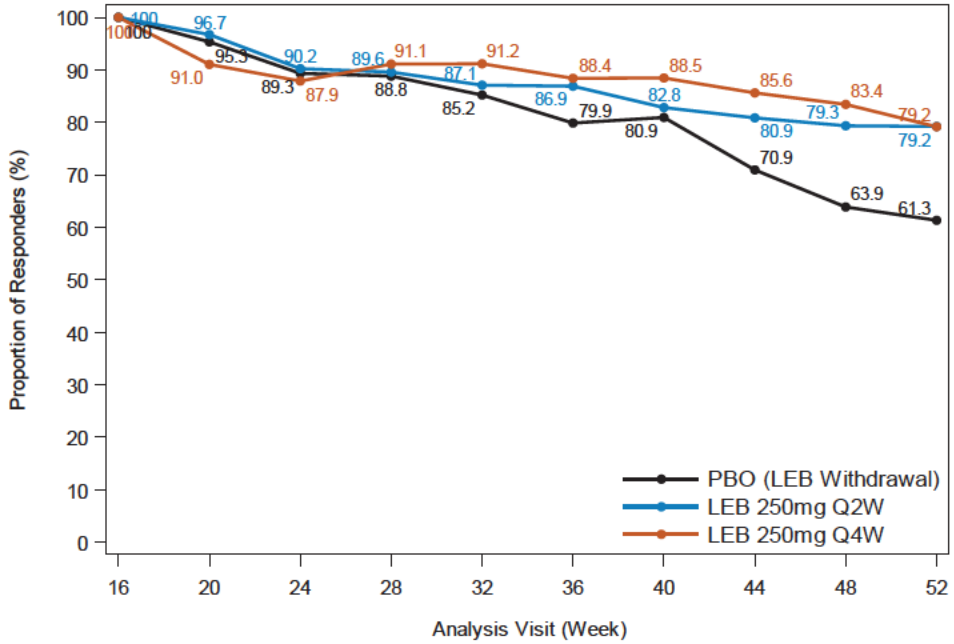
[1] Cochran-Mantel-Haenszel (CMH) test adjusted by geographic region (US versus EU versus rest of world).
Source: reviewer analysis; adsl.xpt, adeasimc.xpt, and adigamc.xpt

Figure 8. Percentage of Subjects Having Achieved IGA 0 or 1 and a ≥ 2-point Improvement from Baseline at Week 16 in Lebrikizumab-treated Group who Continued to Exhibit IGA 0 or 1 and a ≥ 2-point Improvement from Baseline by Visit in Study KGAB



Abbreviations: IGA = Investigator Global Assessment; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: reviewer analysis; adsl.xpt and adigamc.xpt

Figure 9. Percentage of Subjects Having Achieved EASI75 at Week 16 who Maintain EASI75 Response by Visit in Study KGAB



Abbreviations: EASI = Eczema Area and Severity Index; EASI 75 = 75% reduction in EASI; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: reviewer analysis; adsl.xpt and adeasimc.xpt

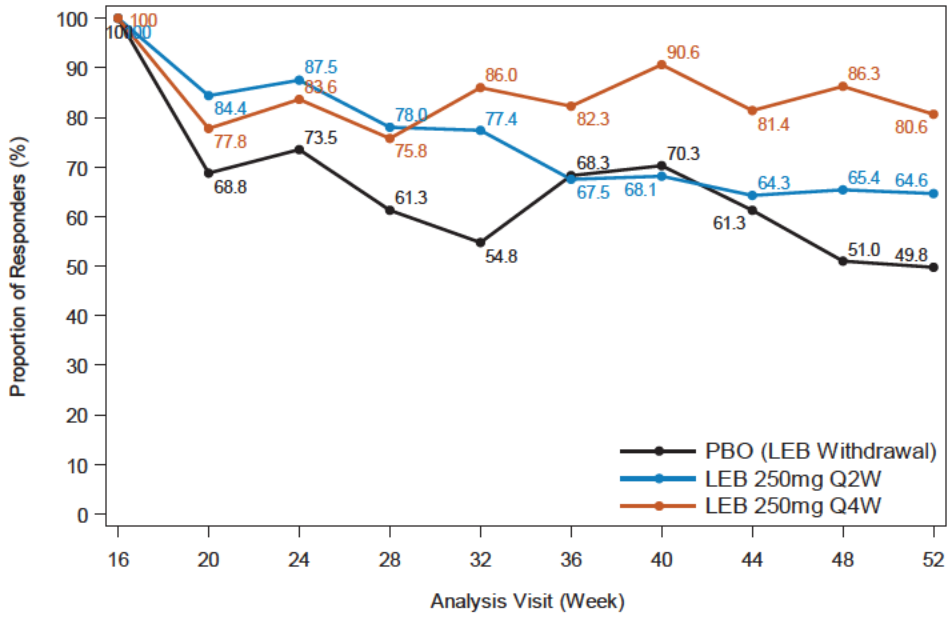
Table 35. Major Secondary Endpoints for Maintenance Period in Lebrikizumab Responder at Week 16 in Study KGAC

	PBO	LEB250Q4W			LEB250Q2W		
	n / N (%)	n / N (%)	Difference (95% CI)[1]	p-value[1]	n / N (%)	Difference (95% CI)[1]	p-value[1]
IGA at Week 52	8 / 16 (49.8)	26/ 32 (80.6)	32.6 (2.6, 62.5)	0.03	21 / 32 (64.6)	13.4 (-17.5, 44.3)	0.41
EASI 75 at Week 16	19 / 27 (72.0)	45 / 53 (84.7)	12.8 (-9.5, 35.1)	0.24	39 / 51 (77.4)	4.8 (-17.8, 27.3)	0.61

Abbreviations: CI = confidence interval; IGA = Investigator Global Assessment score 0 (clear) or 1 (almost clear) with 2-point improvement; EASI = Eczema Area and Severity Index; EASI75 = greater than or equal to 75% Improvement in EASI score from baseline; LEB = Lebrikizumab; n = number of patients in the specified category; N = number of patients in the analysis population; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.

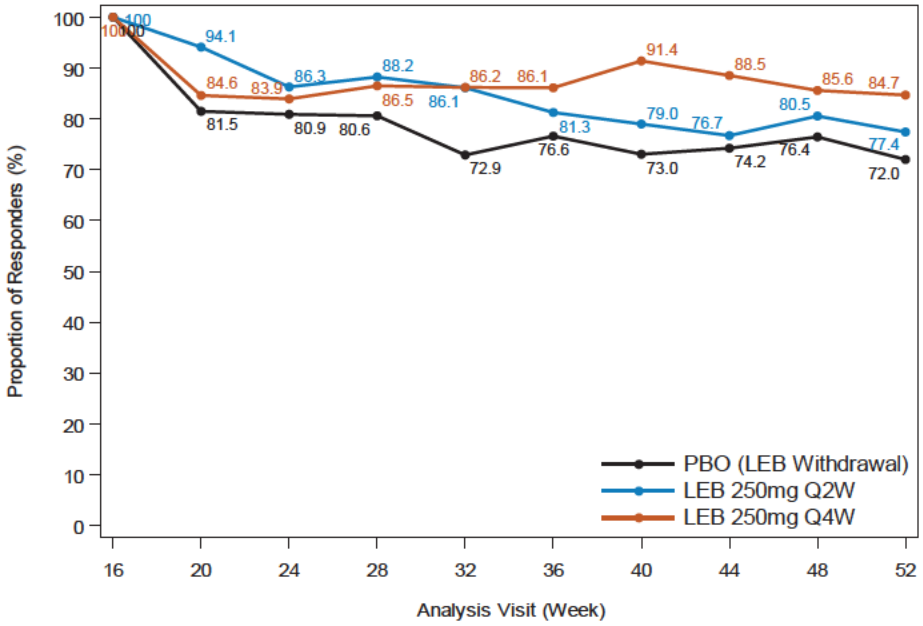
[1] Cochran-Mantel-Haenszel (CMH) test adjusted by geographic region (US versus EU versus rest of world).
Source: reviewer analysis; adsl.xpt, adeasimc.xpt, and adigamc.xpt

Figure 10. Percentage of Subjects Having Achieved IGA 0 or 1 and a ≥ 2-point Improvement from Baseline at Week 16 who Continued to Exhibit IGA 0 or 1 and a ≥ 2-point Improvement from Baseline by Visit in Study KGAC



Abbreviations: IGA = Investigator Global Assessment; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: reviewer analysis; adsl.xpt and adigamc.xpt

Figure 11. Percentage of Subjects Having Achieved EASI75 at Week 16 who Maintain EASI75 Response by Visit in Study KGAC



Abbreviations: EASI = Eczema Area and Severity Index; EASI 75 = 75% reduction in EASI; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.
Source: reviewer analysis; adsl.xpt and adeasimc.xpt

8.1.3. Assessment of Efficacy Across Trials

Primary Endpoints

Lebrikizumab was statistically superior to placebo in Studies KGAB and KGAC in the target AD population for the primary endpoint of IGA success (defined as scoring 0 or 1 with ≥2-point reduction from Baseline) at Week 16. Treatment effects (lebrikizumab – placebo) for the primary endpoint were 29% and 21% for the two studies, respectively. The results were robust to the handling of missing data, and for Study KGAC, the impact of the inclusion or exclusion of the audited site. The results from Study KGAD are supportive because the prespecified primary analysis for Study KGAD was not statistically significant for the primary endpoint of IGA success for the ITT population, and the mITT analysis population was defined after analyzing the data. In addition, a substantial proportion of subjects (60%) in Study KGAD were enrolled through investigators who also participated in either Study KGAB or KGAC. Thus, Study KGAD is not independent from Studies KGAB and KGAC. See Table 28.

Subpopulations

Subgroup analyses were conducted for the primary IGA endpoint by age, sex, race, ethnicity, region, and baseline IGA score in the induction period.

In Studies KGAB, KGAC, and KGAD, Tables 36, 37, and 38 show that the treatment effects of

lebrikizumab observed across subgroups are consistent with effects seen in the overall study population except some subgroups due to the small number of subjects in the specified subgroups.

Table 36. IGA (0,1) with 2-Point Improvement Response Rates at Week 16 by Subgroup Primary Estimand, Markov Chain Monte Carlo Multiple Imputation (MCMC-MI), ITT Population in Study KGAB

	PBO N=141 n / Ns (%)[1]	LEB250Q2W N=283 n / Ns (%)[1]	Difference (95% CI)[2]
Age			
Adolescents (12 to <18)	4 / 18 (22.2)	18 / 37 (48.6)	26.4 (1.4, 51.5)
Adults (≥ 18 to < 65)	14 / 113 (12.3)	95 / 225 (42.3)	30.0 (20.7, 39.2)
Adults (≥ 65)	0 / 10 (0.0)	9 / 21 (41.9)	41.5 (18.3, 64.7)
Sex			
Female	8 / 73 (11.4)	73 / 141 (51.7)	40.3 (28.8, 51.8)
Male	10 / 68 (14.1)	49 / 142 (34.5)	20.4 (8.8, 32.1)
Race			
American Indian or Alaska Native	-	2 / 7 (28.6)	-
Asian	1 / 31 (3.4)	10 / 39 (25.7)	22.4 (7.2, 37.6)
Black or African American	1 / 16 (8.8)	12 / 33 (37.7)	28.9 (6.0, 51.9)
Native Hawaiian or Other Pacific Islander	-	2 / 2 (100)	-
White	15 / 93 (16.5)	93 / 196 (47.3)	30.8 (20.1, 41.6)
Multiple	0 / 1 (16.0)	1 / 4 (25.0)	9.0 (-79.5, 97.5)
Other	-	1 / 1 (100.0)	-
Not Reported	-	1 / 1 (72.0)	-
Ethnicity			
Hispanic or Latino	4 / 16 (27.0)	12 / 25 (49.6)	22.6 (-8.2, 53.4)
Not Hispanic or Latino	14 / 125 (10.9)	107 / 252 (42.4)	31.5 (23.0, 39.9)
Not Reported	-	3 / 4 (68.0)	-
Unknown	-	0 / 2 (0.0)	-
Region			
US	8 / 62 (13.4)	55 / 128 (42.9)	29.5 (16.6, 42.3)
Europe	9 / 46 (18.7)	47 / 92 (51.6)	32.9 (17.5, 48.3)
Rest of World	1 / 33 (3.0)	20 / 63 (31.0)	28.0 (15.0, 40.9)
Baseline IGA 3 vs. 4			
IGA = 3	12 / 83 (14.2)	84 / 170 (49.2)	35.1 (23.8, 46.4)
IGA = 4	6 / 58 (10.6)	38 / 113 (33.8)	23.1 (11.3, 35.0)

Abbreviations: CI = confidence interval; IGA(0,1) = Investigator Global Assessment score 0 (clear) or 1 (almost clear); ITT = intent to treat; LEB = Lebrikizumab; n = number of responders in the specified category; N = number of patients in the analysis population; Ns = number of patients in the specified subgroup; PBO = placebo; Q2W = every 2 weeks.

Note: patients who received topical or systemic rescue medication, or discontinued treatment due to lack of efficacy, had values set to their baseline value subsequent to this time through Week 16; MCMC-MI was used to handle the remaining missing data. The analysis results were combined across all multiply imputed datasets using SAS PROC MIANALYZE. Percentage is calculated after MCMC-MI is used to handle the missing data.

[1] Unadjusted response rate and confidence interval.
[2] Treatment group differences are evaluated within each subgroup using the chi-square test.
Source: reviewer analysis; page 714 - 755 of KGAB. Clinical Study Report; adsl.xpt and adigamc.xpt

Table 37. IGA (0,1) with 2-Point Improvement Response Rates at Week 16 by Subgroup Primary Estimand, Markov Chain Monte Carlo Multiple Imputation (MCMC-MI), mITT Population in Study KGAC

	PBO N=146 n / Ns (%)[1]	LEB250Q2W N=281 n / Ns (%)[1]	Difference (95% CI)[2]
Age			
Adolescents (12 to <18)	1 / 17 (5.9)	13 / 30 (44.1)	38.3 (17.1, 59.4)
Adults (≥ 18 to < 65)	14 / 119 (11.6)	74 / 228 (32.3)	20.7 (12.1, 29.3)
Adults (≥ =65)	1 / 10 (10.0)	6 / 23 (27.1)	17.1 (-9.1, 43.4)
Sex			
Female	10 / 75 (13.5)	53 / 136 (38.6)	25.1 (13.6, 36.6)
Male	6 / 71 (7.9)	41 / 145 (28.0)	20.1 (10.1, 30.0)
Race			
American Indian or Alaska Native	0 / 2 (0.0)	2 / 3 (66.7)	66.7 (NA, NA)
Asian	2 / 44 (4.5)	19 / 78 (24.8)	20.3 (8.8, 31.7)
Black or African American	2 / 10 (20.4)	7 / 25 (27.2)	6.8 (-24.3, 37.9)
Native Hawaiian or Other Pacific Islander	1 / 1 (100.0)	0 / 2 (4.0)	-96.0 (NA, NA)
White	10 / 85 (11.6)	65 / 168 (38.6)	27.1 (16.8, 37.3)
Multiple	1 / 3 (33.3)	0 / 4 (0.0)	-33.3 (NA, NA)
Other	0 / 1 (0.0)	0 / 1 (0.0)	0.0 (NA, NA)
Ethnicity			
Hispanic or Latino	2 / 17 (11.8)	11 / 33 (32.1)	20.4 (-2.4, 43.1)
Not Hispanic or Latino	14 / 127 (10.9)	82 / 244 (33.4)	22.6 (14.3, 30.8)
Not Reported	0 / 2 (0.0)	1 / 4 (25.0)	25.0 (NA, NA)
Region			
US	13 / 60 (21.2)	34 / 107 (31.6)	10.4 (-3.6, 24.4)
Europe	2 / 38 (5.5)	32 / 76 (42.1)	36.6 (23.0, 50.1)
Rest of World	1 / 48 (2.1)	27 / 98 (27.9)	25.8 (16.0, 35.6)
Baseline IGA 3 vs. 4			
IGA = 3	14 / 95 (14.5)	65 / 175 (37.4)	22.8 (12.5, 33.2)
IGA = 4	2 / 51 (3.9)	28 / 106 (26.2)	22.3 (12.3, 32.3)

Abbreviations: CI = confidence interval; IGA(0,1) = Investigator Global Assessment score 0 (clear) or 1 (almost clear); LEB = Lebrikizumab; mITT = modified intent to treat; n = number of responders in the specified category; N = number of patients in the analysis population; NA = not available; Ns = number of patients in the specified subgroup; PBO = placebo; Q2W = every 2 weeks.

Note: some values are not available, denoted by NA, due to the small number of responders in the specified category.
Patients who received topical or systemic rescue medication, or discontinued treatment due to lack of efficacy, had values set to their baseline value subsequent to this time through Week 16; MCMC-MI was used to handle the remaining missing data. The analysis results were combined across all multiply imputed datasets using SAS PROC MIANALYZE. Percentage is calculated after MCMC-MI is used to handle the missing data.

[1] Unadjusted response rate and confidence interval.
[2] Treatment group differences are evaluated within each subgroup using the chi-square test.
Source: reviewer analysis; page 720 - 759 of KGAC. Clinical Study Report; adsl.xpt and adigamc.xpt

Table 38. IGA (0,1) with 2-Point Improvement Response Rates at Week 16 by Subgroup Primary Estimand, Markov Chain Monte Carlo Multiple Imputation (MCMC-MI), mITT Population in Study KGAD

	PBO + TCS N=66 n / Ns (%)	LEB250Q2W + TCS N=145 n / Ns (%)	Difference (95% CI)[1]
Age			

Adolescents (12 to <18)	4 / 14 (28.6)	18 / 32 (57.3)	28.7 (-0.7, 58.0)
Adults (≥ 18 to < 65)	9 / 47 (18.3)	37 / 98 (37.9)	19.6 (4.1, 35.1)
Adults (≥ 65)	2 / 5 (40.0)	4 / 15 (28.3)	-11.7 (-60.7, 37.2)
Sex			
Female	9 / 33 (27.8)	25 / 70 (35.9)	8.2 (-11.5, 27.9)
Male	5 / 33 (16.5)	35 / 75 (46.1)	29.6 (11.8, 47.4)
Race			
American Indian or Alaska Native	0 / 2 (0.0)	3 / 5 (68.8)	68.8 (NA, NA)
Asian	4 / 13 (27.4)	5 / 18 (30.0)	2.6 (-31.0, 36.2)
Black or African American	1 / 9 (11.1)	7 / 19 (36.8)	25.7 (-4.1, 55.6)
Native Hawaiian or Other Pacific Islander	-	0 / 3 (0.0)	-
White	9 / 40 (22.6)	37 / 90 (41.0)	18.4 (1.1, 35.7)
Multiple	1 / 1 (100.0)	6 / 8 (75.0)	-25.0 (NA, NA)
Other	0 / 1 (0.0)	1 / 2 (50.0)	50.0 (NA, NA)
Ethnicity			
Hispanic or Latino	4 / 15 (24.5)	12 / 30 (38.9)	14.4 (-16.2, 45.0)
Not Hispanic or Latino	11 / 51 (21.4)	45 / 112 (40.2)	18.8 (4.1, 33.5)
Not Reported	-	2 / 2 (100.0)	-
Unknown	-	1 / 1 (100.0)	-
Region			
US	12 / 48 (24.2)	36 / 103 (35.4)	11.3 (-4.9, 27.4)
Europe	2 / 10 (20.0)	18 / 28 (63.7)	43.7 (13.1, 74.4)
Rest of World	1 / 8 (12.5)	5 / 14 (38.6)	26.1 (-8.9, 61.0)
Baseline IGA 3 vs. 4			
IGA = 3	11 / 48 (23.3)	42 / 98 (43.1)	19.8 (3.4, 36.1)
IGA = 4	3 / 18 (18.9)	17 / 47 (37.2)	18.3 (-5.5, 42.1)

Abbreviations: CI = confidence interval; IGA(0,1) = Investigator Global Assessment score 0 (clear) or 1 (almost clear); LEB = Lebrikizumab; mITT = modified intent to treat; n = number of responders in the specified category; N = number of patients in the analysis population; NA = not available; Ns = number of patients in the specified subgroup; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.

Note: some values are not available, denoted by NA, due to the small number of responders in the specified category. Patients who received topical or systemic rescue medication, or discontinued treatment due to lack of efficacy, had values set to their baseline value subsequent to this time through Week 16; MCMC-MI was used to handle the remaining missing data. The analysis results were combined across all multiply imputed datasets using SAS PROC MIANALYZE. Percentage is calculated after MCMC-MI is used to handle the missing data.

[1] Unadjusted response rate and confidence interval.
[2] Treatment group differences are evaluated within each subgroup using the chi-square test.
Source: reviewer analysis; page 411 – 451 of KGAD. Clinical Study Report; adsl.xpt and adigamc.xpt

When combining Studies KGAB and KGAC, subgroup analyses for the primary IGA endpoint are also consistent except some subgroups with the small number of subjects. See Table 39.

Table 39. IGA (0,1) with 2-Point Improvement Response Rates at Week 16 by Subgroup Primary Estimand, Markov Chain Monte Carlo Multiple Imputation (MCMC-MI), mITT Population in Studies KGAB and KGAC

	PBO N=287 n / Ns (%)	LEB250Q2W N=564 n / Ns (%)	Difference (95% CI)[1]
Age			
Adolescents (12 to <18)	5 / 35 (14.3)	31 / 67 (46.6)	32.3 (15.6, 49.0)
Adults (≥ 18 to < 65)	28 / 232 (11.9)	169 / 453 (37.3)	25.3 (19.0, 31.7)
Adults (≥ 65)	1 / 20 (5.2)	15 / 44 (34.2)	29.0 (11.4, 46.6)

Sex			
Female	18 / 148 (12.5)	125 / 277 (45.3)	32.8 (24.6, 41.0)
Male	15 / 139 (11.0)	90 / 287 (31.2)	20.3 (12.6, 27.9)
Race			
American Indian or Alaska Native	0 / 2 (0.0)	4 / 10 (40.0)	40.0 (9.6, 70.4)
Asian	3 / 75 (4.1)	29 / 117 (25.1)	21.1 (12.0, 30.2)
Black or African American	3 / 26 (13.2)	19 / 58 (33.2)	19.9 (1.2, 38.7)
Native Hawaiian or Other Pacific Islander	1 / 1 (100.0)	2 / 4 (52.0)	-48.0 (NA, NA)
White	25 / 178 (14.1)	158 / 364 (43.3)	29.2 (21.7, 36.7)
Multiple	1 / 4 (29.3)	1 / 8 (12.5)	-14.5 (-68.3, 39.3)
Other	0 / 1 (0.0)	1 / 2 (50.0)	50.0 (NA, NA)
Not Reported	-	1 / 1 (72.0)	-
Ethnicity			
Hispanic or Latino	6 / 33 (19.2)	23 / 58 (39.7)	20.5 (1.2, 39.8)
Not Hispanic or Latino	27 / 252 (10.9)	188 / 496 (38.0)	27.1 (21.2, 33.0)
Not Reported	0 / 2 (0.0)	4 / 8 (46.5)	46.5 (NA, NA)
Missing	-	0 / 2 (0.0)	-
Region			
US	21 / 122 (17.2)	89 / 235 (37.8)	20.5 (10.8, 30.2)
Europe	11 / 84 (12.7)	79 / 168 (47.3)	34.5 (24.0, 45.1)
Rest of World	2 / 81 (2.5)	47 / 161 (29.1)	26.6 (18.8, 34.5)
Baseline IGA 3 vs. 4			
IGA = 3	26 / 178 (14.4)	149 / 345 (43.2)	28.9 (21.2, 36.6)
IGA = 4	8 / 109 (7.5)	66 / 219 (30.1)	22.6 (14.7, 30.5)

Abbreviations: CI = confidence interval; IGA(0,1) = Investigator Global Assessment score 0 (clear) or 1 (almost clear); LEB = Lebrikizumab; mITT = modified intent to treat; n = number of responders in the specified category; N = number of patients in the analysis population; Ns = number of patients in the specified subgroup; PBO = placebo; Q2W = every 2 weeks.

Note: some values are not available, denoted by NA, due to the small number of responders in the specified category.
Patients who received topical or systemic rescue medication, or discontinued treatment due to lack of efficacy, had values set to their baseline value subsequent to this time through Week 16; MCMC-MI was used to handle the remaining missing data. The analysis results were combined across all multiply imputed datasets using SAS PROC MIANALYZE. Percentage is calculated after MCMC-MI is used to handle the missing data.

[1] Unadjusted response rate and confidence interval.
[2] Treatment group differences are evaluated within each subgroup using the chi-square test.
Source: reviewer analysis; adsl.xpt and adigamc.xpt

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant's safety database is comprised of safety data from adult and adolescent subjects with AD from 8 studies:

- one phase 2, randomized, open-label Study KGAH
- 5 multi-center, randomized, double-blind, placebo-controlled studies, which include
  - two phase 2 Studies KGAG and KGAF, and
  - three phase 3 Studies KGAB (ADvocate 1), KGAC (ADvocate 2), and KGAD (ADhere)
- one phase 3, open-label, adolescent single-arm Study KGAE (ADore), and
- one phase 3, long-term safety Study KGAA (ADjoin).

However, the primary focus of this safety review is on the data from the placebo-controlled induction and maintenance periods from the 3 phase 3 studies (KGAB, KGAC, and KGAD).

The Applicant integrated safety data to form 6 analysis sets, which are described in the table below:

Table **40**. Description of Clinical Safety Analysis Sets

Analysis Set Name	Studies Included	Pooled Treatment Groups	Description	Purpose of Analysis Set
Placebo-Controlled Induction Period (Week 0-16)				
AD ALL PC Weeks 0-16	KGAF; KGAB; KGAC; KGAD	PBO ± TCS LEB 250mg Q2W ± TCS	Atopic Dermatitis Induction Period Placebo-Controlled Analysis Set	To evaluate the induction safety profile of lebrikizumab with or without TCS
AD Mono PC Weeks 0-16	KGAF; KGAB; KGAC	PBO LEB 250mg Q2W	Atopic Dermatitis Monotherapy Induction Period Placebo-Controlled Analysis Set	To evaluate the induction safety profile of lebrikizumab without TCS
AD TCS PC Weeks 0-16	KGAD	PBO + TCS LEB 250mg Q2W + TCS	Atopic Dermatitis TCS Combination Induction Period Placebo-Controlled Analysis Set	To evaluate the induction safety profile of lebrikizumab with TCS
Maintenance Period (Week 16-52)				
AD Mono PC Weeks 16-52	KGAB; KGAC	Placebo (LEB withdrawal) LEB 250mg Q4W LEB 250mg Q2W	Atopic Dermatitis Monotherapy Maintenance Period Placebo-Controlled Analysis Set	To evaluate the maintenance safety profile of lebrikizumab monotherapy at Q2W or Q4W
Combined Induction and Maintenance Periods (Week 0 – 52/56)				
AD Mono/TCS Weeks 0-52/56	KGAF; KGAB;	PBO ± TCS LEB 250mg Q4W	Atopic Dermatitis	To evaluate the safety profile of

	KGAC; KGAD; KGAA	LEB 250mg Q2W ± TCS	Combined Induction and Maintenance Periods Analysis Set	lebrikizumab used up to 52/56 weeks
Any Exposure to Lebrikizumab				
AD All LEB	KGAG; KGAH; KGAF; KGAB; KGAC; KGAD; KGAA; KGAE	Any LEB 250mg Q2W Any LEB 250mg Q4W Any lebrikizumab (AD)	Atopic Dermatitis All Lebrikizumab Exposure Integrated Analysis Set	To evaluate the lebrikizumab safety profile across all AD studies and identify more unusual or rare events, or events with long latency that might require further evaluation, case review, and discussion.

Source: Modified from Table 2.5.2.4 of Clinical Overview and Table 2.7.4.3 of Summary of Clinical Safety

Safety Analysis Population

The safety population is generally defined as all randomized participants who receive at least 1 dose of their study treatment. However, the primary analysis population for this application is the modified safety population described below.

Modified Safety Population

The modified safety population includes all participants receiving at least 1 dose of study drug minus 38 participants excluded due to site audit findings.

In Study KGAD, following the primary outcome database lock (Week 16), a site audit initiated by implausible data at one study site resulted in a critical finding. The Applicant's audit revealed noncompliance with protocol entry criteria related to severity of AD at baseline. As a result, the data from this site was determined to be unreliable. The same site also participated in Studies KGAC and KGAA, thus impacting participant data for these studies as well. The safety data from the noncompliant site were excluded (38 participants) from the main safety analyses in the SCS as the associated data were unreliable.

Although that the data for the aforementioned 38 subjects was deemed unreliable due to issues related to entry criteria, this clinical reviewer believed the safety data to still be usable. Therefore, unless specified otherwise, the safety analyses were performed for the entire safety population (including the 38 excluded subjects) rather than the modified safety population.

120-Day Safety Update

The Applicant submitted a 120-day Safety Update Report (SUR) on January 12, 2023, which included information from participants in Study KGAA with a longer duration of exposure, as well as an additional 286 participants from Study KGAL, with a data cutoff of September 15, 2022. Study KGAL, a placebo-controlled evaluation of lebrikizumab in combination with TCS, was conducted in Japan. Additional data from the safety follow up period in KGAB, KGAC, and KGAE were also included in this safety update. Overall, the safety data update was consistent with the safety profile of lebrikizumab from the safety review of the initial BLA submission and did not identify any new safety concerns.

I conclude that the safety database is adequate in size and extent of exposure of study subjects to permit a reasonable assessment of the safety of lebrikizumab.

8.2.2. Review of the Safety Database

Overall Exposure

The atopic dermatitis development program for lebrikizumab included a total of 1756 subjects, including 382 adolescents, who were exposed to any dose of lebrikizumab. A total of 903 subjects were exposed to any dose of lebrikizumab for at least 1 year; of those, 272 were adolescents. A total of 754 subjects were exposed to Lebrikizumab 250 mg Q2W as the only treatment (never received Lebrikizumab 250 mg Q4W) for at least 1 year; of those, 247 were adolescents.

Table **41.** Overview of Exposure Duration by Age Group in the Lebrikizumab Atopic Dermatitis Development Program

	LEB250Q2W only			Any LEB250Q2W			Any LEB		
	Adolescents (12<18) years (N=352)	Adults >=18 - < 65 years (N=805)	Adults >=65 (N=92)	Adolescents (12<18) years (N=381)	Adults >=18 - < 65 years (N=920)	Adults >=65 (N=101)	Adolescents (12<18) years (N=382)	Adults >=18 - < 65 years (N=1250)	Adults >=65 (N=124)
> 0 Weeks of Exposure	352 (100.0)	805 (100.0)	92 (100.0)	381 (100.0)	920 (100.0)	101 (100.0)	382 (100.0)	1250 (100.0)	124 (100.0)
>= 4 Weeks of Exposure	350 (99.4)	792 (98.4)	90 (97.8)	379 (99.5)	907 (98.6)	99 (98.0)	380 (99.5)	1232 (98.6)	121 (97.6)
>= 16 Weeks of Exposure	332 (94.3)	726 (90.2)	79 (85.9)	356 (93.4)	820 (89.1)	85 (84.2)	362 (94.8)	1132 (90.6)	107 (86.3)
>= 24 Weeks of Exposure	316 (89.8)	672 (83.5)	71 (77.2)	316 (82.9)	677 (73.6)	72 (71.3)	345 (90.3)	893 (71.4)	93 (75.0)
>= 32 Weeks of Exposure	300 (85.2)	610 (75.8)	64 (69.6)	300 (78.7)	613 (66.6)	64 (63.4)	327 (85.6)	800 (64.0)	82 (66.1)
>= 40 Weeks of Exposure	291 (82.7)	525 (65.2)	54 (58.7)	291 (76.4)	527 (57.3)	54 (53.5)	316 (82.7)	646 (51.7)	62 (50.0)
>= 52(a) Week of Exposure	250 (71.0)	466 (57.9)	47 (51.1)	250 (65.6)	467 (50.8)	47 (46.5)	275 (72.0)	582 (46.6)	55 (44.4)
>= 52 Weeks of Exposure	247 (70.2)	460 (57.1)	47 (51.1)	247 (64.8)	461 (50.1)	47 (46.5)	272 (71.2)	576 (46.1)	55 (44.4)

>= 78 Weeks of Exposure	42 (11.9)	142 (17.6)	19 (20.7)	42 (11.0)	143 (15.5)	19 (18.8)	54 (14.1)	196 (15.7)	26 (21.0)
>= 104 Weeks of Exposure	5 (1.4)	25 (3.1)	4 (4.3)	5 (1.3)	25 (2.7)	4 (4.0)	13 (3.4)	39 (3.1)	7 (5.6)
Patient Days of Exposure Mean (SD) Median (Min, Max)	391.9 (147.88) 396.0 (17, 815)	370.5 (189.35) 378.0 (1, 892)	357.9 (219.16) 374.5 (18, 939)	370.6 (160.39) 394.0 (17, 815)	339.3 (196.23) 364.0 (1, 892)	336.5 (220.15) 313.0 (18, 939)	402.8 (158.99) 401.5 (17, 900)	331.8 (196.66) 297.0 (1, 909)	343.0 (226.46) 267.0 (16, 939)
Total Patient Years	377.73	816.54	90.14	386.63	854.67	93.04	421.23	1135.56	116.46
Amount of Lebrikizumab Doses Taken for Treatment Period (mg) Mean (SD) Median (Min, Max)	7420.5 (2735.63) 7750.0 (500, 15250)	6805.0 (3571.11) 7250.0 (500, 16750)	6502.7 (4132.84) 6375.0 (500, 16750)	7042.7 (2941.48) 7750.0 (500, 15250)	6284.0 (3628.45) 6750.0 (500, 16750)	6151.0 (4102.60) 5250.0 (500, 16750)	7306.3 (2699.36) 7750.0 (500, 15250)	5141.2 (3967.92) 5125.0 (125, 16750)	5465.7 (4243.16) 4500.0 (125, 16750)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTNEW = 'Any LEB250Q2W' or 'Any LEB250Q4W' or 'LEB250Q2W only (All EXP)' or 'LEB250Q2W/Q4W only (All EXP)' or 'Any LEB', SAFFL = 'Y'.
> 0 Weeks of Exposure - Dataset: Exposure; Filter: EXPFLNEW = 'Y', EXPWK = '>= 52' or '> 104' or '>= 24' or '>= 32' or '>= 52 (a)' or '>= 40' or '>= 4' or '>= 16' or '>= 78' or '> 0'.
> 4 Weeks of Exposure - Dataset: Exposure; Filter: EXPFLNEW = 'Y', EXPWK = '>= 52' or '> 104' or '>= 24' or '>= 32' or '>= 52 (a)' or '>= 40' or '>= 4' or '>= 16' or '>= 78'.
>= 16 Weeks of Exposure - Dataset: Exposure; Filter: EXPFLNEW = 'Y', EXPWK = '>= 52' or '> 104' or '>= 24' or '>= 32' or '>= 40' or '>= 16' or '>= 52 (a)' or '>= 78'.
>= 24 Weeks of Exposure - Dataset: Exposure; Filter: EXPFLNEW = 'Y', EXPWK = '>= 24' or '>= 32' or '>= 40' or '>= 52' or '> 104' or '>= 52 (a)' or '>= 78'.
>= 32 Weeks of Exposure - Dataset: Exposure; Filter: EXPWK = '>= 52' or '> 104' or '>= 32' or '>= 40' or '>= 52 (a)' or '>= 78', EXPFLNEW = 'Y'.
>= 40 Weeks of Exposure - Dataset: Exposure; Filter: EXPFLNEW = 'Y', EXPWK = '>= 52' or '> 104' or '>= 40' or '>= 52 (a)' or '>= 78'.
>= 52(a) Week of Exposure - Dataset: Exposure; Filter: EXPFLNEW = 'Y', EXPWK = '>= 52' or '> 104' or '>= 52 (a)' or '>= 78'.
>= 52 Weeks of Exposure - Dataset: Exposure; Filter: EXPFLNEW = 'Y', EXPWK = '>= 52' or '> 104' or '>= 78'.
>= 78 Weeks of Exposure - Dataset: Exposure; Filter: EXPFLNEW = 'Y', EXPWK = '> 104' or '>= 78'.
>= 104 Weeks of Exposure - Dataset: Exposure; Filter: EXPFLNEW = 'Y', EXPWK = '> 104'.
Weeks of Exposure - Dataset: Exposure; Filter: EXPFLNEW = 'Y'.
Patient Days of Exposure - Dataset: Exposure; Filter: EXPFLNEW = 'Y'.
Total Patient Years - Dataset: Exposure; Filter: EXPFLNEW = 'Y'. Values manually entered based on JMP Analysis.
Amount of Lebrikizumab Doses Taken for Treatment Period (mg) - Dataset: Exposure; Filter: DOSFLNEW = 'Y'.
SD = Standard Deviation.
52 (a): according to the minimum protocol window of 5 days = 360 days.

120-Day Safety Update

The 120-day safety update report included data from an additional 276 subjects (including 20 adolescents) from Study KGAL, as well as an additional 223.57 PY from subjects included in the original submission, for a total of 502.47 PY.

Adequacy of the safety database:

The safety database submitted by the Applicant is sufficient to characterize the safety profile of lebrikizumab for the treatment of moderate-to-severe AD.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of lebrikizumab. The Applicant's translation of verbatim terms to MedDRA preferred terms and subsequent categorization of preferred terms was adequate. There were no significant deficiencies discovered that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

Adverse events were reported based on the MedDRA Version 25. A TEAE was defined as an event that first occurred or worsened in severity after baseline.

The severity of an AE was designated as mild, moderate or severe.

Serious Adverse Events (SAEs)
An SAE was defined as any untoward medical occurrence that,

- Resulted in death
- Was, in the opinion of the Investigator, immediately life threatening (i.e., the patient was at immediate risk of death; it did not include a reaction that, had it occurred in a more severe form, might have caused death)
- Required inpatient hospitalization or resulted in prolongation of an existing hospitalization
- Resulted in persistent or significant disability or incapacity
- Was a congenital anomaly or birth defect
- Was an important medical event that may not have been immediately life-threatening, resulted in death, or required hospitalization, but based on appropriate medical judgment, it jeopardized the patient, or may have required medical or surgical intervention to prevent one of the outcomes

Relationship of an AE to the Study Drug
The relationship of the AE to the study treatment was determined by the Investigator and was based on the following two definitions:

- Not related: The AE is judged to not be associated with the study drug and is most likely attributable to another cause.
- Related: A causal relationship between the AE and the study drug is a reasonable possibility, i.e., there is evidence (e.g., dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

Adverse Events of Special Interest (AESIs)
The following treatment emergent adverse events were designated adverse events of special interest (AESI):

- Conjunctivitis/keratitis
- Infections, including herpes infection or zoster

- Parasitic infection or an infection related to an intracellular pathogen

Additional safety topics of special interest included:

- Eosinophilia and eosinophil-related disorders
- Hypersensitivity reactions
- Injection site reactions
- Atopic dermatitis exacerbations
- Hepatic safety
- Suicide/self-injury
- Malignancies

Routine Clinical Tests

The Applicant performed routine clinical laboratory testing (hematology, chemistry, urinalysis), as well as physical examinations and vital signs, throughout the development program. The frequency and schedule of testing varied according to the study.

The safety assessments methods appear reasonable and adequate for the population, disease, and indication and allowed for adequate characterization of the safety of lebrikizumab.

8.2.4. Safety Results

Deaths

Five deaths occurred in the development program for AD. The Applicant reported that none of the deaths were assessed as related to lebrikizumab. The subject reports are described below:

Subject KGAC-(b) (6) (Myocardial Infarction)
During the induction period of Study KGAC, a 56-year-old male with history of borderline hypertension, hyperlipidemia, allergic asthma, anemia, allergic rhinitis, allergic conjunctivitis, and vitiligo died of a myocardial infarction on Study Day 8, as reported by the investigator. The participant was receiving placebo and received the first and only administration on Study Day 1. The participant experienced a fatal heart attack without signs or symptoms prior to the event. The investigator assessed the event to be unrelated to study treatment.

KGAC-(b) (6) (Pancreatic Carcinoma Metastatic, Metastases to Liver, Metastases to Bone)
During the maintenance escape treatment period of Study KGAC, a 74-year-old black male participant with medical history of hypertension, hypercholesterolemia, and penicillin allergy died of pancreatic cancer with evidence of metastasis to the liver, bone, and kidney on Study Day 310 as reported by the investigator. The participant was randomly assigned to lebrikizumab 250 mg Q2W on Study Day 1 and continued to receive lebrikizumab 250 mg Q2W during the maintenance period. He received his last dose of lebrikizumab on Study Day 309. A nonserious

event of weight decreased was reported on Study Day 281 preceding, the participant was admitted to the hospital for evaluation and diagnosed with metastatic pancreatic cancer. This participant was discharged to hospice and passed away on Study Day 337. The participant had risk factors including high BMI, race/ethnicity, and alcohol use. The investigator assessed the event as unrelated to study treatment.

KGAA-(b) (6) (Death due to Natural Causes)

A 56-year-old male participant was randomly assigned to lebrikizumab 250 mg Q2W on Study Day 1 in Study KGAD and continued to receive lebrikizumab 250 mg Q2W. On Study Day 115 in Study KGAD, the participant entered the long-term extension Study KGAA. During the long-term extension Study KGAA, the participant died of natural causes on Study Day 462, as reported by the investigator. The participant had a medical history of hypertension, cardiac ablation, AD, insomnia, and gastroesophageal reflux disease. The event was reported by a neighbor when the site attempted to contact the participant for a missed appointment. No autopsy was performed, and no death certificate was available. The investigator assessed the event to be unrelated to study treatment.

KGAE-(b) (6) (Cardiac Arrest)

During the open-label Study KGAE, a 13-year-old male participant died of cardiac arrest on Study Day 155, as reported by the investigator. The participant was assigned to open label lebrikizumab 250 mg Q2W on Study Day 1. The participant had a past medical history of craniosynostosis status post cranio-expansion; omphalocele status post repair; scoliosis; asthma; seasonal allergic rhinitis with sensitivity to cat, dog, dust mites, and grass pollen; severe peanut allergy; and pectus deformity on examination of the chest. There was no history of cardiac disease. The participant had no signs or symptoms of cardiac distress and was found on the floor, unresponsive. The participant was declared to have expired when brought to the hospital emergency room. The participant tested positive for COVID-19 in the hospital emergency room as part of screening. The participant had not tested positive prior to the event, and no symptoms were reported in the past and had no known close contacts who were symptomatic or who had tested positive. The investigator reported the cardiac arrest was likely due to COVID-19. The investigator assessed the event to be unrelated to study treatment. Per the investigator, the emergency room records show cause of death as cardiac arrest and COVID-19 positive. The family chose not to pursue further evaluations and no autopsy was performed. No additional information is available. Omphalocele has been associated with various anomalies including major cardiac and chromosomal defects (Mayer et al. 1980).

KGAD-(b) (6) (Pancreatic Carcinoma Metastatic)

A 64-year-old male with coronary artery disease and myocardial infarction status post coronary artery bypass, hypertension, type 2 diabetes mellitus, hyperuricemia, duodenal ulcer, benign prostatic hyperplasia, and basal cell carcinoma and prior treated with tacrolimus receiving lebrikizumab 250 mg Q2W through Week 16 in Study KGAD and continued receiving lebrikizumab 250 mg Q2W in Study KGAA. On Study Day 582, he was admitted to the hospital

with constipation, gas retention, decreased appetite, and intended weight loss of approximately 5 kilograms. On examination, he was found to have a distended abdomen and ascites. Laboratory results showed mild normocytic anemia, elevated D-dimer, C-reactive protein, gamma-glutamyl transpeptidase, and creatinine. A computed tomography scan of the abdomen showed several metastatic foci in the liver, ascites, and a pathological focal lesion in the tail of the pancreas and an ultrasound confirmed metastatic lesions. He was diagnosed with metastatic pancreatic carcinoma. Paracentesis was performed and symptomatic treatment was administered, leading to general condition improvement. Participant was discharged from the hospital and referred to gastrointestinal surgery. On Study Day 608, he died due to pancreatic cancer with metastasis to liver. It was unknown if an autopsy was performed. The event was assessed as not related to study drug by the investigator.

Reviewer Comment: *This reviewer agrees with the assessment that the five deaths do not appear to be related to the investigational product.*

Serious Adverse Events

Placebo-Controlled Induction Period (Weeks 0 to 16)

The frequency of subjects reporting at least 1 SAE was similar in the lebrikizumab and placebo groups. The frequencies of subjects reporting at least 1 SAE were similar for lebrikizumab-treated participants in the LEB monotherapy and LEB+TCS group and were similar to placebo.

Table **42**. Summary of Serious Adverse Events by System Organ Class and Preferred Term from the Induction Period Placebo-Controlled Analysis Sets

System Organ Class - Preferred Term	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (ADhere)	
	PBO	LEB 250 mg Q2W	PBO	LEB 250 mg Q2W	PBO + TCS	LEB 250 mg Q2W + TCS
	N = 417	N = 805	N= 342	N = 652	N = 75	N = 153
	n (%)		n (%)		n (%)	
Cardiac disorders	**1 (0.2)**	**3 (0.4)**	**1 (0.3)**	**2 (0.3)**	**0 (0.0)**	**1 (0.7)**
Cardiac failure	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Myocardial infarction	1 (0.2)	1 (0.1)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)
Sinus node dysfunction	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
General disorders and administration site conditions	**1 (0.2)**	**1 (0.1)**	**1 (0.3)**	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**
Oedema peripheral	1 (0.2)	1 (0.1)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)
Infections and infestations	**1 (0.2)**	**1 (0.1)**	**1 (0.3)**	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**
Cellulitis	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Large intestine infection	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

Sepsis	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**1 (0.2)**	**3 (0.4)**	**1 (0.3)**	**2 (0.3)**	**0 (0.0)**	**1 (0.7)**
Accidental overdose	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Fall	0 (0.0)	1 (0.1)	0 (0.)	0 (0.0)	0 (0.0)	1 (0.7)
Fibula fracture	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple injuries	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Tibia fracture	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (1.3)**	**0 (0.0)**
Dehydration	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**2 (0.2)**	**0 (0.0)**	**2 (0.3)**	**0 (0.0)**	**0 (0.0)**
Arthralgia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Synovitis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.2)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Uterine leiomyoma	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	**0 (0.0)**	**2 (0.2)**	**0 (0.0)**	**2 (0.3)**	**0 (0.0)**	**0 (0.0)**
Carpal tunnel syndrome	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Cerebellar syndrome	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Renal and urinary disorders	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (1.3)**	**0 (0.0)**
Acute kidney injury	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**1 (0.2)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Pulmonary embolism	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	**1 (0.2)**	**1 (0.1)**	**1 (0.3)**	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**
Dermatitis atopic	1 (0.2)	1 (0.1)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "PQ2W" and ALLPCFL = "Y" and SAFFL = "Y" (PQ2W); TRT01A = "L250Q2W" and ALLPCFL = "Y" and SAFFL = "Y" (L250Q2W); TRTEMFL = "Y" and AESER = "Y" and TEMONDFL = "Y" and ANL02FL = "Y" and AESER = "Y" (Adverse Events).
Filters: TRT01A = "Lebrikizumab 250mg Q2W" and SAFFL = "Y" (Lebrikizumab 250mg Q2W); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).
Filters: TRT01A = "PQ2W" and INDSAFFL = "Y" and SAFFL = "Y" (PQ2W); TRT01A = "L250Q2W" and INDSAFFL = "Y" and SAFFL = "Y" (L250Q2W); TRTEMFL = "Y" and AESER = "Y" and TEMONDFL = "Y" and ANL02FL = "Y" and AESER = "Y" (Adverse Events).

Brief vignettes describing SAEs in lebrikizumab-treated subjects during the placebo-controlled induction period are provided below:

KGAB-(b) (6) (Myocardial Infarction):
A 50-year-old male participant receiving lebrikizumab 250 mg Q2W, with a medical history of hypertension treated with perindopril and 20 years of smoking, presented with moderate pain in the lower jaw region and behind the chest, and difficulty of breathing while skiing. He reported an AE of myocardial infarction on Study Day 49. He

was hospitalized due to myocardial infarction (ECG showed anterolateral ST elevations and reciprocal ST depression and troponin 67.8 ng/L). The participant underwent percutaneous transluminal coronary angioplasty and stenting of the occluded left anterior descending coronary on the same day. The participant was recovered and discharged, and the investigator assessed the event as not related to study treatment.

KGAC-(b) (6) (Cardiac Failure):
A 67-year-old female participant receiving lebrikizumab 250 mg Q2W, with a medical history of chronic heart failure, arterial hypertension, hypothyroidism, asthma, allergic rhinitis, chronic obstructive pulmonary disease, allergic conjunctivitis, depression, restless leg syndrome, hysterectomy, and chronic pain syndrome, was hospitalized for a moderate event of cardiac failure on Study Day 7. During hospitalization, the participant had a lab evaluation that included an elevated brain natriuretic peptide 1058 pg/mL (RR less than 301 pg/mL) consistent with heart failure and was diagnosed with deterioration of coronary heart disease due to asthma. ECG showed normal sinus rhythm and thoracic echocardiogram with good left ventricular ejection fraction. The event resolved on Study Day 16 and the participant was discharged. The participant continued in the study without further recurrence. The event was assessed as not related by the investigator. This participant reported 5 additional SAEs, 1 moderate SAE of dermatitis atopic and 1 mild SAE of multiple injuries after a fall during the induction period, and 3 separate SAEs of acrodermatitis, erysipelas, and spinal osteoporosis during the maintenance escape period. All events resolved and did not lead to treatment discontinuation.

KGAD-(b) (6) (Sinus Node Dysfunction):
An 82-year-old female participant with medical history of anxiety, hypertension, spinal stenosis, asthma, osteoarthritis, bilateral ankle edema, and bilateral glaucoma receiving lebrikizumab 250 mg Q2W reported an SAE of sinus node dysfunction 5 days after receiving her last dose of lebrikizumab. On Study Day 48, the participant presented with a pulse of 30 bpm and “weight on her chest,” and a diagnosis of sinus node dysfunction was made. During investigation, a troponin less than 0.015 ng/mL (RR 0 – 0.50) was noted. An automatic implantable cardioverter defibrillator was placed. The participant´s ECG showed atrial fibrillation with rapid ventricular rate (112 bpm) and was later repeated to show sinus bradycardia (33 bpm) with 2-1 conduction. Troponin levels were 0.092 and 0.151 ng/mL which were considered as critically high (reference range was not provided). The event resolved with sequelae on Study Day 49 and subject was discharged. The participant continued in the study without further recurrence. The event was assessed as not related by the investigator.

KGAC-(b) (6) (Severe Infectious Colitis and Cerebellar Syndrome):
A 32-year-old male participant with no significant previous medical history and fexofenadine and emollient as concomitant medications was randomly assigned to

lebrikizumab 250 mg Q2W on Study Day 1. He reported a mild nonserious event of tinnitus on Study Day 13 that resolved on Study Day 129. He reported an SAE large intestine infection (severe infectious colitis) on Study Day 64. He confirmed eating prepackaged food prior to onset of event which may have led to infectious colitis. During hospitalization, he also reported symptoms of abdominal pain, nausea, dizziness/giddiness upon standing. He was hospitalized and treated with ciprofloxacin and metronidazole. The event was recovered on Study Day 68. On Study Day 74, he reported an SAE of cerebellar syndrome requiring hospitalization. He presented with non-vertiginous dizziness worsened from initial symptoms during previous hospitalization. He underwent an extensive lab and imaging evaluation including infectious panels and magnetic resonance imaging, magnetic resonance angiogram, and computed tomography of the brain, all of which were unremarkable. No etiology was identified for cerebellar syndrome. The event led to treatment discontinuation on Study Day 129 and the event was resolved with sequelae on Study Day 157. Patient was treated with multiple medications for infective colitis and dizziness including metronidazole, metoclopramide, and hyoscyamine during his hospitalizations which have the potential of causing or worsening the symptoms he reported. Certain infective colitis can also lead to similar symptoms.

No single PT within a systemic organ class (SOC) was reported by more than 1 subject in each treatment group. In general, the number of SAEs was low across subgroups. No specific clusters of safety issues were identified.

Maintenance period (AD Mono PC Weeks 16 to 52)

During the monotherapy maintenance period, the frequencies of SAEs were low, and no SAE was reported by more than 1 subject. The frequencies of participants with at least 1 SAE were similar for both lebrikizumab groups and placebo (LEB withdrawal).

Table 43. Summary of Serious Adverse Events by Preferred Term During the Monotherapy Maintenance Period (Weeks 16 to 52)

System Organ Class - Preferred Term	PBO (N=62)		LEB 250 mg Q4W (N=122)		LEB 250 mg Q2W (N=121)	
	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.8)**
Pancreatitis	0	(0.0)	0	(0.0)	1	(0.8)
Hepatobiliary disorders	**0**	**(0.0)**	**1**	**(0.8)**	**0**	**(0.0)**
Cholecystitis	0	(0.0)	1	(0.8)	0	(0.0)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.8)**
Humerus fracture	0	(0.0)	0	(0.0)	1	(0.8)
Ulna fracture	0	(0.0)	0	(0.0)	1	(0.8)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(0.8)**	**0**	**(0.0)**

Somatic symptom disorder	0	(0.0)	1	(0.8)	0	(0.0)
Renal and urinary disorders	**1**	**(1.6)**	**0**	**(0.0)**	**0**	**(0.0)**
Ureterolithiasis	1	(1.6)	0	(0.0)	0	(0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: MPSAFFL = "Y" and TRT02A = "PQ2W" and SAFFL = "Y" (PBO); TRT02A = "L250Q4W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q4W); TRT02A = "L250Q2W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL03FL = "Y" and AESER = "Y" (Adverse Events).

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)

In the combined induction and maintenance period analysis set, with the exception of COVID-19 and atopic dermatitis, SAEs were not reported by more than 1 subject.

Table 4444. Summary of Serious Treatment-Emergent Adverse Events for the Combined Induction and Maintenance Periods Analysis Set (Studies KGAB, KGAC, KGAD, and KGAA)

System Organ Class – Preferred Term	LEB250Q2W only		LEB250Q2W/ Q4W only		All LEB250Q2W		All LEB250Q2W/ Q4W		PBO	
	(N=872)		(N=151)		(N=1023)		(N=1023)		(N=365)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**6**	**(0.7)**	**1**	**(0.7)**	**7**	**(0.7)**	**4**	**(0.4)**	**1**	**(0.3)**
Fall	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Humerus fracture	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Multiple injuries	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Paternal exposure during pregnancy	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Road traffic accident	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Thermal burn	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Ulna fracture	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Accidental overdose	0	(0.0)	1	(0.7)	1	(0.1)	1	(0.1)	0	(0.0)
Fibula fracture	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Tibia fracture	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Infections and infestations	**5**	**(0.6)**	**0**	**(0.0)**	**5**	**(0.5)**	**3**	**(0.3)**	**2**	**(0.5)**
Covid-19	2	(0.2)	0	(0.0)	2	(0.2)	1	(0.1)	0	(0.0)
Acarodermatitis	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Erysipelas	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Large intestine infection	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Pneumonia	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	1	(0.3)
Cellulitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Sepsis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Cardiac disorders	**3**	**(0.3)**	**0**	**(0.0)**	**3**	**(0.3)**	**3**	**(0.3)**	**1**	**(0.3)**
Cardiac failure	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)

Myocardial infarction	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	1	(0.3)
Sinus node dysfunction	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Musculoskeletal and connective tissue disorders	**3**	**(0.3)**	**1**	**(0.7)**	**4**	**(0.4)**	**2**	**(0.2)**	**0**	**(0.0)**
Arthritis	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Spinal osteoarthritis	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Synovitis	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Arthralgia	0	(0.0)	1	(0.7)	1	(0.1)	1	(0.1)	0	(0.0)
Skin and subcutaneous tissue disorders	**3**	**(0.3)**	**0**	**(0.0)**	**3**	**(0.3)**	**1**	**(0.1)**	**1**	**(0.3)**
Dermatitis atopic	3	(0.3)	0	(0.0)	3	(0.3)	1	(0.1)	1	(0.3)
Eye disorders	**2**	**(0.2)**	**0**	**(0.0)**	**2**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**
Cataract	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Rhegmatogenous retinal detachment	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Sudden visual loss	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Nervous system disorders	**2**	**(0.2)**	**0**	**(0.0)**	**2**	**(0.2)**	**2**	**(0.2)**	**0**	**(0.0)**
Carpal tunnel syndrome	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Cerebellar syndrome	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Reproductive system and breast disorders	**2**	**(0.2)**	**0**	**(0.0)**	**2**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**
Dysmenorrhoea	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Micromastia	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Pancreatitis	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**	**0**	**(0.0)**
Oedema peripheral	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.3)**
Metastases to bone	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Metastases to liver	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Pancreatic carcinoma metastatic	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Uterine leiomyoma	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Hepatobiliary disorders	**0**	**(0.0)**	**1**	**(0.7)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**
Cholecystitis	0	(0.0)	1	(0.7)	0	(0.0)	1	(0.1)	0	(0.0)
Metabolism and nutrition disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.3)**
Dehydration	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Psychiatric disorders	**0**	**(0.0)**	**2**	**(1.3)**	**0**	**(0.0)**	**2**	**(0.2)**	**0**	**(0.0)**
Depression	0	(0.0)	1	(0.7)	0	(0.0)	1	(0.1)	0	(0.0)
Somatic symptom disorder	0	(0.0)	1	(0.7)	0	(0.0)	1	(0.1)	0	(0.0)

Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.3)**
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Source: OCS Analysis Studio, Safety Explorer.										
Filters: TRTNEW = “LEB250Q2W only” and COMBIMFL = “Y” and SAFFL = “Y” (LEB250Q2W only); TRTNEW = “LEB250Q2W/Q4W only” and COMBIMFL = “Y” and SAFFL = “Y” (LEB250Q2W/Q4W only); TRTNEW = “All LEB250Q2W” and COMBIMFL = “Y” and SAFFL = “Y” (All LEB250Q2W); TRTNEW = “All LEB250Q2W/Q4W” and COMBIMFL = “Y” and SAFFL = “Y” (All LEB250Q2W/Q4W); TRTNEW = “PBO” and COMBIMFL = “Y” and SAFFL = “Y” (PBO); TEFLNEW = “Y” and AESER = “Y” (Adverse Events).										

Any AD lebrikizumab exposure (AD All LEB)

The incidence rates (IRs) per 100 PY of SAEs were

- 3.5 in the Any LEB group
  - 3.5 in the Any LEB 250 mg Q2W group, and
  - 2.2 in the Any LEB 250 mg Q4W group.

These IRs for any lebrikizumab-treated participant were similar to those reported in the LEB 250 mg Q2W group in the placebo-controlled induction period.

Table 4455. Summary of Serious Treatment-Emergent Adverse Events for All Lebrikizumab Exposure Integrated Analysis Set (Studies KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, KGAA, and KGAE)

System Organ Class - Preferred Term	Any LEB250Q2W (N=1402)		Any LEB250Q4W (N=250)		Any LEB (N=1756)	
	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**11**	**(0.8)**	**0**	**(0.0)**	**12**	**(0.7)**
Multiple injuries	2	(0.1)	0	(0.0)	2	(0.1)
Accidental overdose	1	(0.1)	0	(0.0)	1	(0.1)
Ankle fracture	1	(0.1)	0	(0.0)	1	(0.1)
Fall	1	(0.1)	0	(0.0)	1	(0.1)
Hip fracture	1	(0.1)	0	(0.0)	1	(0.1)
Humerus fracture	1	(0.1)	0	(0.0)	1	(0.1)
Paternal exposure during pregnancy	1	(0.1)	0	(0.0)	1	(0.1)
Road traffic accident	1	(0.1)	0	(0.0)	1	(0.1)
Subdural haematoma	1	(0.1)	0	(0.0)	1	(0.1)
Thermal burn	1	(0.1)	0	(0.0)	1	(0.1)
Ulna fracture	1	(0.1)	0	(0.0)	1	(0.1)
Periprosthetic fracture	0	(0.0)	0	(0.0)	1	(0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6**	**(0.4)**	**0**	**(0.0)**	**6**	**(0.3)**
Endometrial adenocarcinoma	1	(0.1)	0	(0.0)	1	(0.1)

Invasive breast carcinoma	1	(0.1)	0	(0.0)	1	(0.1)
Metastases to bone	1	(0.1)	0	(0.0)	1	(0.1)
Metastases to liver	1	(0.1)	0	(0.0)	1	(0.1)
Neuroendocrine tumour	1	(0.1)	0	(0.0)	1	(0.1)
Ovarian germ cell teratoma benign	1	(0.1)	0	(0.0)	1	(0.1)
Pancreatic carcinoma metastatic	1	(0.1)	0	(0.0)	1	(0.1)
Prostate cancer	1	(0.1)	0	(0.0)	1	(0.1)
Infections and infestations	**5**	**(0.4)**	**0**	**(0.0)**	**5**	**(0.3)**
Covid-19	2	(0.1)	0	(0.0)	2	(0.1)
Acarodermatitis	1	(0.1)	0	(0.0)	1	(0.1)
Erysipelas	1	(0.1)	0	(0.0)	1	(0.1)
Large intestine infection	1	(0.1)	0	(0.0)	1	(0.1)
Pneumonia	1	(0.1)	0	(0.0)	1	(0.1)
Cardiac disorders	**4**	**(0.3)**	**0**	**(0.0)**	**4**	**(0.2)**
Cardiac arrest	1	(0.1)	0	(0.0)	1	(0.1)
Cardiac failure	1	(0.1)	0	(0.0)	1	(0.1)
Myocardial infarction	1	(0.1)	0	(0.0)	1	(0.1)
Sinus node dysfunction	1	(0.1)	0	(0.0)	1	(0.1)
Musculoskeletal and connective tissue disorders	**4**	**(0.3)**	**0**	**(0.0)**	**5**	**(0.3)**
Arthralgia	1	(0.1)	0	(0.0)	1	(0.1)
Arthritis	1	(0.1)	0	(0.0)	1	(0.1)
Spinal osteoarthritis	1	(0.1)	0	(0.0)	1	(0.1)
Synovitis	1	(0.1)	0	(0.0)	1	(0.1)
Myopathy	0	(0.0)	0	(0.0)	1	(0.1)
Nervous system disorders	**4**	**(0.3)**	**0**	**(0.0)**	**5**	**(0.3)**
Carpal tunnel syndrome	1	(0.1)	0	(0.0)	1	(0.1)
Cerebellar syndrome	1	(0.1)	0	(0.0)	1	(0.1)
Cervical cord compression	1	(0.1)	0	(0.0)	1	(0.1)
Seizure	1	(0.1)	0	(0.0)	1	(0.1)
Dizziness	0	(0.0)	0	(0.0)	1	(0.1)
Hypoaesthesia	0	(0.0)	0	(0.0)	1	(0.1)
Multiple sclerosis	0	(0.0)	0	(0.0)	1	(0.1)
Sensory loss	0	(0.0)	0	(0.0)	1	(0.1)
Skin and subcutaneous tissue disorders	**4**	**(0.3)**	**1**	**(0.4)**	**5**	**(0.3)**
Dermatitis atopic	3	(0.2)	1	(0.4)	4	(0.2)
Stevens-Johnson syndrome	1	(0.1)	0	(0.0)	1	(0.1)

General disorders and administration site conditions	**3**	**(0.2)**	**0**	**(0.0)**	**4**	**(0.2)**
Death	1	(0.1)	0	(0.0)	1	(0.1)
Influenza like illness	1	(0.1)	0	(0.0)	1	(0.1)
Oedema peripheral	1	(0.1)	0	(0.0)	1	(0.1)
Cyst	0	(0.0)	0	(0.0)	1	(0.1)
Reproductive system and breast disorders	**3**	**(0.2)**	**0**	**(0.0)**	**3**	**(0.2)**
Dysmenorrhoea	1	(0.1)	0	(0.0)	1	(0.1)
Micromastia	1	(0.1)	0	(0.0)	1	(0.1)
Testicular torsion	1	(0.1)	0	(0.0)	1	(0.1)
Eye disorders	**2**	**(0.1)**	**0**	**(0.0)**	**3**	**(0.2)**
Cataract	1	(0.1)	0	(0.0)	1	(0.1)
Rhegmatogenous retinal detachment	1	(0.1)	0	(0.0)	1	(0.1)
Sudden visual loss	1	(0.1)	0	(0.0)	1	(0.1)
Diplopia	0	(0.0)	0	(0.0)	1	(0.1)
Gastrointestinal disorders	**2**	**(0.1)**	**0**	**(0.0)**	**3**	**(0.2)**
Pancreatitis	1	(0.1)	0	(0.0)	1	(0.1)
Small intestinal obstruction	1	(0.1)	0	(0.0)	1	(0.1)
Inguinal hernia	0	(0.0)	0	(0.0)	1	(0.1)
Hepatobiliary disorders	**1**	**(0.1)**	**2**	**(0.8)**	**3**	**(0.2)**
Bile duct stone	1	(0.1)	0	(0.0)	1	(0.1)
Cholecystitis	0	(0.0)	1	(0.4)	1	(0.1)
Hepatic steatosis	0	(0.0)	1	(0.4)	1	(0.1)
Investigations	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Blood potassium decreased	1	(0.1)	0	(0.0)	1	(0.1)
Metabolism and nutrition disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Hypokalaemia	1	(0.1)	0	(0.0)	1	(0.1)
Psychiatric disorders	**1**	**(0.1)**	**2**	**(0.8)**	**3**	**(0.2)**
Depression suicidal	1	(0.1)	0	(0.0)	1	(0.1)
Depression	0	(0.0)	1	(0.4)	1	(0.1)
Somatic symptom disorder	0	(0.0)	1	(0.4)	1	(0.1)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.1)**
Nephrolithiasis	0	(0.0)	0	(0.0)	1	(0.1)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "Any LEB250Q2W" and SAFFL = "Y" (Any LEB250Q2W); TRTNEW = "Any LEB250Q4W" and SAFFL = "Y" (Any LEB250Q4W); TRTNEW = "Any LEB" and SAFFL = "Y" (Any LEB); TEFLNEW = "Y" and AESER = "Y" (Adverse Events).

120-Day Safety Update

Since the initial BLA submission, 17 additional subjects reported 18 SAEs. Three subjects who reported SAEs in the initial BLA submission reported 1 SAE each in the safety update.

Consistent with the initial BLA submission, no SAEs were reported by more than 1 subject.

Reviewer Comment: *This reviewer agrees with the investigators' assessments that the SAEs were not related to the study drug. Plausible explanations for the occurrences are the subjects' medical histories. The additional SAEs described in the 120-day safety update report did not identify any new safety concerns.*

APPEARS THIS WAY ON ORIGINAL

/pouts and/or Discontinuations Due to Adverse Effects

Placebo-Controlled Induction Period (Weeks 0 to 16)

Frequencies of AEs leading to permanent discontinuation of study treatment were low in lebrikizumab-treated subjects (2.3%) and placebo-treated subjects (1.4%). The most frequently reported AEs leading to discontinuation of study treatment were conjunctivitis in the lebrikizumab group and atopic dermatitis in the placebo group.

In the AD TCS study (KGAD -- ADhere), 3 AEs leading to permanent discontinuation of study treatment were reported in the LEB + TCS group. No single event leading to discontinuation was reported by more than 1 subject in the LEB + TCS group.

Table 4466. Adverse Events Leading to Permanent Discontinuation of Study Drug from the Induction Period Placebo-Controlled Analysis Sets

System Organ Class - Preferred Term	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (ADhere)	
	PBO	LEB 250 Q2W	PBO	LEB 250 Q2W	PBO + TCS	LEB 250 Q2W + TCS
	N=417	N=805	N=342	N=652	N=75	N=153
	n (%)		n (%)		n (%)	
Cardiac disorders	**1 (0.2)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Myocardial infarction	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	**0 (0.0)**	**2 (0.2)**	**0 (0.0)**	**2 (0.3)**	**0 (0.0)**	**0 (0.0)**
Atopic keratoconjunctivitis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Keratitis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	**0 (0.0)**	**4 (0.5)**	**0 (0.0)**	**3 (0.5)**	**0 (0.0)**	**1 (0.7)**

Injection site dermatitis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Injection site erythema	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Injection site pain	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Injection site rash	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.7)
Injection site swelling	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Oedema peripheral	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Immune system disorders	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.7)**
Drug hypersensitivity	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Infections and infestations	**2 (0.5)**	**4 (0.5)**	**2 (0.6)**	**3 (0.5)**	**0 (0.0)**	**1 (0.7)**
Conjunctivitis	1 (0.2)	2 (0.2)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.7)
Conjunctivitis bacterial	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Folliculitis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Skin infection	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**
Cerebellar syndrome	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Psychiatric disorders	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**
Panic attack	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	**4 (1.0)**	**6 (0.7)**	**4 (1.2)**	**6 (0.9)**	**0 (0.0)**	**0 (0.0)**
Dermatitis allergic	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Dermatitis atopic	4 (1.0)	4 (0.5)	4 (1.2)	4 (0.6)	0 (0.0)	0 (0.0)
Dermatitis exfoliative generalised	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: ALLPCFL = "Y" and TRT01A = "PQ2W" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and ALLPCFL = "Y" and SAFFL = "Y" (LEB 250Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).
Filters: INDSAFFL = "Y" and TRT01A = "PQ2W" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and INDSAFFL = "Y" and SAFFL = "Y" (LEB 250Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).
Filters: TRT01A = "Placebo" and SAFFL = "Y" (PBO); TRT01A = "Lebrikizumab 250mg Q2W" and SAFFL = "Y" (LEB 250Q2W); TRTEMFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

Monotherapy Maintenance Period (AD Mono PC Weeks 16 to 52)

The interpretation of AEs leading to discontinuation during the maintenance period is limited by infrequent events and the small sample size of this analysis set. The frequencies of AEs leading to permanent discontinuation of study treatment were:

- 1 (0.8%) event of vernal keratoconjunctivitis was reported in the LEB 250 mg Q2W group, and
- 2 (1.6%) events (1 event of conjunctivitis allergic and 1 event of conjunctivitis) were reported in the LEB 250 mg Q4W group.

Table 47. Adverse Events Leading to Permanent Discontinuation of Study Drug During the Monotherapy Maintenance Period			
System Organ Class - Preferred Term	**PBO**	**LEB 250 mg Q4W**	**LEB 250 mg Q2W**

	(N=62)		(N=122)		(N=121)	
	n	(%)	n	(%)	n	(%)
Eye disorders	**0**	**(0.0)**	**1**	**(0.8)**	**1**	**(0.8)**
Conjunctivitis allergic	0	(0.0)	1	(0.8)	0	(0.0)
Vernal keratoconjunctivitis	0	(0.0)	0	(0.0)	1	(0.8)
Infections and infestations	**0**	**(0.0)**	**1**	**(0.8)**	**0**	**(0.0)**
Conjunctivitis	0	(0.0)	1	(0.8)	0	(0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: MPSAFFL = "Y" and TRT02A = "PQ2W" and SAFFL = "Y" (PBO); TRT02A = "L250Q4W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q4W); TRT02A = "L250Q2W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2w); TRTEMFL = "Y" and ANL03FL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)

Conjunctivitis and dermatitis atopic were the most common events leading to discontinuation.

Table 48. Summary of Treatment-Emergent Adverse Events Leading to Discontinuation for the Combined Induction and Maintenance Periods Analysis Set (Studies KGAB, KGAC, KGAD, and KGAA

System Organ Class - Preferred Term	LEB250Q2W only		LEB250Q2W/Q4W only		All LEB250Q2W		All LEB250Q2W/Q4W		PBO	
	(N=872)		(N=151)		(N=1023)		(N=1023)		(N=365)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**8**	**(0.9)**	**2**	**(1.3)**	**9**	**(0.9)**	**9**	**(0.9)**	**2**	**(0.5)**
Conjunctivitis	5	(0.6)	2	(1.3)	6	(0.6)	6	(0.6)	1	(0.3)
Conjunctivitis bacterial	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Eye infection	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Folliculitis	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Skin infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Skin and subcutaneous tissue disorders	**6**	**(0.7)**	**0**	**(0.0)**	**6**	**(0.6)**	**4**	**(0.4)**	**3**	**(0.8)**
Dermatitis atopic	5	(0.6)	0	(0.0)	5	(0.5)	4	(0.4)	3	(0.8)
Dermatitis allergic	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Eye disorders	**5**	**(0.6)**	**1**	**(0.7)**	**5**	**(0.5)**	**4**	**(0.4)**	**0**	**(0.0)**
Atopic keratoconjunctivitis	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Cataract	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Conjunctivitis allergic	1	(0.1)	1	(0.7)	1	(0.1)	2	(0.2)	0	(0.0)
Keratitis	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Vernal keratoconjunctivitis	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**3**	**(0.3)**	**0**	**(0.0)**	**3**	**(0.3)**	**2**	**(0.2)**	**0**	**(0.0)**

Injection site rash	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0 (0.0)
Injection site reaction	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0 (0.0)
Oedema peripheral	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0 (0.0)
Immune system disorders	**3**	**(0.3)**	**0**	**(0.0)**	**3**	**(0.3)**	**2**	**(0.2)**	**0 (0.0)**
Drug hypersensitivity	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0 (0.0)
Hypersensitivity	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0 (0.0)
Sarcoidosis	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0 (0.0)
Injury, poisoning and procedural complications	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**	**0 (0.0)**
Road traffic accident	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0 (0.0)
Investigations	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**0 (0.0)**
White blood cell count increased	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**0 (0.0)**
Arthritis	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**0 (0.0)**
Metastases to bone	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0 (0.0)
Metastases to liver	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0 (0.0)
Pancreatic carcinoma metastatic	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0 (0.0)
Nervous system disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**	**0 (0.0)**
Cerebellar syndrome	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0 (0.0)
Psychiatric disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**	**0 (0.0)**
Panic attack	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0 (0.0)
Vascular disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**	**0 (0.0)**
Peripheral arterial occlusive disease	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0 (0.0)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1 (0.3)**
Myocardial infarction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1 (0.3)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "LEB250Q2W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W only); TRTNEW = "LEB250Q2W/Q4W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W/Q4W only); TRTNEW = "All LEB250Q2W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W); TRTNEW = "All LEB250Q2W/Q4W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W/Q4W); TRTNEW = "PBO" and COMBIMFL = "Y" and SAFFL = "Y" (PBO); TEFLNEW = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

Any AD lebrikizumab exposure (AD All LEB)

Conjunctivitis and dermatitis atopic were the most common events leading to discontinuation.

Table 4949. Summary of Treatment-Emergent Adverse Events Leading to Discontinuation for All Lebrikizumab Exposure Integrated Analysis Set (Studies KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, KGAA, and KGAE)

System Organ Class - Preferred Term	Any LEB250Q2W	Any LEB250Q4W	Any LEB

	(N=1402)		(N=250)		(N=1756)	
	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**14**	**(1.0)**	**1**	**(0.4)**	**16**	**(0.9)**
Dermatitis atopic	6	(0.4)	0	(0.0)	7	(0.4)
Dermatitis allergic	3	(0.2)	0	(0.0)	3	(0.2)
Psoriasis	2	(0.1)	0	(0.0)	2	(0.1)
Dermatitis exfoliative generalised	1	(0.1)	0	(0.0)	1	(0.1)
Rosacea	1	(0.1)	0	(0.0)	1	(0.1)
Stevens-johnson syndrome	1	(0.1)	0	(0.0)	1	(0.1)
Skin irritation	0	(0.0)	1	(0.4)	1	(0.1)
Infections and infestations	**13**	**(0.9)**	**1**	**(0.4)**	**16**	**(0.9)**
Conjunctivitis	10	(0.7)	0	(0.0)	11	(0.6)
Conjunctivitis bacterial	1	(0.1)	0	(0.0)	1	(0.1)
Eye infection	1	(0.1)	0	(0.0)	1	(0.1)
Folliculitis	1	(0.1)	0	(0.0)	1	(0.1)
Skin infection	0	(0.0)	1	(0.4)	2	(0.1)
General disorders and administration site conditions	**8**	**(0.6)**	**1**	**(0.4)**	**9**	**(0.5)**
Injection site pain	2	(0.1)	1	(0.4)	3	(0.2)
Death	1	(0.1)	0	(0.0)	1	(0.1)
Fatigue	1	(0.1)	0	(0.0)	1	(0.1)
Injection site dermatitis	1	(0.1)	0	(0.0)	1	(0.1)
Injection site erythema	1	(0.1)	1	(0.4)	2	(0.1)
Injection site rash	1	(0.1)	0	(0.0)	1	(0.1)
Injection site reaction	1	(0.1)	0	(0.0)	1	(0.1)
Injection site swelling	1	(0.1)	0	(0.0)	1	(0.1)
Oedema peripheral	1	(0.1)	0	(0.0)	1	(0.1)
Injection site oedema	0	(0.0)	1	(0.4)	1	(0.1)
Injection site pruritus	0	(0.0)	1	(0.4)	1	(0.1)
Eye disorders	**7**	**(0.5)**	**2**	**(0.8)**	**9**	**(0.5)**
Conjunctivitis allergic	3	(0.2)	2	(0.8)	5	(0.3)
Atopic keratoconjunctivitis	1	(0.1)	0	(0.0)	1	(0.1)
Cataract	1	(0.1)	0	(0.0)	1	(0.1)
Keratitis	1	(0.1)	0	(0.0)	1	(0.1)
Vernal keratoconjunctivitis	1	(0.1)	0	(0.0)	1	(0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6**	**(0.4)**	**0**	**(0.0)**	**6**	**(0.3)**
Cutaneous t-cell lymphoma	1	(0.1)	0	(0.0)	1	(0.1)

Endometrial adenocarcinoma	1	(0.1)	0	(0.0)	1	(0.1)
Invasive breast carcinoma	1	(0.1)	0	(0.0)	1	(0.1)
Metastases to bone	1	(0.1)	0	(0.0)	1	(0.1)
Metastases to liver	1	(0.1)	0	(0.0)	1	(0.1)
Neuroendocrine tumour	1	(0.1)	0	(0.0)	1	(0.1)
Pancreatic carcinoma metastatic	1	(0.1)	0	(0.0)	1	(0.1)
Prostate cancer	1	(0.1)	0	(0.0)	1	(0.1)
Immune system disorders	**5**	**(0.4)**	**0**	**(0.0)**	**5**	**(0.3)**
Hypersensitivity	3	(0.2)	0	(0.0)	3	(0.2)
Drug hypersensitivity	1	(0.1)	0	(0.0)	1	(0.1)
Sarcoidosis	1	(0.1)	0	(0.0)	1	(0.1)
Investigations	**3**	**(0.2)**	**1**	**(0.4)**	**4**	**(0.2)**
Blood potassium decreased	1	(0.1)	0	(0.0)	1	(0.1)
Hepatic enzyme increased	1	(0.1)	0	(0.0)	1	(0.1)
White blood cell count increased	1	(0.1)	0	(0.0)	1	(0.1)
Alanine aminotransferase increased	0	(0.0)	1	(0.4)	1	(0.1)
Aspartate aminotransferase increased	0	(0.0)	1	(0.4)	1	(0.1)
Blood and lymphatic system disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Haemolytic anaemia	1	(0.1)	0	(0.0)	1	(0.1)
Injury, poisoning and procedural complications	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Road traffic accident	1	(0.1)	0	(0.0)	1	(0.1)
Musculoskeletal and connective tissue disorders	**1**	**(0.1)**	**0**	**(0.0)**	**3**	**(0.2)**
Arthritis	1	(0.1)	0	(0.0)	1	(0.1)
Back pain	0	(0.0)	0	(0.0)	1	(0.1)
Myopathy	0	(0.0)	0	(0.0)	1	(0.1)
Nervous system disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Cerebellar syndrome	1	(0.1)	0	(0.0)	1	(0.1)
Psychiatric disorders	**1**	**(0.1)**	**0**	**(0.0)**	**2**	**(0.1)**
Panic attack	1	(0.1)	0	(0.0)	1	(0.1)
Anxiety	0	(0.0)	0	(0.0)	1	(0.1)
Vascular disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Peripheral arterial occlusive disease	1	(0.1)	0	(0.0)	1	(0.1)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "Any LEB250Q2W" and SAFFL = "Y" (Any LEB250Q2W); TRTNEW = "Any LEB250Q4W" and SAFFL = "Y" (Any LEB250Q4W); TRTNEW = "Any LEB" and SAFFL = "Y" (Any LEB); TEFLNEW = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

120-Day Safety Update
In the placebo-controlled period, 2 additional lebrikizumab-treated participants permanently discontinued treatment due to AEs of cerebral infarction and swelling since the initial BLA submission.

In addition to the 2 participants in the placebo-controlled period, 6 more participants reported the following AEs that led to treatment discontinuation in AD ALL LEB since the initial BLA submission:

- Conjunctivitis
- Dermatitis atopic
- Hodgkin's disease
- Ovarian cyst
- Pancreatic carcinoma metastatic, and
- Pruritus.

Reviewer Comment: *Across all analysis sets, the most common AE leading to drug discontinuation was conjunctivitis in the lebrikizumab-treated groups and atopic dermatitis in the placebo-treated groups; these findings are not unexpected given the mechanism of action of the drug and subjects' underlying disease. The additional AEs leading to permanent discontinuation reported in the 120-day safety update do not change the assessment presented in the initial BLA.*

Significant Adverse Events

In the lebrikizumab AD clinical trials, severity of AEs was determined based on medical judgment of the investigator. Categories of severity were defined in study protocols as follows:

- Mild: event that is easily tolerated by participant, causing minimal discomfort
- Moderate: an event that causes sufficient discomfort and interferes with normal everyday activities, and
- Severe: an event that prevents normal everyday activities.

Placebo-Controlled Induction Period (Weeks 0 to 16)
The frequency of subjects reporting at least 1 severe TEAE was 2.2% in the LEB 250 mg Q2W group and 4.3% in the placebo group. No more than 2 lebrikizumab-treated subjects reported a severe event for a specific PT. Severe TEAEs reported by more than 1 lebrikizumab-treated subjects were:

- AD (0.2%)
- arthralgia (0.2%)
- dermatitis exfoliative (0.2%), and
- abdominal pain (0.2%).

The most frequently reported severe TEAE in the placebo treatment group was AD (1.2%).

Monotherapy Maintenance Period (AD Mono PC Weeks 16 to 52)
Most events were mild or moderate in severity. A higher proportion of subjects reported severe TEAEs in the LEB 250 mg Q4W (n = 6, 4.9%) and LEB 250 mg Q2W (n = 5, 4.1%) groups compared with placebo (LEB withdrawal) (0%), although sample sizes were small, and frequencies were low. No more than 1 lebrikizumab-treated subject reported a severe TEAE for a specific PT.

Severe TEAEs reported by subjects in the LEB 250 mg Q2W group were 1 event each of

- back pain
- hypertension
- vernal keratoconjunctivitis
- nasopharyngitis
- anxiety, and
- humerus/ulna fracture.

Severe TEAEs reported by participants in the LEB 250 mg Q4W group were 1 event each of

- food allergy
- Sciatica
- Adenomyosis
- Cholecystitis
- eyelid edema, and
- somatic symptom disorder.

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)
Most events were mild or moderate in severity.

The frequencies of subjects reporting at least 1 severe TEAE remained low, however, frequencies through Weeks 52/56 were numerically higher in both LEB groups compared to the LEB 250 mg Q2W group in the placebo-controlled induction period (2.2%). This was not unexpected based on longer exposure to lebrikizumab.

The frequencies of subjects reporting severe TEAEs through Weeks 52/56 were

- 4.4% in the LEB 250 mg Q2W only group
- 7.9% in the LEB 250 mg Q2W/Q4W only group, and
- 4.4% in the placebo group.

Most severe TEAEs were reported by a single subject each, except for severe AD which was reported more frequently in the placebo group compared with lebrikizumab group. The frequencies of subjects reporting severe AD were

- 0.8% in the LEB 250 mg Q2W only group
- 0 events in the LEB 250 mg Q2W/Q4W only group, and
- 1.4% in the placebo group.

Any AD lebrikizumab exposure (AD All LEB)
Most events were mild or moderate in severity.

The frequencies of subjects reporting at least 1 severe TEAE in the Any LEB group (6.6%) were numerically higher than the LEB 250 mg Q2W group in the placebo-controlled induction period (2.2%). This was not unexpected based on longer exposure to lebrikizumab.

The frequencies of severe TEAEs were
- 6.6% in the Any LEB group
    - 5.7% in the Any LEB 250 mg Q2W group, and
    - 4.0% in the Any LEB Q4W group.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant defined common treatment emergent adverse events (TEAEs) as those reported at a frequency of greater than or equal to 1% before rounding of the lebrikizumab-treated group.

Placebo-Controlled Induction Period (Weeks 0 to 16)
The overall frequency of subjects with at least 1 TEAE was similar in the lebrikizumab and placebo groups. Conjunctivitis and dermatitis atopic were the most frequently reported events, with conjunctivitis reported more frequently for lebrikizumab-treated subjects and dermatitis atopic reported more frequently for placebo-treated subjects.

Conjunctivitis and headache TEAEs were reported at ≥ 1% and at a higher incidence in both the lebrikizumab monotherapy and lebrikizumab + TCS groups compared to placebo. Other TEAEs, such as nasopharyngitis, conjunctivitis allergic, dry eye, rhinitis allergic, hypertension, herpes zoster, and urinary tract infection occurred at ≥ 1% and at a higher incidence than placebo but in either the lebrikizumab monotherapy group or the lebrikizumab + TCS group, but not both.

Table 50. Treatment-Emergent Adverse Events Occurring in at Least 1% of Lebrikizumab-Treated Subjects from the Induction Period Placebo-Controlled Analysis Sets

Preferred Term	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (ADhere)	
	PBO	LEB 250 mg Q2W	PBO	LEB 250 mg Q2W	PBO + TCS	LEB 250 mg Q2W + TCS
	(N=417)	(N=805)	(N=342)	(N=652)	(N=75)	(N=153)
	N (%)		N (%)		N (%)	

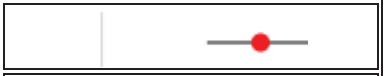
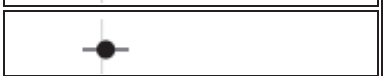
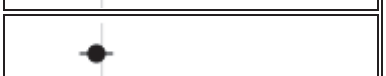
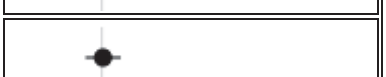
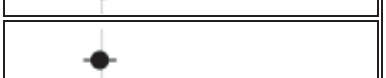
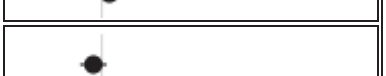
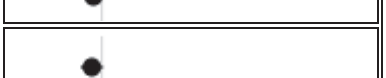
Subjects with at least 1 TEAE	221 (53)	394 (48.9)	194 (56.7)	328 (50.3)	27 (36)	66 (43.1)
Conjunctivitis	7 (1.7)	51 (6.3)	7 (2.0)	44 (6.7)	0 (0.0)	7 (4.6)
Dermatitis atopic	74 (17.7)	47 (5.8)	71 (20.8)	44 (6.7)	3 (4.0)	3 (2.0)
Nasopharyngitis	14 (3.4)	35 (4.3)	9 (2.6)	32 (4.9)	5 (6.7)	3 (2.0)
Headache	14 (3.4)	35 (4.3)	13 (3.8)	28 (4.3)	1 (1.3)	7 (4.6)
Oral herpes	9 (2.2)	15 (1.9)	8 (2.3)	13 (2.0)	1 (1.3)	2 (1.3)
Conjunctivitis allergic	3 (0.7)	14 (1.7)	3 (0.9)	14 (2.1)	0 (0.0)	0 (0.0)
Dry eye	4 (1.0)	11 (1.4)	4 (1.2)	8 (1.2)	0 (0.0)	3 (2.0)
Pruritis	7 (1.7)	9 (1.1)	7 (2.0)	9 (1.4)	0 (0.0)	0 (0.0)
Covid-19	5 (1.2)	9 (1.1)	5 (1.5)	7 (1.1)	0 (0.0)	2 (1.3)
Hypertension	4 (1.0)	9 (1.1)	3 (0.9)	5 (0.8)	1 (1.3)	4 (2.6)
Rhinitis allergic	1 (0.2)	8 (1.0)	1 (0.3)	7 (1.1)	0 (0.0)	1 (0.7)
Injection site pain	4 (1.0)	7 (0.9)	4 (1.2)	7 (1.1)	0 (0.0)	0 (0.0)
Herpes zoster	0 (0.0)	5 (0.6)	0 (0.0)	3 (0.5)	0 (0.0)	2 (1.3)
Impetigo	6 (1.4)	6 (0.7)	5 (1.5)	4 (0.6)	1 (1.3)	2 (1.3)
Urinary tract infection	2 (0.5)	9 (1.1)	2 (0.6)	6 (0.9)	0 (0.0)	3 (2.0)
Fall	1 (0.2)	3 (0.4)	1 (0.3)	1 (0.2)	0 (0.0)	2 (1.3)
Type 2 diabetes mellitus	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)
Nausea	3 (0.7)	7 (0.9)	3 (0.9)	5 (0.8)	0 (0.0)	2 (1.3)
Vomiting	1 (0.2)	4 (0.5)	1 (0.3)	2 (0.3)	0 (0.0)	2 (1.3)
Thrombocytopenia	0 (0.0)	4 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	2 (1.3)
Injection site rash	0 (0.0)	3 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	2 (1.3)
Injection site reaction	1 (0.2)	5 (0.6)	0 (0.0)	3 (0.5)	1 (1.3)	2 (1.3)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "PQ2W" and ALLPCFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and ALLPCFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" (Adverse Events).
Percent Threshold: LEB 250 mg Q2W ≥ 1%.
Filters: TRT01A = "PQ2W" and INDSAFFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and INDSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); ANL02FL = "Y" and TEMONDFL = "Y" (Adverse Events).
Filters: TRT01A = "Placebo" and SAFFL = "Y" (PBO + TCS); TRT01A = "Lebrikizumab 250mg Q2W" and SAFFL = "Y" (LEB 250 mg Q2W + TCS); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: LEB 250 mg Q2W + TCS ≥ 1%.

Of note, hypertension was reported more frequently by subjects treated with lebrikizumab + TCS compared with placebo + TCS; this difference was not observed with lebrikizumab monotherapy. In the AD ALL PC analysis set, the frequency of hypertension was similar in the lebrikizumab (1.1%) and placebo groups (1%). Of the 4 subjects reporting hypertension in the LEB+TCS group, 1 subject had a medical history of hypertension, and 1 subject had a medical history of type II diabetes mellitus and a carotid endarterectomy. All subjects had single elevations in blood pressure and returned to baseline by Week 16. None of these events led to treatment discontinuation.

Analysis of risk differences for the AD ALL PC analysis set demonstrates that the only TEAEs with statistically significant risk differences were conjunctivitis and dermatitis atopic.

Table 51. Risk Differences for Treatment-Emergent Adverse Events Occurring in at Least 1% of Lebrikizumab-Treated Subjects from the Induction Period Placebo-Controlled Analysis Sets

Preferred Term	PBO (N=417)		LEB 250 mg Q2W (N=805)		Risk Difference		
	n	(%)	n	(%)	RD	(95% CI)	Forest Plot
Conjunctivitis	7	(1.7)	51	(6.3)	-4.66	(-6.74, -2.57)	
Dermatitis atopic	74	(17.7)	47	(5.8)	11.91	(7.90, 15.92)	
Headache	14	(3.4)	35	(4.3)	-0.99	(-3.22, 1.24)	
Nasopharyngitis	14	(3.4)	35	(4.3)	-0.99	(-3.22, 1.24)	
Oral herpes	9	(2.2)	15	(1.9)	0.29	(-1.38, 1.97)	
Conjunctivitis allergic	3	(0.7)	14	(1.7)	-1.02	(-2.23, 0.19)	
Dry eye	4	(1.0)	11	(1.4)	-0.41	(-1.64, 0.83)	
Covid-19	5	(1.2)	9	(1.1)	0.08	(-1.19, 1.35)	
Hypertension	4	(1.0)	9	(1.1)	-0.16	(-1.34, 1.03)	
Pruritus	7	(1.7)	9	(1.1)	0.56	(-0.87, 1.99)	
Urinary tract infection	2	(0.5)	9	(1.1)	-0.64	(-1.62, 0.35)	
Rhinitis allergic	1	(0.2)	8	(1.0)	-0.75	(-1.58, 0.08)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "PQ2W" and ALLPCFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and ALLPCFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" (Adverse Events).
Percent Threshold: LEB 250 mg Q2W ≥ 1%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Maintenance Period (AD Mono PC Weeks 16 to 52)

During the maintenance period, the frequencies of common TEAEs were generally similar between the LEB 250 mg Q2W and placebo groups, except for folliculitis which was reported more frequently in the LEB 250 Q2W group compared to placebo.

The following TEAEs were more frequently reported in the LEB 250 mg Q4W group compared

to placebo

- COVID-19
- Headache
- Folliculitis
- Conjunctivitis allergic, and
- Oral herpes.

The following TEAEs were more frequently reported in the LEB 250 mg Q4W group compared to the LEB 250 mg Q2W group

- COVID-19
- Nasopharyngitis
- conjunctivitis allergic
- headache
- conjunctivitis, and
- oral herpes.

Table 52. Treatment-Emergent Adverse Events Occurring in at Least 1% of Lebrikizumab-Treated Subjects from the Maintenance Period Analysis Set (AD Mono PC Weeks 16 to 52)

Preferred Term	PBO (N=62)		LEB 250 mg Q4W (N=122)		LEB 250 mg Q2W (N=121)	
	n	(%)	n	(%)	n	(%)
Subjects with at least 1 TEAE	30	(48.4)	65	(53.3)	61	(50.4)
Covid-19	2	(3.2)	11	(9.0)	3	(2.5)
Nasopharyngitis	3	(4.8)	9	(7.4)	5	(4.1)
Conjunctivitis allergic	2	(3.2)	7	(5.7)	2	(1.7)
Dermatitis atopic	7	(11.3)	7	(5.7)	5	(4.1)
Conjunctivitis	3	(4.8)	6	(4.9)	0	(0.0)
Headache	1	(1.6)	5	(4.1)	2	(1.7)
Oral herpes	1	(1.6)	4	(3.3)	1	(0.8)
Urinary tract infection	2	(3.2)	4	(3.3)	3	(2.5)
Folliculitis	0	(0.0)	3	(2.5)	3	(2.5)
Food allergy	0	(0.0)	3	(2.5)	1	(0.8)
Herpes dermatitis	0	(0.0)	3	(2.5)	1	(0.8)
Vaccination complication	2	(3.2)	3	(2.5)	3	(2.5)
Acne	1	(1.6)	2	(1.6)	1	(0.8)
Aspartate aminotransferase increased	0	(0.0)	2	(1.6)	1	(0.8)
Back pain	1	(1.6)	2	(1.6)	2	(1.7)
Contusion	0	(0.0)	2	(1.6)	1	(0.8)

Cough	0	(0.0)	2	(1.6)	0	(0.0)
Erythema	0	(0.0)	2	(1.6)	1	(0.8)
Ligament sprain	0	(0.0)	2	(1.6)	1	(0.8)
Pneumonia	0	(0.0)	2	(1.6)	0	(0.0)
Sciatica	0	(0.0)	2	(1.6)	0	(0.0)
Sinusitis	0	(0.0)	2	(1.6)	0	(0.0)
Upper respiratory tract infection	3	(4.8)	2	(1.6)	2	(1.7)
Vaccination site pain	0	(0.0)	2	(1.6)	2	(1.7)
Weight increased	0	(0.0)	2	(1.6)	1	(0.8)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "PQ2W" and MPSAFFL = "Y" and SAFFL = "Y" (PBO); TRT02A = "L250Q4W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q4W); TRT02A = "L250Q2W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL03FL = "Y" and TEMAPFL = "Y" (Adverse Events).
Percent Threshold: LEB 250 mg Q4W ≥ 1%.

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)

In addition to common TEAEs reported in the placebo-controlled period, the following TEAEs were reported by at least 1% of lebrikizumab-treated subjects through Weeks 52/56: vaccination complication, folliculitis, upper respiratory tract infection (URTI), back pain, vaccination site pain, herpes dermatitis, acne, asthma, arthralgia, dizziness, eye pruritus, fatigue, and blepharitis.

The IRs of common TEAEs were similar in the lebrikizumab groups compared to the LEB 250 mg Q2W group from the placebo-controlled induction period, except for COVID-19. The Applicant posits that the noted increase in the IR of COVID-19 with extended exposure may be due to the trial conduct during the pandemic, the delta variant expansion, and the duration of the pandemic.

Any AD lebrikizumab exposure (AD All LEB)

In addition to the previously reported common TEAEs, the following TEAEs were reported by at least 1% of participants in the Any LEB group: alanine aminotransferase increased, anxiety, cough, diarrhea, and eosinophilia.

The IRs of common TEAEs in the LEB 250 mg Q2W group in the placebo-controlled induction period were similar compared to the AD ALL LEB analysis set, except for COVID-19.

TEAEs that have been identified as adverse reactions by the Applicant include conjunctivitis, keratitis, herpes zoster, eosinophilia, and ISRs.

Reviewer Comment: *This reviewer agrees with the Applicant's proposed list of adverse reactions. Although headache TEAEs were reported at a higher incidence in the lebrikizumab groups compared to placebo, the Sponsor notes that no plausible biologic mechanism was*

identified to support an association between headache and lebrikizumab. Therefore, it will not be included as an adverse reaction in labeling.

Laboratory Findings

The integrated safety analysis sets were used to evaluate clinical chemistries, hormones (for adolescent subjects only), and hematology. Abnormal hepatic tests and eosinophils are discussed separately, in sections 8.4.4.6 and 8.4.4.3, respectively.

Chemistry

The chemistry parameters assessed included electrolytes (sodium, potassium, calcium, chloride, bicarbonate, phosphate), renal function parameters (creatinine, urea nitrogen, albumin, total protein, urate), liver enzymes, lipids (total cholesterol), glucose (nonfasting), and lactate dehydrogenase.

No clinically meaningful changes in chemistry parameters occurred that were considered related to lebrikizumab treatment.

Hormones

Hormone levels were measured in adolescent participants only. Estradiol was measured in 80 female participants and testosterone in 67 male participants. While there were some differences between the treatment groups, levels for both hormones were varied, as shown by the large SDs of the means. However, differences in changes from baseline between treatment groups were not considered clinically meaningfully different than what would be expected for this aged population for either estradiol or testosterone.

Table **53**. Changes in Hormone Levels from Last Baseline to Last Post-baseline from the AD ALL PC Analysis Set

	Estradiol pmol/L		Testosterone nmol/L	
	PBO	LEB 250mg Q2W	PBO	LEB 250mg Q2W
	N = 15	N = 32	N = 13	N = 32
Mean change	-69.4	-8.94	-2.88	1.38
SD	425.16	415.73	12.85	11.59

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; N = Number of patients with a baseline and at least one post baseline value; PBO = placebo; PC = placebo-controlled; Q2W = every 2 weeks.

Source: Clinical Summary of Safety, Table 2.7.4.24

Due to the small population tested and the natural variation in hormone levels, it is difficult to make any specific conclusions. Furthermore, menstrual cycle dates were not recorded, so interpreting any potential effect of participants' cycles on hormone levels was not possible.

Hematology

The hematology parameters assessed included basophils, hemoglobin, hematocrit, erythrocytes, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, leukocytes, neutrophils, lymphocytes, monocytes, and platelet count.

Differences were seen between the lebrikizumab and placebo groups for some hematology analytes related to blood cells including low hemoglobin, low erythrocyte and related hematology analytes (high erythrocyte mean corpuscular volume, high embryonic hemoglobin concentration, and low erythrocyte mean corpuscular hemoglobin) which represent the same clinical picture.

Placebo-Controlled Induction Period (Weeks 0 to 16)
The frequencies of low hemoglobin observed in the AD ALL PC analyses set were as follows:

- 8.0% in the LEB 250 mg Q2W group, and
- 5.5% in the placebo group.

The mean changes from baseline in hemoglobin were
- -0.05 mmol/L^{-Fe} in the LEB 250 mg Q2W group, and
- -0.04 mmol/L^{-Fe} in the placebo group.

Maintenance Period (AD Mono PC Weeks 16 to 52)
The frequency of low hemoglobin was higher in the LEB 250 mg Q2W and Q4W groups compared with placebo. The frequencies of low hemoglobin observed were as follows:
- n = 4, 4.6% in the LEB 250 mg Q2W group
- n = 4, 4.4% in the LEB 250 mg Q4W group, and
- n = 1, 2.2% in the placebo (LEB withdrawal) group.

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)
The frequencies of low hemoglobin observed through Weeks 52/56 were as follows:
- n = 54, 7.4% in the LEB 250 mg Q2W only group
- n = 19, 14.2% in the LEB 250 mg Q2W/Q4W only, and
- n = 17, 5.4% in the placebo group.

The frequency in the LEB 250 mg Q2W/Q4W only group was higher than in the lebrikizumab group in the placebo-controlled induction period (8.0%).

Any AD lebrikizumab exposure (AD All LEB)
The frequencies of low hemoglobin observed were as follows:

- n = 140, 9.1% in the Any LEB group
    - n = 116, 9.7% in the Any LEB Q2W, and
    - n = 18, 8.5% in the Any LEB Q4W group.

These frequencies were similar to those of the LEB 250 mg Q2W group in the placebo-controlled induction period (8.0%).

Although low hemoglobin and related hematology analyte changes were seen with a higher frequency in lebrikizumab-treated subjects compared to placebo, most hemoglobin changes were to CTCAE Grade 1 or 2, and mean decreases from baseline were small with minimal clinical impact.

Table 54. Hematology CTCAE Grade Changes from the Induction Period Placebo-Controlled Analysis Sets

	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (ADhere)	
	PBO	LEB 250mg Q2W	PBO	LEB 250 mg Q2W	PBO +TCS	LEB 250mg Q2W+TCS
	N = 404 n (adj %)	N = 783 n (adj %)	N = 338 n (adj %)	N = 638 n (adj %)	N = 66 n (%)	N = 145 n (%)
Neutrophil count						
Any CTCAE Grade increase[a]	18 (4.6)	22 (2.8)	14 (4.3)	14 (2.3)	4 (6.1)	8 (5.5)
Increase to CTCAE Grade ≥3 (<1.0 × 10^9/L)	1 (0.2)	2 (0.3)	1 (0.3)	2 (0.3)	0	0
Increase to CTCAE Grade ≥4 (<0.5 × 10^9/L)	0	0	0	0	0	0
Lymphocyte count						
Any CTCAE Grade increase[a]	25 (6.5)	34 (4.4)	21 (6.5)	26 (4.2)	4 (6.1)	8 (5.5)
Increase to CTCAE Grade ≥3 (<0.5 × 10^9/L)	1 (0.3)	0	1 (0.3)	0	0	0
Increase to CTCAE Grade ≥4 (<0.2 × 10^9/L)	0	0	0	0	0	0
Hemoglobin						
Any CTCAE Grade increase[a]	13 (3.3)	38 (4.9)	12 (3.7)	26 (4.1)	1 (1.5)	12 (8.3)
Increase to CTCAE Grade ≥3 (<8.0 g/dL)	0	0	0	0	0	0
Increase to CTCAE Grade ≥4 (<6.5 g/dL)	0	0	0	0	0	0
Platelets						
Any CTCAE Grade increase[a]	7 (1.8)	17 (2.2)	7 (2.2)	13 (2.0)	0	4 (2.8)
Increase to CTCAE Grade ≥3 (<50 × 10^9/L)	1 (0.3)	0	1 (0.3)	0	0	0
Increase to CTCAE Grade ≥4 (<25 × 10^9/L)	0	0	0	0	0	0

Abbreviations: AD = atopic dermatitis; adj % = adjusted percentage; LEB = lebrikizumab; CTCAE = Common Terminology Criteria for Adverse Events; Mono = monotherapy; N = number of patients in the safety analysis set; n = number of patients in the specified category; PBO = placebo; PC = placebo-controlled; Q2W = every 2 weeks; TCS = topical corticosteroids.

[a] CTCAE grade increases are reflective of decreases changes in blood cell measure, consistent with Version 5.0 of the CTCAE guidelines.

Source: Clinical Summary of Safety, Table 2.7.4.25

There were no neutrophil, lymphocyte, hemoglobin, or platelet increases to CTCAE Grade 4 noted in any lebrikizumab treatment group across all analysis sets in the placebo-controlled induction period (table above). Neutrophil increases to Grade 3 were noted in 2 subjects in the LEB 250 mg Q2W group of the AD ALL PC analysis set.

Reviewer Comment: *This reviewer agrees that there were no clinically meaningful differences observed for changes in hematology and chemistry analytes including hormones (estradiol and testosterone) for lebrikizumab-treated subjects compared to those treated with placebo. In*

some of the analytes, differences were observed, but mean changes from baseline were small and not clinically meaningful.

Vital Signs

Evaluation of vital signs and physical characteristic included TE-low or high values for all variables in all analysis sets for both adults and adolescents. Vital signs and physical characteristics included:

- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Pulse
- body weight (analyzed separately for adults and adolescents)
- BMI (adolescents), and
- height (adolescents).

Blood Pressure
For adult subjects, treatment-emergent low SBP was defined as SBP ≤ 90 mm Hg and a decrease from baseline of ≥20 mm Hg; treatment-emergent high SBP was defined as SBP ≥ 140 mm Hg and an increase from baseline of ≥20 mm Hg. Treatment-emergent low DBP was defined as DBP ≤ 50 mm Hg and a decrease from baseline of ≥ 10 mm Hg, and treatment-emergent high DBP was defined as ≥ 90 mm Hg and an increase from baseline of ≥ 10 mm Hg. For adolescents 13-17 years of age, low SBP was defined as SBP ≤ 90 mm Hg and a decrease of ≥ 20 mm Hg; elevated SBP was defined as SBP ≥ 129 mm Hg and an increase of ≥ 20 mm Hg. For adolescents 13-17 years of age, low DBP was defined as DBP ≤ 50 and a decrease of ≥ 10 mm Hg; elevated DBP was defined as DBP ≥ 86 mm Hg and an increase of ≥ 10 mm Hg. For adolescent 12 years of age, low SBP was defined as SBP ≤ 85 mm Hg and decrease from baseline of ≥ 20 mm Hg; elevated SBP was defined as SBP ≥ 126 and increase from baseline of ≥ 20 mm Hg. For adolescents 12 years of age, low DBP was defined as DBP ≤ 50 mm Hg and decrease from baseline of ≥10 mm Hg; elevated DBP was defined as DBP ≥ 82 mm Hg and increase from baseline of ≥ 10 mm Hg.

<u>Placebo-Controlled Induction Period (Weeks 0 to 16)</u>
The frequency of subjects with TE-high shift in SBP was numerically higher in the LEB 250 mg Q2W group compared to the placebo group, and a similar frequency of subjects in both treatment groups had TE-low shift in SBP.

The frequency of subjects with TE-high shift in DBP was similar in the LEB 250 mg Q2W group compared to the placebo group, and a higher frequency of TE-low shift in DBP was noted in the LEB 250 mg Q2W group compared to placebo.

A similar frequency of subjects reported a TEAE of hypertension in both treatment groups.

Table 55. Blood Pressure Mean Changes from Baseline and TE Shifts for the Placebo-Controlled Induction Period

	PBO (N=417)	LEB 250 mg Q2W (N=805)
Systolic BP Mean Changes from Baseline Mean (SD) Median (Min, Max)	 -0.3 (10.90) 0.0 (-30, 41)	 -0.9 (11.27) -1.0 (-61, 34)
SBP TE-Low Shifts (n (%))	3 (0.7)	7 (0.9)
SBP TE-High Shifts (n (%))	8 (1.9)	24 (3.0)
Diastolic BP Mean Changes from Baseline Mean (SD) Median (Min, Max)	 -0.2 (8.48) 0.0 (-36, 39)	 -0.4 (8.51) 0.0 (-45, 27)
DBP TE-Low Shifts (n (%))	1 (0.2)	4 (0.5)
DBP TE-High Shifts (n (%))	22 (5.3)	47 (5.8)
Treatment-Emergent Adverse Events -- Hypertension (n (%))	4 (1.0)	9 (1.1)
Treatment-Emergent Adverse Events -- Blood Pressure Increased (n (%))	3 (0.7)	2 (0.2)
Treatment-Emergent Adverse Events -- Hypertensive Crisis (n (%))	1 (0.2)	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: ALLPCFL = 'Y', SAFFL = 'Y'.
Systolic BP Mean Changes from Baseline - Dataset: Vital Signs; Filter: PARAMCD = 'SYSBP', AVISIT = 'BASELINE LAST INDUCTION' or 'POST BASELINE LAST INDUCTION'.
SBP TE-Low Shifts (n (%)) - Dataset: Vital Signs; Filter: ANL02FL = 'Y', PARAMCD = 'SYSBP', DTYPE = 'MINIMUM', CRIT2FL = 'Y'.
SBP TE-High Shifts (n (%)) - Dataset: Vital Signs; Filter: ANL02FL = 'Y', PARAMCD = 'SYSBP', DTYPE = 'MAXIMUM', CRIT1FL = 'Y'.
Diastolic BP Mean Changes from Baseline - Dataset: Vital Signs; Filter: PARAMCD = 'DIABP', AVISIT = 'BASELINE LAST INDUCTION' or 'POST BASELINE LAST INDUCTION'.
DBP TE-Low Shifts (n (%)) - Dataset: Vital Signs; Filter: ANL02FL = 'Y', DTYPE = 'MINIMUM', PARAMCD = 'DIABP', CRIT2FL = 'Y'.
DBP TE-High Shifts (n (%)) - Dataset: Vital Signs; Filter: ANL02FL = 'Y', DTYPE = 'MAXIMUM', PARAMCD = 'DIABP', CRIT1FL = 'Y'.
Treatment-Emergent Adverse Events – Hypertension (n (%)) - Dataset: Adverse Events; Filter: ANL02FL = 'Y', TEMONDFL = 'Y', AEDECOD = 'Hypertension'.
Treatment-Emergent Adverse Events – Blood Pressure Increased (n (%)) - Dataset: Adverse Events; Filter: ANL02FL = 'Y', TEMONDFL = 'Y', AEDECOD = 'Blood pressure increased'.
Treatment-Emergent Adverse Events – Hypertensive Crisis (n (%)) - Dataset: Adverse Events; Filter: ANL02FL = 'Y', TEMONDFL = 'Y', AEDECOD = 'Hypertensive crisis'.
SD = Standard Deviation.

Maintenance Period (AD Mono PC Weeks 16 to 52)

No difference was observed in the frequency of TE-low shift in SBP in the combined lebrikizumab groups compared with placebo (LEB withdrawal). No dose difference was observed. TE-high shift in SBP was not observed in any subject.

TE-low DBP was not observed in any subject. The frequency of subjects with TE-high shift in DBP was numerically higher in the placebo group compared to either lebrikizumab treatment group.

Table 56. Blood Pressure Mean Changes from Baseline and TE Shifts for the Maintenance Period

	PQ2W (N=62)	L250Q4W (N=122)	L250Q2W (N=121)
Systolic BP Mean Changes from Baseline Mean (SD) Median (Min, Max)	 0.7 (8.40) 1.0 (-19, 18)	 1.1 (10.85) 1.0 (-28, 41)	 0.7 (11.77) 0.0 (-29, 41)
SBP TE-Low Shifts (n (%))	0	0	1 (0.8)
SBP TE-High Shifts (n (%))	0	0	0
Diastolic BP Mean Changes from Baseline Mean (SD) Median (Min, Max)	 -0.4 (7.76) 0.0 (-20, 18)	 1.3 (8.49) 1.0 (-26, 33)	 -0.2 (8.46) 0.0 (-26, 24)

DBP TE-Low Shift (n (%))	0	0	0
DBP TE-High Shifts (n (%))	4 (6.5)	3 (2.5)	2 (1.7)
Treatment-Emergent Adverse Events -- Hypertension (n (%))	1 (1.6)	0	2 (1.7)
Treatment-Emergent Adverse Events -- Blood Pressure Increased (n (%)	0	0	0
Treatment-Emergent Adverse Events -- Hypertensive Crisis (n (%))	0	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: MPSAFFL = 'Y', SAFFL = 'Y'.
Systolic BP Mean Changes from Baseline - Dataset: Vital Signs; Filter: PARAMCD = 'SYSBP', AVISIT = 'BASELINE LAST MAINTENANCE' or 'POST BASELINE LAST MAINTENANCE'.
SBP TE-Low Shifts (n (%)) - Dataset: Vital Signs; Filter: PARAMCD = 'SYSBP', DTYPE = 'MINIMUM', CRIT2FL = 'Y', ANL03FL = 'Y'.
SBP TE-High Shifts (n (%)) - Dataset: Vital Signs; Filter: PARAMCD = 'SYSBP', DTYPE = 'MAXIMUM', CRIT1FL = 'Y', ANL03FL = 'Y'.
Diastolic BP Mean Changes from Baseline - Dataset: Vital Signs; Filter: PARAMCD = 'DIABP', AVISIT = 'BASELINE LAST MAINTENANCE' or 'POST BASELINE LAST MAINTENANCE'.
DBP TE-Low Shifts (n (%)) - Dataset: Vital Signs; Filter: DTYPE = 'MINIMUM', PARAMCD = 'DIABP', CRIT2FL = 'Y', ANL03FL = 'Y'.
DBP TE-High Shifts (n (%)) - Dataset: Vital Signs; Filter: DTYPE = 'MAXIMUM', PARAMCD = 'DIABP', CRIT1FL = 'Y', ANL03FL = 'Y'.
Treatment-Emergent Adverse Events – Hypertension (n (%)) - Dataset: Adverse Events; Filter: AEDECOD = 'Hypertension', ANL03FL = 'Y', TEMAPFL = 'Y'.
Treatment-Emergent Adverse Events – Blood Pressure Increased (n (%)) - Dataset: Adverse Events; Filter: AEDECOD = 'Blood pressure increased', ANL03FL = 'Y', TEMAPFL = 'Y'.
Treatment-Emergent Adverse Events – Hypertensive Crisis (n (%)) - Dataset: Adverse Events; Filter: AEDECOD = 'Hypertensive crisis', ANL03FL = 'Y', TEMAPFL = 'Y'.
SD = Standard Deviation.

Pulse

There was no clinical impact of treatment with lebrikizumab on pulse in the induction and maintenance periods or with any lebrikizumab exposure.

Weight

Weight gain was defined as at least a 7% increase at any time post-baseline. Although weight gain in the adult population was observed more frequently observed in lebrikizumab-treated subjects during the placebo-controlled induction period, the analysis of the mean change from last baseline to last post-baseline showed a small variation in weight that could be secondary to intrinsic fluctuation. Additionally, the mean was influenced by the presence of a few extreme values in both treatment groups, either for weight gain or weight loss. The median change from last baseline to last postbaseline was similar across both treatment groups. For the total adult population, no differences between treatment groups were noted in the distribution according to BMI category.

In the maintenance period, weight loss (at least 7%) at any time was also observed in the adult population at a higher frequency for those treated with lebrikizumab compared to placebo (LEB withdrawal). The maintenance population sample size was smaller compared to induction, limiting conclusions.

In lebrikizumab-treated subjects, the frequencies of weight gain and weight loss at any time was higher during the combined induction and maintenance phase and the AD All LEB analysis set compared to the placebo-controlled induction period. Weight fluctuations are not unexpected over longer observation periods given natural variability over time. No sustained weight gain could be verified when analyzing the variation of weight of subjects during the induction and maintenance phases.

Reviewer Comment: *Based upon a review of vital sign data from placebo-controlled induction and maintenance periods and extended exposure, this reviewer agrees that lebrikizumab was not associated with clinically meaningful changes in BP over time. There was no impact on pulse, and the data did not support a causal association between lebrikizumab and weight changes.*

Electrocardiograms (ECGs)

Comprehensive 12-lead ECGs were collected for detailed safety assessments in 3 clinical pharmacology studies (KGAY, KGAZ, and KGBB). In other clinical pharmacology studies (J2T-DM-KGBA and J2T-MC-KGBG [KGBG]), single 12-lead ECGs were collected at designated time points and used for subject's safety monitoring during the study. There were no clinically significant ECG findings or TEAEs related to ECG findings across the integrated biopharmaceutic and clinical pharmacology studies in healthy subjects.

QT

Monoclonal antibodies are not expected to interact with ion channels due to their large molecular size and weight, and high specificity. Therefore, a thorough QT/QTc study was not necessary

Immunogenicity

The safety analysis evaluated the frequency of hypersensitivity reactions and ISRs in patients who were TE ADA positive versus TE ADA negative using the AD combined induction and maintenance periods immunogenicity analysis set.

In the hypersensitivity SMQ (narrow), a similar proportion of subjects in LEB 250 mg Q2W only group reported events who were TE ADA positive (N = 28, n = 4, 14.3%) compared to subjects who were TE ADA negative (N = 792, n = 138, 17.4%). In the lebrikizumab 250 mg Q2W/Q4W only treatment group, no TE ADA positive subjects reported potential hypersensitivity reactions compared to TE ADA negative participants (N = 140, n = 22, 15.7%). Similar results were seen for the continuous placebo treatment group.

The frequency of ISRs (HLT) was higher in the LEB 250 mg Q2W only subjects who were TE ADA positive (N = 28, n = 3, 10.7%) compared to those who were TE ADA negative (N = 792, n = 23, 2.9%). Although the frequency of ISRs was higher in subjects who were TE ADA positive treated with lebrikizumab 250 mg Q2W compared to placebo, overall, few events of ISRs were reported in TE ADA positive lebrikizumab-treated participants, and there was no temporal association with ISRs and development of TE ADA.

In both the LEB 250 mg Q2W/Q4W only treatment group and continuous placebo treatment group, no TE ADA positive participants had ISRs, compared to 3 of 140 (2.1%) and 5 of 327

(1.5%) of TE ADA negative participants in each treatment group, respectively.

No clinically meaningful differences in the frequency of hypersensitivity events were observed in TE ADA positive subjects compared with TE ADA negative participants. With regard to Injection site reactions, a numerically higher frequency of events was observed in TE ADA positive subjects compared to TE ADA negative participants; however, no temporal association was found.

Reviewer Comment: *The risk of immunogenicity for subjects treated with lebrikizumab is low and is unlikely to impact the clinical benefit-risk profile.*

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Conjunctivitis and Keratitis

Conjunctivitis was defined as an adverse event of special interest due to the potential association with the mechanism of action of lebrikizumab, the AEs observed for other drugs in the same class as lebrikizumab, and the heightened likelihood for this disorder in the AD population. Ocular complications, including conjunctivitis and keratitis, are more common in patients with AD compared to the general population.

Placebo-Controlled Induction Period (Weeks 0 to 16)

Ocular events, including conjunctivitis, blepharitis, and keratitis (including atopic keratoconjunctivitis and vernal keratoconjunctivitis) were reported more frequently in the lebrikizumab group compared to placebo.

Table 57. Summary of Ocular AESIs for AD ALL PC Analysis Set (Lebrikizumab with or without TCS)

Preferred Term	PBO (N=417)		LEB 250 mg Q2W (N=805)		Risk Difference		
	n	(%)	n	(%)	RD	(95% CI)	Forest Plot
Conjunctivitis	7	(1.7)	51	(6.3)	-4.66	(-6.74, -2.57)	
Dry eye	4	(1.0)	11	(1.4)	-0.41	(-1.64, 0.83)	
Blepharitis	1	(0.2)	6	(0.7)	-0.51	(-1.26, 0.25)	
Eye irritation	0	(0.0)	4	(0.5)	-0.50	(-0.98, -0.01)	
Atopic keratoconjunctivitis	0	(0.0)	2	(0.2)	-0.25	(-0.59, 0.10)	
Eye pruritus	0	(0.0)	2	(0.2)	-0.25	(-0.59, 0.10)	

Table 57. Summary of Ocular AESIs for AD ALL PC Analysis Set (Lebrikizumab with or without TCS)

Preferred Term	PBO (N=417)		LEB 250 mg Q2W (N=805)		Risk Difference		
	n	(%)	n	(%)	RD	(95% CI)	Forest Plot
Vernal keratoconjunctivitis	0	(0.0)	2	(0.2)	-0.25	(-0.59, 0.10)	
Keratitis	1	(0.2)	1	(0.1)	0.12	(-0.41, 0.64)	
Xerophthalmia	0	(0.0)	1	(0.1)	-0.12	(-0.37, 0.12)	

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "PQ2W" and ALLPCFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and ALLPCFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and TEMONDFL = "Y" and ANL02FL = "Y" and AEDECOD = "Conjunctivitis" or "Conjunctivitis viral" or "Conjunctival disorder" or "Xerophthalmia" or "Keratitis" or "Blepharitis" or "Punctate keratitis" or "Eye pruritus" or "Eye infection" or "Dry eye" or "Atopic keratoconjunctivitis" or "Vernal keratoconjunctivitis" or "Eye irritation" (Adverse Events).

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Subjects from both the LEB monotherapy and LEB+TCS groups had a higher frequency of events within the conjunctivitis, keratitis, ocular symptom, or blepharitis clusters compared to placebo.

Table 58. Summary of Ocular AESIs for AD Mono PC Analysis Set (Lebrikizumab Monotherapy)

Preferred Term	PBO (N=342)		LEB 250 mg Q2W (N=652)		Risk Difference		
	n	(%)	n	(%)	RD	(95% CI)	Forest Plot
Conjunctivitis	7	(2.0)	44	(6.7)	-4.70	(-7.14, -2.26)	
Dry eye	4	(1.2)	8	(1.2)	-0.06	(-1.48, 1.36)	
Blepharitis	1	(0.3)	5	(0.8)	-0.47	(-1.36, 0.41)	
Eye irritation	0	(0.0)	3	(0.5)	-0.46	(-0.98, 0.06)	
Atopic keratoconjunctivitis	0	(0.0)	2	(0.3)	-0.31	(-0.73, 0.12)	
Eye pruritus	0	(0.0)	2	(0.3)	-0.31	(-0.73, 0.12)	
Keratitis	1	(0.3)	1	(0.2)	0.14	(-0.51, 0.79)	
Vernal keratoconjunctivitis	0	(0.0)	1	(0.2)	-0.15	(-0.45, 0.15)	

Source: OCS Analysis Studio, Safety Explorer.

Table 58. Summary of Ocular AESIs for AD Mono PC Analysis Set (Lebrikizumab Monotherapy)

Preferred Term	PBO (N=342)		LEB 250 mg Q2W (N=652)		Risk Difference		
	n	(%)	n	(%)	RD	(95% CI)	Forest Plot

Filters: TRT01A = "PQ2W" and INDSAFFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and INDSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and TEMONDFL = "Y" and ANL02FL = "Y" and AEDECOD = "Conjunctivitis" or "Conjunctivitis viral" or "Conjunctival disorder" or "Xerophthalmia" or "Keratitis" or "Blepharitis" or "Punctate keratitis" or "Eye pruritus" or "Eye infection" or "Dry eye" or "Atopic keratoconjunctivitis" or "Vernal keratoconjunctivitis" or "Eye irritation" (Adverse Events).

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Table 59. Summary of Ocular AESIs for AD TCS Analysis Set (ADhere Study)

Preferred Term	PBO (N=75)		LEB 250 mg Q2W (N=153)		Risk Difference		
	n	(%)	n	(%)	RD	(95% CI)	Forest Plot
Conjunctivitis	0	(0.0)	7	(4.6)	-4.58	(-7.89, -1.26)	
Dry eye	0	(0.0)	3	(2.0)	-1.96	(-4.16, 0.24)	
Blepharitis	0	(0.0)	1	(0.7)	-0.65	(-1.93, 0.62)	
Eye irritation	0	(0.0)	1	(0.7)	-0.65	(-1.93, 0.62)	
Vernal keratoconjunctivitis	0	(0.0)	1	(0.7)	-0.65	(-1.93, 0.62)	

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SAFFL = "Y" (PBO); TRT01A = "Lebrikizumab 250mg Q2W" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and AEDECOD = "Conjunctivitis" or "Vernal keratoconjunctivitis" or "Blepharitis" or "Dry eye" or "Eye irritation" (Adverse Events).

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

All ocular events, except for one, were nonserious and mild or moderate in severity. One lebrikizumab-treated participant reported a severe event of blepharitis.

Five lebrikizumab-treated subjects reported ocular AEs that led to treatment discontinuation:

- conjunctivitis (n = 2)
- conjunctivitis bacterial (n = 1)
- keratitis (n = 1), and
- atopic keratoconjunctivitis (n = 1).

One placebo-treated subject reported conjunctivitis that led to treatment discontinuation.

Maintenance Period (AD Mono PC Weeks 16 to 52)

The frequency of ocular events during the monotherapy maintenance period was similar in LEB 250 mg Q4W group compared to placebo and was lower in LEB 250 mg Q2W compared to placebo.

Table 60. Summary of Ocular AESIs During the Monotherapy Maintenance Period

Preferred Term	PBO (N=62)		LEB 250 mg Q4W (N=122)		LEB 250 mg Q2W (N=121)	
	n	(%)	n	(%)	n	(%)
Conjunctivitis allergic	2	(3.2)	7	(5.7)	2	(1.7)
Conjunctivitis	3	(4.8)	6	(4.9)	0	(0.0)
Atopic keratoconjunctivitis	0	(0.0)	1	(0.8)	0	(0.0)
Dry eye	0	(0.0)	1	(0.8)	1	(0.8)
Blepharitis	0	(0.0)	0	(0.0)	1	(0.8)
Vernal keratoconjunctivitis	0	(0.0)	0	(0.0)	1	(0.8)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "PQ2W" and MPSAFFL = "Y" and SAFFL = "Y" (PBO); TRT02A = "L250Q4W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q4W); TRT02A = "L250Q2W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL03FL = "Y" and TEMAPFL = "Y" and AEDECOD = "Conjunctivitis" or "Conjunctivitis viral" or "Keratitis" or "Atopic keratoconjunctivitis" or "Vernal keratoconjunctivitis" or "Blepharitis" or "Dry eye" or "Eye irritation" or "Eye infection" or "Conjunctivitis allergic" (Adverse Events).

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)

For the combined induction and maintenance period, ocular symptoms were reported more frequently in lebrikizumab-treated subjects than placebo-treated subjects.

Table 61. Ocular AESIs: Atopic Dermatitis Monotherapy and TCS Combination Safety Population (Ph3) Induction and Maintenance Periods (Weeks 0 – 52/56) Atopic Dermatitis Combined Induction and Maintenance Periods Analysis Set (Studies KGAB, KGAC, KGAD, and KGAA)

	LEB250Q2W only (N=872)	LEB250Q2W/Q4W only (N=151)	All LEB250Q2W (N=1023)	All LEB250Q2W/Q4W (N=1023)	PBO (N=365)
Dry Eye Cluster	17 (1.9)	3 (2.0)	19 (1.9)	14 (1.4)	2 (0.5)
Blepharitis Cluster	7 (0.8)	3 (2.0)	10 (1.0)	6 (0.6)	1 (0.3)
Keratitis	6 (0.7)	1 (0.7)	7 (0.7)	5 (0.5)	1 (0.3)
Conjunctivitis	60 (6.9)	18 (11.9)	73 (7.1)	67 (6.5)	7 (1.9)
Conjunctivitis allergic	42 (4.8)	9 (6.0)	45 (4.4)	36 (3.5)	3 (0.8)
Vernal keratoconjunctivitis	3 (0.3)	0	3 (0.3)	2 (0.2)	0
Conjunctivitis bacterial	5 (0.6)	3 (2.0)	7 (0.7)	6 (0.6)	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: COMBIMFL = 'Y', SAFFL = 'Y', TRTNEW = 'LEB250Q2W only' or 'LEB250Q2W/Q4W only' or 'All LEB250Q2W' or 'All LEB250Q2W/Q4W' or 'PBO'.
CMQ or SMQ Term - Dataset: Adverse Events; Filter: TEFLNEW = 'Y'.

120-Day Safety Update

Consistent with the initial BLA submission, ocular events such as conjunctivitis, keratitis, dry eye, and blepharitis were reported more frequently in lebrikizumab-treated subjects compared to placebo-treated subjects. The events were mostly nonserious, mild or moderate in severity, and did not generally lead to treatment discontinuation. One event of conjunctivitis allergic (KGAE-(b) (6)) reported in the initial BLA submission was updated to a severe and serious event, and this event led to treatment discontinuation. One additional KGAA subject discontinued treatment due to an event of conjunctivitis. Overall, the ocular findings from this safety update are consistent with the initial BLA, and no new safety signals were identified.

Reviewer Comment: *Clinically meaningful differences were observed in the frequencies of conjunctivitis and keratitis events between the lebrikizumab and placebo groups. This reviewer agrees with the Applicant's proposal to include conjunctivitis and keratitis as ADRs in labeling.*

8.2.5.2. Infections, Including Herpes Infections, Relevant Parasitic (Helminth) Infections, Opportunistic Infections, and Serious Infections

Placebo-Controlled Induction Period (Weeks 0 to 16)

Overall Infections

Events reported in at least 1% of lebrikizumab-treated participants excluding ocular-related disorders (discussed separately), were

- nasopharyngitis
- oral herpes
- COVID-19, and
- Urinary tract infection

Table 62. Treatment-Emergent Infections Occurring in at Least 1% of Lebrikizumab-Treated Participants for the Induction Period Placebo-Controlled Analysis Sets

	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS PC Weeks 0-16 (ADhere)	
Preferred Term	PBO	LEB 250 mg Q2W	PBO	LEB 250 mg Q2W	PBO + TCS	LEB 250 mg Q2W + TCS
	N=417	N=805	N=342	N=652	N=75	N=153
	n (%)		n (%)		n (%)	
Conjunctivitis	7 (1.7)	51 (6.3)	7 (2.0)	44 (6.7)	0 (0.0)	7 (4.6)
Nasopharyngitis	14 (3.4)	35 (4.3)	9 (2.6)	32 (4.9)	5 (6.7)	3 (2.0)
Oral herpes	9 (2.2)	15 (1.9)	8 (2.3)	13 (2.0)	1 (1.3)	2 (1.3)
COVID-19	5 (1.2)	9 (1.1)	5 (1.5)	7 (1.1)	0 (0.0)	2 (1.3)

Urinary tract infection	2 (0.5)	9 (1.1)	2 (0.6)	6 (0.9)	0 (0.0)	3 (2.0)
Impetigo	6 (1.4)	6 (0.7)	5 (1.5)	4 (0.6)	1 (1.3)	2 (1.3)
Herpes Zoster	0 (0.0)	5 (0.6)	0 (0.0)	3 (0.5)	0 (0.0)	2 (1.3)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "PQ2W" and ALLPCFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and ALLPCFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" and CQ06NAM = "Infections and infestations" (Adverse Events).
TRT01A = "PQ2W" and INDSAFFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and INDSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" and CQ06NAM = "Infections and infestations" (Adverse Events).
Filters: TRT01A = "Placebo" and SAFFL = "Y" (PBO); TRT01A = "Lebrikizumab 250mg Q2W" and SAFFL = "Y" (LEB 250 mg Q2W + TCS); TRTEMFL = "Y" (Adverse Events).

Conjunctivitis, nasopharyngitis, herpes zoster, and urinary tract infections were reported at a higher frequency in the LEB 250 mg Q2W group compared to placebo. Most events were mild or moderate in severity.

The clinical reviewer conducted a customized MedDRA query (CMQ) to investigate whether other upper respiratory infections (URIs), beyond nasopharyngitis, occurred more frequently in lebrikizumab-treated subjects compared to those treated with placebo. URIs were not reported more frequently in lebrikizumab-treated subjects.

Table 63. Summary of Upper Respiratory Infections During the Placebo-Controlled Induction Period - Grouped Terms

Grouped Term	PBO	LEB 250 mg Q2W	PBO	LEB 250 mg Q2W	PBO + TCS	LEB 250 mg Q2Q + TCS
	(N=417)	(N=805)	(N=342)	(N=652)	(N=75)	(N=153)
	n (%)		n (%)		n (%)	
Upper Respiratory Infections*	27 (6.5)	43 (5.3)	21 (6.1)	38 (5.8)	6 (8.0)	5 (3.3)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "PQ2W" and INDSAFFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and INDSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" (Adverse Events).
Upper Respiratory Infections* includes: Nasopharyngitis, Pharyngitis, Pharyngotonsillitis, Rhinitis, Sinusitis, Tonsillitis, Upper respiratory tract infection, Viral tonsillitis, Viral upper respiratory tract infection.

Herpes Infections

Similar proportions of subjects reported any treatment-emergent oral herpes infection in the lebrikizumab and placebo groups. Herpes zoster infections occurred more frequently in lebrikizumab-treated subjects.

Table 6465. Summary of Infectious TEAEs During the Placebo-Controlled Induction Period

System Organ Class - Preferred Term	PBO		LEB 250 mg Q2W		Risk Difference		
	(N=417)		(N=805)				
	n	(%)	n	(%)	RD	(95% CI)	Forest Plot
Infections and infestations	**78**	**(18.7)**	**170**	**(21.1)**	-2.41	(-7.10, 2.27)	

Table 6465. Summary of Infectious TEAEs During the Placebo-Controlled Induction Period

System Organ Class - Preferred Term	PBO (N=417)		LEB 250 mg Q2W (N=805)		Risk Difference		
	n	(%)	n	(%)	RD	(95% CI)	Forest Plot
Conjunctivitis	7	(1.7)	51	(6.3)	-4.66	(-6.74, -2.57)	
Nasopharyngitis	14	(3.4)	35	(4.3)	-0.99	(-3.22, 1.24)	
Oral herpes	9	(2.2)	15	(1.9)	0.29	(-1.38, 1.97)	
Covid-19	5	(1.2)	9	(1.1)	0.08	(-1.19, 1.35)	
Urinary tract infection	2	(0.5)	9	(1.1)	-0.64	(-1.62, 0.35)	
Impetigo	6	(1.4)	6	(0.7)	0.69	(-0.59, 1.98)	
Folliculitis	5	(1.2)	5	(0.6)	0.58	(-0.60, 1.76)	
Gastroenteritis	1	(0.2)	5	(0.6)	-0.38	(-1.10, 0.34)	
Herpes zoster	0	(0.0)	5	(0.6)	-0.62	(-1.16, -0.08)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "PQ2W" and ALLPCFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and ALLPCFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" and CQ06NAM = "Infections and infestations" (Adverse Events).
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Parasitic Infections/Opportunistic Infections

No events of parasitic infections were reported for the lebrikizumab and placebo groups in any of the placebo-controlled induction period analysis sets.

There were no confirmed opportunistic infections reported during the induction period.

One (0.2%) placebo-treated participant (KGAB-(b) (6)) reported 2 serious events of cellulitis of the right extremity and sepsis. One (0.1%) lebrikizumab-treated participant reported a serious event of severe infectious colitis.

Maintenance Period (AD Mono PC Weeks 16 to 52)

Overall Infections

During the maintenance period, the most frequently reported AEs in the Infections and Infestations SOC were COVID-19, nasopharyngitis, and conjunctivitis for lebrikizumab-treated subjects. A higher frequency of subjects reported AEs in the LEB 250 mg Q4W group, as compared to the placebo and LEB 250 mg Q2W groups.

Table 656667. 68Treatment-Emergent Infections Occurring in at Least 1% of Lebrikizumab-Treated Participants for the Maintenance Period

Preferred Term	PBO (N=62)		LEB 250 mg Q4W (N=122)		LEB 250 mg Q2W (N=121)	
	n	(%)	n	(%)	n	(%)
Covid-19	2	(3.2)	11	(9.0)	3	(2.5)
Nasopharyngitis	3	(4.8)	9	(7.4)	5	(4.1)
Conjunctivitis	3	(4.8)	7	(5.7)	0	(0.0)
Oral herpes	1	(1.6)	4	(3.3)	1	(0.8)
Urinary tract infection	2	(3.2)	4	(3.3)	5	(4.1)
Folliculitis	0	(0.0)	3	(2.5)	3	(2.5)
Herpes dermatitis	0	(0.0)	3	(2.5)	1	(0.8)
Pneumonia	0	(0.0)	2	(1.6)	0	(0.0)
Sinusitis	0	(0.0)	2	(1.6)	0	(0.0)
Upper respiratory tract infection	3	(4.8)	2	(1.6)	2	(1.7)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "PQ2W" and MPSAFFL = "Y" and SAFFL = "Y" (PBO); TRT02A = "L250Q4W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q4W); TRT02A = "L250Q2W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL03FL = "Y" and CQ06NAM = "Infections and infestations" (Adverse Events).

Herpes Infections

A higher proportion of treatment-emergent herpes events was reported in the LEB 250 mg Q4W group as compared to placebo and LEB 250 mg Q2W groups. However, the relatively small sample sizes limit drawing conclusions.

Parasitic Infections/Opportunistic Infections

No events of parasitic infections were reported for the lebrikizumab and placebo (LEB withdrawal) groups in the maintenance period, Weeks 16 to 52.

There were no confirmed opportunistic infections reported during the maintenance period.

No serious events within the Infections and Infestations SOC were reported during the maintenance period.

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)

Overall Infections

Consistent with the placebo-controlled period, the most frequently reported AEs across all treatment groups were nasopharyngitis, oral herpes, and COVID-19.

Table 6669. Treatment-Emergent Infections Occurring in at Least 1% of Lebrikizumab-Treated Participants for the Combined Induction and Maintenance Periods (Weeks 0 – 52/56)

Preferred Term	LEB250Q2W only		LEB250Q2W/Q4W only		All LEB250Q2W		All LEB250Q2W/Q4W		PBO	
	(N=872)		(N=151)		(N=1023)		(N=1023)		(N=365)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infection	**208**	**(23.9)**	**57**	**(37.7)**	**237**	**(23.2)**	**163**	**(15.9)**	**62**	**(17.0)**
Nasopharyngitis	57	(6.5)	19	(12.6)	66	(6.5)	40	(3.9)	12	(3.3)
Covid-19	39	(4.5)	13	(8.6)	40	(3.9)	25	(2.4)	5	(1.4)
Oral herpes	21	(2.4)	7	(4.6)	27	(2.6)	21	(2.1)	9	(2.5)
Urinary tract infection	21	(2.4)	4	(2.6)	21	(2.1)	15	(1.5)	2	(0.5)
Folliculitis	13	(1.5)	4	(2.6)	14	(1.4)	9	(0.9)	4	(1.1)
Upper respiratory tract infection	13	(1.5)	3	(2.0)	14	(1.4)	6	(0.6)	6	(1.6)
Herpes dermatitis	8	(0.9)	3	(2.0)	8	(0.8)	4	(0.4)	2	(0.5)
Impetigo	8	(0.9)	1	(0.7)	8	(0.8)	9	(0.9)	6	(1.6)
Tonsillitis	7	(0.8)	1	(0.7)	8	(0.8)	4	(0.4)	2	(0.5)
Gastroenteritis	6	(0.7)	1	(0.7)	7	(0.7)	5	(0.5)	1	(0.3)
Herpes zoster	5	(0.6)	2	(1.3)	6	(0.6)	6	(0.6)	0	(0.0)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRTNEW = "LEB250Q2W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W only); TRTNEW = "LEB250Q2W/Q4W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W/Q4W only); TRTNEW = "All LEB250Q2W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W); TRTNEW = "All LEB250Q2W/Q4W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W/Q4W); TRTNEW = "PBO" and COMBIMFL = "Y" and SAFFL = "Y" (PBO); TEFLNEW = "Y" (Adverse Events).

According to the Applicant's calculations for the modified safety analysis set, the incidence rates (IRs) per 100 patient years (PY) of treatment-emergent infections for Weeks 0 to 52/56 were as follows:

- 50.9 in the LEB 250 mg Q2W only group
- 64.8 in the LEB 250 mg Q2W/Q4W only group, and
- 70.8 in the placebo group.

The IR of treatment-emergent infection for any lebrikizumab-treated subject from Weeks 0 to 52/56 was lower than the IR for lebrikizumab-treated subjects in the placebo-controlled induction period.

Parasitic Infections/Opportunistic Infections

There was 1 (0.7%) parasitic infection reported in the LEB 250 mg Q2W/Q4W only group (KGAD-(b) (6)). This subject had a mild enterobiasis and ascariasis coinfection, was treated with albendazole and fully recovered. These events did not lead to treatment discontinuation.

There were no confirmed opportunistic infections reported.

Five additional serious events within the Infections and infestations SOC were reported in 4 participants. All events were recovered/resolved and did not lead to treatment discontinuation.

- COVID-19 (n = 2)
- acrodermatitis and erysipelas (n = 1), and
- pneumonia (n = 1).

Any AD lebrikizumab exposure (AD All LEB)

Overall Infections
According to the Applicant's calculations for the modified safety analysis set, the IRs per 100 PY of TE-infections in the AD All LEB analysis set were as follows:

- 50.2 in the Any LEB group
  - 48.0 in the Any LEB 250 mg Q2W group, and
  - 44.0 in the Any LEB 250 mg Q4W group.

The IR of TE-infection in any lebrikizumab-treated participant was lower than the IR in lebrikizumab-treated participants in the placebo-controlled induction period.
For any lebrikizumab exposure, most AEs were mild or moderate in severity and nonserious. Five subjects (0.3%) reported an SAE within the SOC of Infections and infestations, 15 (0.9%) subjects reported a severe event, and 16 (0.9%) subjects had an infection AE that led to treatment discontinuation.

Table 6770. Treatment-Emergent Infections Occurring in at Least 1% of Lebrikizumab-Treated Participants for the All Lebrikizumab Exposure Integrated Analysis Set (Studies KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, KGAA, and KGAE)

Preferred Term	Any LEB250Q2W (N=1402)		Any LEB250Q4W (N=250)		Any LEB (N=1756)	
	n	(%)	n	(%)	n	(%)
Infection	415	(29.6)	75	(30.0)	550	(31.3)

Nasopharyngitis	118	(8.4)	19	(7.6)	159	(9.1)
Covid-19	111	(7.9)	22	(8.8)	133	(7.6)
Oral herpes	45	(3.2)	7	(2.8)	50	(2.8)
Upper respiratory tract infection	39	(2.8)	9	(3.6)	66	(3.8)
Urinary tract infection	35	(2.5)	6	(2.4)	43	(2.4)
Folliculitis	16	(1.1)	4	(1.6)	21	(1.2)
Herpes dermatitis	14	(1.0)	4	(1.6)	18	(1.0)
Impetigo	13	(0.9)	2	(0.8)	17	(1.0)
Gastroenteritis	12	(0.9)	1	(0.4)	14	(0.8)
Bronchitis	11	(0.8)	1	(0.4)	14	(0.8)
Herpes simplex	10	(0.7)	0	(0.0)	13	(0.7)
Herpes zoster	10	(0.7)	2	(0.8)	14	(0.8)
Sinusitis	10	(0.7)	4	(1.6)	15	(0.9)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRTNEW = "Any LEB250Q2W" and SAFFL = "Y" (Any LEB250Q2W); TRTNEW = "Any LEB250Q4W" and SAFFL = "Y" (Any LEB250Q4W); TRTNEW = "Any LEB" and SAFFL = "Y" (Any LEB); TEFLNEW = "Y" (Adverse Events).

Parasitic Infections/Opportunistic Infections

There were no additional parasitic infection events reported in the AD ALL LEB.

No confirmed opportunistic infections were reported across AD All LEB.

No additional serious events within Infections and infestations SOC were reported in AD All LEB.

120-Day Safety Update

Since the initial BLA submission, the Applicant reported that the frequency of participants who reported events in the Infection and infestation SOC was 22.5% {21.2%} for lebrikizumab-treated participants and 21.2% {18.9%} for placebo-treated participants and were similar between the safety update report and the initial BLA submission. The additional reports in the Infection and infestation SOC were mostly due to conjunctivitis, nasopharyngitis, oral herpes, folliculitis, and COVID-19 PTs, which is consistent with the initial submission.

Reviewer Comment: *The increase in the incidence rate of COVID-19 with extended exposure was likely due to the trial conduct during the pandemic, the delta variant expansion, and the duration of the pandemic. The 120-day safety update did not identify any new infectious safety concerns. Overall, herpes zoster infections did occur more frequently among lebrikizumab-treated subjects, and this should be reflected in labeling. Although nasopharyngitis occurred more frequently in lebrikizumab-treated subjects, a CMQ conducted by this reviewer demonstrated that URIs overall were not reported more frequently in lebrikizumab-treated*

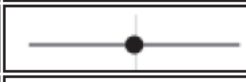
subjects. Therefore, this reviewer does not believe that nasopharyngitis should be included in labeling as an adverse reaction.

8.2.5.3. Eosinophilia and Eosinophil-Related Disorders

Placebo-Controlled Induction Period (Weeks 0 to 16)

During the placebo-controlled period, the frequency of subjects who reported eosinophilia TEAEs was similar in the LEB 250 mg Q2W group (n = 5, 0.6%) and the placebo group (n = 3, 0.8%). All events were nonserious and did not lead to treatment discontinuation. There were no reported events of eosinophil-related disorders.

Table 6871. Summary of Eosinophil Related TEAEs During the Placebo-Controlled Induction Period

Preferred Term	PBO (N=417)		LEB 250 mg Q2W (N=805)		Risk Difference		
	n	(%)	n	(%)	RD	(95% CI)	Forest Plot
Eosinophil count increased	1	(0.2)	2	(0.2)	-0.01	(-0.59, 0.57)	
Eosinophilia	2	(0.5)	3	(0.4)	0.11	(-0.68, 0.89)	

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "PQ2W" and SAFFL = "Y" and ALLPCFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and SAFFL = "Y" and ALLPCFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" and AEDECOD = "Eosinophil count increased" or "Eosinophilia" (Adverse Events).

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Post-baseline blood eosinophils (greater than the upper limit of normal) were observed at a higher frequency in lebrikizumab-treated subjects compared to placebo. In the LEB 250 mg Q2W group, the following blood eosinophil category shift increases were observed compared to placebo:

- normal to mild: LEB 250 mg Q2W (n = 123, 15.6 %) versus placebo (n = 49, 12.3 %)
- normal to moderate: LEB 250 mg Q2W (n = 3, 0.4 %) versus placebo (n = 2, 0.5 %)
- mild to moderate: LEB 250 mg Q2W (n = 53, 6.7 %) versus placebo (n = 14, 3.5 %)
- mild to severe: LEB 250 mg Q2W (n = 1, 0.1 %) versus placebo 0, and
- moderate to severe: LEB 250 mg Q2W (n = 2, 0.3 %) versus placebo 0.

Table 6972. Eosinophil Shift Tables of Maximum Baseline Category to Maximum Postbaseline Category Atopic Dermatitis Monotherapy and TCS Combination Safety Population Induction Period (Weeks 0 - 16)

	Maximum Post Baseline Result

Treatment	Maximum Baseline Category	Normal	Mild	Moderate	Severe
L250Q2W (N = 790)	Normal	421 (53.29%)	123 (15.57%)	3 (0.38%)	0 (0%)
	Mild	32 (4.05%)	133 (16.84%)	53 (6.71%)	1 (0.13%)
	Moderate	1 (0.13%)	9 (1.14%)	11 (1.39%)	2 (0.25%)
	Severe	0 (0%)	0 (0%)	0 (0%)	1 (0.13%)
PQ2W (N = 399)	Normal	212 (53.13%)	49 (12.28%)	2 (0.5%)	0 (0%)
	Mild	38 (9.52%)	75 (18.8%)	14 (3.51%)	0 (0%)
	Moderate	0 (0%)	5 (1.25%)	4 (1%)	0 (0%)
	Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: OCS Analysis Studio, Shift Table Tool.
X Cutoffs: Normal <= 0.49; 0.49 < Mild <= 1.49; 1.49 < Moderate <= 4.99; 4.99 < Severe.
Y Cutoffs: Normal <= 0.49; 0.49 < Mild <= 1.49; 1.49 < Moderate <= 4.99; 4.99 < Severe.
Population Filter: SAFFL = 'Y', ALLPCFL = 'Y'.
Multiple readings for same timepoint or flag were averaged.
(N =) indicates the subjects for each group in the shift table.

Most shifts were from the normal to mild category. Three lebrikizumab-treated subjects (0.4%) and 0 placebo-treated participants had an increase in blood eosinophils to severe category (>5000 per microliter).

The 3 cases of severe eosinophilia (eosinophilia greater than 5000 cells/microliter) that occurred during the placebo-controlled induction period are described below:

- A 35-year-old male (KGAC [redacted] (b) (6)) with medical history of hypertension with a mild baseline elevation of blood eosinophils (1.2 x 10^9/L) at screening to a severe elevation of blood eosinophils (greater than 5.0 x 10^9/L) on Study Day 58 (6.6 x 10^9/L). The shift to severe eosinophilia was transient and nonserious but did not return to baseline. This did not lead to treatment discontinuation. Participant discontinued study on Study Day 170 due to lack of efficacy.

- A 67-year-old male (KGAC- [redacted] (b) (6)) with a medical history of hypertension, anemia, and renal failure with baseline moderate elevation in blood eosinophil (1.5 x 10^9/L) at screening to severe elevation of blood eosinophils on Study Day 113 (7.3 x 10^9/L). No eosinophil related AEs were reported. Blood eosinophil elevation was transient and returned to baseline by Study Day 365. The eosinophilia did not lead to treatment discontinuation.

- A 52-year-old male (KGAC [redacted] (b) (6)) with medical history of renal atrophy and with baseline moderate elevation in blood eosinophils (2.1 x 10^9/L) to a severe elevation on

Study Day 58 (5.2 x 10^9/L). The subject reported a nonserious AE of dermatitis atopic on Study Day 49 and then reported an SAE of dermatitis atopic on Study Day 150 which resolved on Study Day 166. Eosinophil count returned to baseline at Study Day 113 and did not lead to treatment discontinuation.

Maintenance Period (AD Mono PC Weeks 16 to 52)
There were no AEs of eosinophilia or eosinophil-related disorders reported in the Weeks 16 to 52 maintenance period.

The frequency of subjects with increased blood eosinophils at any time postbaseline was higher for LEB 250 mg Q2W (5.5%) and LEB 250 mg Q4W (6.0%) treated subjects compared to placebo (LEB withdrawal) (2.7%) participants. A similar frequency of subjects had increased blood eosinophils at any time post-baseline in the LEB 250 mg Q2W group (5.5%) compared to the LEB 250 mg Q4W group (6.0%).

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)
The frequency of subjects reporting increased blood eosinophils at any time post-baseline were

- 147 (21.8%) in the LEB 250 mg Q2W only group
- 27 (20.8%) in the LEB 250 mg Q2W/Q4W only group, and
- 32 (10.9%) in the placebo group.

The frequency of lebrikizumab-treated subjects with increased blood eosinophils any time Post-baseline was similar to lebrikizumab-treated subjects from the placebo-controlled induction period (n = 132, 20.3%).

Three additional subjects reported post-baseline severe (at least 5000 per microliter) elevation of blood eosinophils, 1 normal to severe shift, and 2 mild to severe shifts. These subjects and their eosinophil shifts are described below:

- A 24-year-old male (KGAC-(b) (6)) with a history of food allergy and asthma with normal baseline blood eosinophils (0.3 x 10^9/L) shifted to a severe elevation on Study Day 280 (6.2 x 10^9/L). No other laboratories were drawn. No AEs were reported. The subject completed treatment period and discontinued on Study Day 281 due to lack of efficacy. The eosinophilia was unresolved at the time of study drug discontinuation.

- A 30-year-old male (KGAB-(b) (6)) with history of food allergy and asthma treated with LEB 250 mg Q2W in the maintenance escape arm with mild baseline elevation in blood eosinophils (1.1 x 10^9/L) to a severe elevation on Study Day 279 (6.8 x 10^9/L). No other laboratories were drawn. The subject reported an asymptomatic mild event of strongyloidiasis on Study Day 283 which recovered by Study Day 315. On this day the subject discontinued from the study due to lack of efficacy.

- A 22-year-old male (KGAC-(b) (6)) with history of cellulitis and dyshidrotic eczema treated with LEB 250 mg Q2W during the maintenance arm and with mild baseline elevation in blood eosinophils (0.5 x 10^9/L) to a severe elevation on Study Day 362 (7.5 x 10^9/L). A mild event of asthma exacerbation was reported on Day 354 and a moderate event of dermatitis atopic was reported on Study Day 362. The subject completed Study KGAC and rolled into Study KGAA but was lost to follow-up.

No eosinophil-related disorders were reported.

Any AD lebrikizumab exposure (AD All LEB)

The frequency of subjects reporting increased blood eosinophils at any time post-baseline were

- 317 (23.7%) in the Any LEB group
  - 237 (21.7%) in the Any LEB 250 mg Q2W group, and
  - 26 (14.4%) in the Any LEB 250 mg Q4W group.

The frequency of any LEB subjects with increased blood eosinophils at any time post-baseline was similar compared to lebrikizumab-treated subjects in the placebo-controlled induction period (n = 132, 20.3%).

Two additional subjects reported postbaseline severe (at least 5000 per microliter) elevation of blood eosinophils, described below:

- A 44-year-old female (KGAH-(b) (6)) with medical history of dizziness and with baseline mild elevation in blood eosinophils (0.75 x 10^9/L) to a severe elevation on Study Day 87 (5.4 109/L) that returned to baseline on Study Day 143. No AEs were reported at the time of the eosinophil elevation.

- A 14-year-old male (KGAE-(b) (6)) treated with LEB 250 mg Q2W in the open-label treatment period with baseline moderate elevation in blood eosinophils (2.4 x 10^9/L) to a severe elevation on Study Day 55 (6.4 x 10^9/L) that returned to baseline on Study Day 363. A mild event of eosinophilia was reported on Study Day 56. The event did not lead to treatment discontinuation.

No eosinophil-related disorders were reported

120-Day Safety Update

An additional 4 lebrikizumab-treated subjects reported postbaseline severe (≥5000 per microliter) elevation of blood eosinophils since the initial BLA submission. No eosinophil-related disorders were reported.

Reviewer Comment: *Increased post-baseline blood eosinophils were observed at a higher frequency in lebrikizumab-treated subjects compared to placebo. Although most events were nonserious and mild or moderate in severity, eosinophilia is an expected potential complication of IL-13 blockade and should be included as an ADR in labeling.*

8.2.5.4. Hypersensitivity Reactions

Placebo-Controlled Induction Period (Weeks 0 to 16)
The frequency of hypersensitivity reactions was low in both placebo and lebrikizumab-treated subjects. Three events of urticaria were reported during the induction period, 1 event in lebrikizumab-treated subjects and 2 events in placebo-treated subjects.

The lebrikizumab-treated subject (KGAC-(b) (6)), 22-year-old female with no previous history of urticaria randomly assigned to lebrikizumab 250 mg Q2W during the induction and maintenance period, reported 2 events of urticaria while receiving lebrikizumab. She reported a mild event during the induction period on Study Day 98 (same day of lebrikizumab dosing) and 1 moderate event during the maintenance period on Study Day 249 (10 days after lebrikizumab dosing) which was treated with antihistamine. Both events resolved and did not lead to treatment discontinuation.

An event of drug sensitivity occurred in a 75-year-old male subject (KGAD-(b) (6)) who reported an AD flare/eczema on Study Day 40. On Study Day 45, 2 days after receiving lebrikizumab, a severe event of drug hypersensitivity or paradoxical worsening of AD was reported. He was treated with oral prednisone and the event resolved on Study Day 58. Dermatitis atopic was reported on Study Day 65. The event was assessed as related to lebrikizumab by the investigator and led to treatment discontinuation.

No events of anaphylaxis were reported.

Table 7073. Summary of Hypersensitivity Reactions from the Induction Period Placebo-Controlled Analysis Sets

Preferred Term	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (ADhere)	
	PBO	LEB 250 mg Q2W	PBO	LEB 250 mg Q2W	PBO + TCS	LEB 250 mg Q2W + TCS
	N=417	N=805	N=342	N=652	N = 75	N=153
	n (%)		n (%)		n (%)	
Urticaria	3 (0.7)	3 (0.4)	2 (0.6)	2 (0.3)	1 (1.3)	1 (0.7)
Drug hypersensitivity	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.7)
Drug eruption	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Hypersensitivity	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Angioedema	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: ALLPCFL = "Y" and TRT01A = "PQ2W" and SAFFL = "Y" (PBO); ALLPCFL = "Y" and TRT01A = "L250Q2W" and SAFFL = "Y" (LEB); ANL02FL = "Y" and TEMONDFL = "Y" and AEDECOD = "Urticaria" or "Urticaria papular" or "Drug hypersensitivity" or "Angioedema" or "Drug eruption" or "Hypersensitivity" (Adverse Events).

Maintenance Period (AD Mono PC Weeks 16 to 52)

One subject (0.8%) in the lebrikizumab 250 mg Q4W group and 1 subject (0.8%) in the lebrikizumab 250 mg Q2W group reported events of urticaria during the maintenance period. No subjects in the placebo group reported any events of immediate hypersensitivity. No cases of anaphylaxis reported.

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)

The frequency of immediate hypersensitivity events from Weeks 0 to 52/56 was higher in LEB 250 mg Q2W compared to lebrikizumab-treated subjects during the placebo-controlled induction period.

Table 7174. Summary of Hypersensitivity Reactions for the Combined Induction and Maintenance Periods Analysis Set (Studies KGAB, KGAC, KGAD, and KGAA)

Preferred Term	LEB250Q2W only		LEB250Q2W/Q4W only		All LEB250Q2W		All LEB250Q2W/Q4W		PBO	
	(N=872)		(N=151)		(N=1023)		(N=1023)		(N=365)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hypersensitivity	**10**	**(1.1)**	**2**	**(1.3)**	**11**	**(1.1)**	**10**	**(1.0)**	**4**	**(1.1)**
Urticaria	4	(0.5)	1	(0.7)	4	(0.4)	5	(0.5)	3	(0.8)
Hypersensitivity	3	(0.3)	0	(0.0)	3	(0.3)	2	(0.2)	0	(0.0)
Drug hypersensitivity	2	(0.2)	0	(0.0)	2	(0.2)	2	(0.2)	0	(0.0)
Drug eruption	1	(0.1)	1	(0.7)	2	(0.2)	1	(0.1)	0	(0.0)
Angioedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "LEB250Q2W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W only); TRTNEW = "LEB250Q2W/Q4W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W/Q4W only); TRTNEW = "All LEB250Q2W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W); TRTNEW = "All LEB250Q2W/Q4W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W/Q4W); TRTNEW = "PBO" and COMBIMFL = "Y" and SAFFL = "Y" (PBO); TEFLNEW = "Y" (Adverse Events).

Any AD lebrikizumab exposure (AD All LEB)

The frequency of immediate hypersensitivity events for Any LEB was similar compared to LEB 250 mg Q2W during the placebo-controlled induction period.

Table 7275. Summary of Hypersensitivity Reactions for the All Lebrikizumab Exposure Integrated Analysis Set (Studies KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, KGAA, and KGAE)

Preferred Term	Any LEB250Q2W		Any LEB250Q4W		Any LEB	
	(N=1402)		(N=250)		(N=1756)	
	n	(%)	n	(%)	n	(%)

Hypersensitivity	**25**	**(1.8)**	**1**	**(0.4)**	**27**	**(1.5)**
Urticaria	13	(0.9)	1	(0.4)	15	(0.9)
Hypersensitivity	7	(0.5)	0	(0.0)	7	(0.4)
Drug eruption	3	(0.2)	0	(0.0)	3	(0.2)
Drug hypersensitivity	3	(0.2)	0	(0.0)	3	(0.2)
Angioedema	1	(0.1)	0	(0.0)	1	(0.1)
Stevens-johnson syndrome	1	(0.1)	0	(0.0)	1	(0.1)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "Any LEB250Q2W" and SAFFL = "Y" (Any LEB250Q2W); TRTNEW = "Any LEB250Q4W" and SAFFL = "Y" (Any LEB250Q4W); TRTNEW = "Any LEB" and SAFFL = "Y" (Any LEB); TEFLNEW = "Y" (Adverse Events).

No events of anaphylaxis were reported in AD All LEB. Events of drug eruption were reported and are described below:

- A 15-year-old male (KGAE-(b) (6)) reported a mild event of drug eruption on Study Day 41 during open-label study, same day of lebrikizumab dosing. The event was treated with antihistamines and topical corticosteroid and recovered on Study Day 50. No change to treatment was made and no recurrence of events was reported.
- A 59-year-old female (KGAB-(b) (6)) randomly assigned to lebrikizumab 250 mg Q2W on Study Day 1 and randomly assigned to lebrikizumab 250 mg Q4W on Study Day 114 reported a drug eruption (mild rash on legs) on Study Day 42, same day of lebrikizumab dosing, ended the next day and was considered related to an emollient use. The study drug was continued with no recurrence of the event.

One adolescent subject discontinued study treatment due to a hypersensitivity event. Subject KGAE-(b) (6), a 12-year-old female with medical history of urticaria, was assigned to lebrikizumab 250 mg Q2W on Study Day 1 and continued to receive LEB 250 mg Q2W on Study Day 365 in the long-term extension study. She reported 2 separate moderate events of hypersensitivity (rash on legs, arms, and face) on Study Day 408 and Study Day 433 (days of injection), both resolved the next day. She discontinued due to this event. She additionally had a single event of urticaria on Study Day 1 with no further events of urticaria or hypersensitivity.

120-Day Safety Update

No serious hypersensitivity reactions were reported in the safety update.

Reviewer Comment: *Although no events of anaphylaxis or related angioedema were reported, cases of urticaria and drug hypersensitivity did occur in lebrikizumab-treated subjects and were assessed as related to treatment. Based on these events and the fact that anaphylaxis and angioedema have occurred after administration of other IL-13 antagonists (e.g., tralokinumab), this reviewer recommends that hypersensitivity reactions be included in labeling.*

8.2.5.5. Injection Site Reactions

Placebo-Controlled Induction Period (Weeks 0 to 16)

Injection site reactions were reported more frequently among lebrikizumab-treated subjects as compared to placebo-treated subjects. Most events were mild or moderate in severity and none were serious. One (0.1%) event of injection site dermatitis (KGAF (b) (6)), which occurred within a month of treatment, was severe and led to treatment discontinuation. Another subject (KGAD (b) (6)) discontinued treatment due to injection site rash, which occurred within 15 days of study drug administration.

Table 7376. Summary of Injection Site Reactions from the Induction Period Placebo-Controlled Analysis Sets

Preferred Term	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (ADhere)	
	PBO	LEB 250 mg Q2W	PBO	LEB 250 mg Q2W	PBO + TCS	LEB 250 mg Q2W + TCS
	N=417	N=805	N=342	N=652	N = 75	N=153
	n (%)		n (%)		n (%)	
Injection site erythema	1 (0.2)	7 (0.9)	1 (0.3)	6 (0.9)	0 (0.0)	1 (0.7)
Injection site pain	4 (1.0)	7 (0.9)	4 (1.2)	7 (1.1)	0 (0.0)	0 (0.0)
Injection site reaction	1 (0.2)	5 (0.6)	0 (0.0)	3 (0.5)	1 (1.3)	2 (1.3)
Injection site pruritis	0 (0.0)	3 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.7)
Injection site rash	0 (0.0)	3 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	2 (1.3)
Injection site swelling	1 (0.2)	2 (0.2)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.7)
Injection site dermatitis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Injection site discomfort	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Injection site bruising	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.1)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "PQ2W" and ALLPCFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and ALLPCFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" and AEDECOD = "Injection site pain" or "Injection site rash" or "Injection site erythema" or "Injection site oedema" or "Injection site reaction" or "Injection site bruising" or "Injection site pruritus" or "Injection site swelling" or "Injection site urticaria" or "Injection site haematoma" or "Injection site infection" or "Injection site discomfort" or "Injection site dermatitis" (Adverse Events).

Maintenance Period (AD Mono PC Weeks 16 to 52)

One case of injection site urticaria was reported in the LEB 250 mg Q4W group. This case was mild and did not lead to treatment discontinuation. No other ISRs were reported.

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)

The IRs per 100 PY for ISRs for Weeks 0 to 52/56 were

- 4.3 in the LEB 250 mg Q2W only group
- 2.1 in the LEB 250 mg Q2W/Q4W only group, and

- 4.7 in the placebo group.

The IR for lebrikizumab-treated subjects during Weeks 0 to 52/56 was lower than the IR for lebrikizumab-treated subjects during the placebo-controlled induction period.

Table 7477. Summary of Injection Site Reactions for the Combined Induction and Maintenance Periods Analysis Set (Studies KGAB, KGAC, KGAD, and KGAA)

Preferred Term	LEB250Q2W only		LEB250Q2W/ Q4W only		All LEB250Q2W		All LEB250Q2W/ Q4W		PBO	
	(N=872)		(N=151)		(N=1023)		(N=1023)		(N=365)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
ISR	**26**	**(3.0)**	**4**	**(2.6)**	**28**	**(2.7)**	**21**	**(2.1)**	**5**	**(1.4)**
Injection site reaction	12	(1.4)	1	(0.7)	12	(1.2)	8	(0.8)	1	(0.3)
Injection site erythema	4	(0.5)	0	(0.0)	4	(0.4)	4	(0.4)	0	(0.0)
Injection site pain	4	(0.5)	1	(0.7)	5	(0.5)	4	(0.4)	3	(0.8)
Injection site swelling	4	(0.5)	0	(0.0)	4	(0.4)	2	(0.2)	1	(0.3)
Injection site pruritus	3	(0.3)	0	(0.0)	3	(0.3)	2	(0.2)	0	(0.0)
Injection site rash	2	(0.2)	0	(0.0)	2	(0.2)	2	(0.2)	0	(0.0)
Injection site discomfort	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Injection site haematoma	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Administration site reaction	0	(0.0)	1	(0.7)	1	(0.1)	1	(0.1)	0	(0.0)
Injection site bruising	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Injection site urticaria	0	(0.0)	1	(0.7)	0	(0.0)	1	(0.1)	0	(0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "LEB250Q2W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W only); TRTNEW = "LEB250Q2W/Q4W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W/Q4W only); TRTNEW = "All LEB250Q2W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W); TRTNEW = "All LEB250Q2W/Q4W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W/Q4W); TRTNEW = "PBO" and COMBIMFL = "Y" and SAFFL = "Y" (PBO); TEFLNEW = "Y" (Adverse Events).

Any AD lebrikizumab exposure (AD All LEB)

The IRs per 100 PY for ISRs in the AD All LEB analysis set were

- 3.3 in the Any LEB group,
  - 3.5 in the Any LEB 250 mg Q2W group, and
  - 2.7 in the Any LEB 250 mg Q4W group.

The IR from any lebrikizumab-treated participants was lower than the IR from lebrikizumab-treated participants during the placebo-controlled induction period.

Table 7578. Summary of Injection Site Reactions for the All Lebrikizumab Exposure Integrated Analysis Set (Studies KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, KGAA, and KGAE)

Preferred Term	Any LEB250Q2W (N=1402)		Any LEB250Q4W (N=250)		Any LEB (N=1756)	
	n	(%)	n	(%)	n	(%)
ISR	**46**	**(3.3)**	**6**	**(2.4)**	**56**	**(3.2)**
Injection site reaction	18	(1.3)	1	(0.4)	20	(1.1)
Injection site pain	13	(0.9)	3	(1.2)	16	(0.9)
Injection site erythema	9	(0.6)	2	(0.8)	12	(0.7)
Injection site pruritus	5	(0.4)	1	(0.4)	6	(0.3)
Injection site swelling	5	(0.4)	0	(0.0)	6	(0.3)
Injection site rash	3	(0.2)	0	(0.0)	3	(0.2)
Administration site reaction	1	(0.1)	0	(0.0)	1	(0.1)
Application site rash	1	(0.1)	0	(0.0)	1	(0.1)
Injection site dermatitis	1	(0.1)	0	(0.0)	1	(0.1)
Injection site discomfort	1	(0.1)	0	(0.0)	1	(0.1)
Injection site haematoma	1	(0.1)	0	(0.0)	1	(0.1)
Injection site infection	0	(0.0)	0	(0.0)	1	(0.1)
Injection site oedema	0	(0.0)	1	(0.4)	1	(0.1)
Injection site urticaria	0	(0.0)	1	(0.4)	1	(0.1)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "Any LEB250Q2W" and SAFFL = "Y" (Any LEB250Q2W); TRTNEW = "Any LEB250Q4W" and SAFFL = "Y" (Any LEB250Q4W); TRTNEW = "Any LEB" and SAFFL = "Y" (Any LEB); TEFLNEW = "Y" (Adverse Events).

A total of 5 subjects discontinued treatment due to ISR TEAEs.

120-Day Safety Update

Since the initial BLA submission, no additional ISR events were SAEs, severe AEs, or led to treatment discontinuation.

Reviewer Comment: *ISRs were reported in a numerically higher frequency in lebrikizumab-treated groups compared to placebo. This reviewer agrees with the Applicant's proposal to include ISRs as an ADR in labeling.*

8.2.5.6. Hepatic Safety

Placebo-Controlled Induction Period (Weeks 0 to 16)

During the induction period, no hepatic-related SAEs were reported, and no hepatic-related AEs led to treatment discontinuation. Overall, the frequencies of hepatic-related AEs were low, though more events were reported by lebrikizumab-treated subjects than those in the placebo groups. No subject met laboratory criteria for Hy's law.

Table 7679. Summary of Hepatic Safety TEAEs from the Induction Period Placebo-Controlled Analysis Sets

Preferred Term	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (ADhere)	
	PBO	LEB 250 mg Q2W	PBO	LEB 250 mg Q2W	PBO + TCS	LEB 250 mg Q2W + TCS
	N=417	N=805	N=342	N=652	N = 75	N=153
	n (%)		n (%)		n (%)	
Alanine aminotransferase increased	1 (0.2)	3 (0.4)	0 (0.0)	2 (0.3)	1 (1.3)	1 (0.7)
Aspartate aminotransferase increased	0 (0.0)	3 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.7)
Gamma-glutamyltransferase increased	0 (0.0)	3 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.7)
Hepatic steatosis	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.7)
Hepatic enzyme increased	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Hepatomegaly	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.7)
Non-alcoholic steatohepatitis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "PQ2W" and ALLPCFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and ALLPCFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" and AEDECOD = "Gamma-glutamyltransferase increased" or "Alanine aminotransferase increased" or "Aspartate aminotransferase increased" or "Hepatic enzyme increased" or "Non-alcoholic steatohepatitis" or "Hepatic steatosis" or "Hepatomegaly" or "Bilirubin conjugated increased" (Adverse Events).

Maintenance Period (AD Mono PC Weeks 16 to 52)

Few hepatic-related AEs were reported during the maintenance period. No subjects discontinued from study treatment due to a hepatic related AE. One subject (KGAB-(b) (6)), treated with LEB 250 mg Q4W, reported an SAE of cholecystitis. No subject met laboratory criteria for Hy's law.

Table 7780. Summary of Hepatic Safety TEAEs During the Monotherapy Maintenance Period

Preferred Term	PBO		LEB 250 mg Q4W		LEB 250 mg Q2W	
	(N=62)		(N=122)		(N=121)	
	n	(%)	n	(%)	n	(%)
Aspartate aminotransferase increased	0	(0.0)	2	(1.6)	1	(0.8)
Alanine aminotransferase increased	1	(1.6)	1	(0.8)	1	(0.8)
Cholecystitis	0	(0.0)	1	(0.8)	0	(0.0)

Hepatic steatosis	0	(0.0)	1	(0.8)	0	(0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "PQ2W" and MPSAFFL = "Y" and SAFFL = "Y" (PBO); TRT02A = "L250Q4W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q4W); TRT02A = "L250Q2W" and MPSAFFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL03FL = "Y" and TEMAPFL = "Y" and AEDECOD = "Alanine aminotransferase increased" or "Aspartate aminotransferase increased" or "Gamma-glutamyltransferase increased" or "Hepatic steatosis" or "Hepatic enzyme increased" or "Hepatomegaly" or "Non-alcoholic steatohepatitis" or "Liver function test increased" or "Cholecystitis" (Adverse Events).

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)

The frequency of hepatic TEAEs through Weeks 52/56 were

- 20 (2.3%) in the LEB 250 mg Q2W only group
- 5 (3.3%) in the LEB 250 mg Q2W/Q4W only group, and
- 0 in the placebo group.

The most frequently reported PTs across all treatment groups were AST increased, ALT increased, and GGT increased.

No additional hepatic-related SAEs were reported. No subject met laboratory criteria for Hy's law.

Table 7881. Summary of Hepatic Safety TEAEs for the Combined Induction and Maintenance Periods Analysis Set (Studies KGAB, KGAC, KGAD, and KGAA)

Cluster - Preferred Term	LEB250Q2W only		LEB250Q2W/Q4W only		All LEB250Q2W		All LEB250Q2W/Q4W		PBO	
	(N=872)		(N=151)		(N=1023)		(N=1023)		(N=365)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hepatic safety	**20**	**(2.3)**	**5**	**(3.3)**	**20**	**(2.0)**	**14**	**(1.4)**	**0**	**(0.0)**
Alanine aminotransferase increased	6	(0.7)	1	(0.7)	6	(0.6)	3	(0.3)	0	(0.0)
Aspartate aminotransferase increased	5	(0.6)	2	(1.3)	5	(0.5)	3	(0.3)	0	(0.0)
Blood alkaline phosphatase increased	3	(0.3)	0	(0.0)	3	(0.3)	2	(0.2)	0	(0.0)
Hepatic enzyme increased	3	(0.3)	0	(0.0)	3	(0.3)	2	(0.2)	0	(0.0)
Hepatic steatosis	2	(0.2)	1	(0.7)	2	(0.2)	3	(0.3)	0	(0.0)
Biliary colic	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Blood alkaline phosphatase abnormal	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Cholelithiasis	1	(0.1)	1	(0.7)	1	(0.1)	2	(0.2)	0	(0.0)
Hepatomegaly	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Hypertransaminasaemia	1	(0.1)	1	(0.7)	1	(0.1)	1	(0.1)	0	(0.0)
Non-alcoholic steatohepatitis	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Cholecystitis	0	(0.0)	1	(0.7)	0	(0.0)	1	(0.1)	0	(0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "LEB250Q2W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W only); TRTNEW = "LEB250Q2W/Q4W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W/Q4W only); TRTNEW = "All LEB250Q2W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W); TRTNEW = "All LEB250Q2W/Q4W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W/Q4W); TRTNEW = "PBO" and COMBIMFL = "Y" and SAFFL = "Y" (PBO); TEFLNEW = "Y" (Adverse Events).

Any AD lebrikizumab exposure (AD All LEB)

The frequency of subjects reporting at least 1 TEAE in Any LEB group was 3.1% (n = 55). This was similar across all treatment groups and higher than the placebo-controlled period. The frequencies of subjects reporting at least 1 TEAE were

- 55 (3.1%) in the Any LEB group
  - 39 (2.8%) in the Any LEB Q2W group, and
  - 11 (4.4%) in the Any LEB Q4W group.

Table 7982. Summary of Hepatic Safety TEAEs for the All Lebrikizumab Exposure Integrated Analysis Set (Studies KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, KGAA, and KGAE)

Preferred Term	Any LEB250Q2W (N=1402)		Any LEB250Q4W (N=250)		Any LEB (N=1756)	
	n	(%)	n	(%)	n	(%)
Hepatic safety	**39**	**(2.8)**	**11**	**(4.4)**	**55**	**(3.1)**
Alanine aminotransferase increased	18	(1.3)	3	(1.2)	23	(1.3)
Aspartate aminotransferase increased	10	(0.7)	3	(1.2)	13	(0.7)
Hepatic enzyme increased	5	(0.4)	1	(0.4)	6	(0.3)
Blood alkaline phosphatase increased	3	(0.2)	1	(0.4)	4	(0.2)
Hepatic steatosis	3	(0.2)	2	(0.8)	5	(0.3)
Cholelithiasis	2	(0.1)	1	(0.4)	3	(0.2)
Hypertransaminasaemia	2	(0.1)	1	(0.4)	3	(0.2)
Jaundice	2	(0.1)	0	(0.0)	2	(0.1)
Bile duct stone	1	(0.1)	0	(0.0)	1	(0.1)
Biliary colic	1	(0.1)	0	(0.0)	1	(0.1)
Blood alkaline phosphatase abnormal	1	(0.1)	0	(0.0)	1	(0.1)
Hepatomegaly	1	(0.1)	0	(0.0)	1	(0.1)
Liver function test increased	1	(0.1)	0	(0.0)	2	(0.1)
Non-alcoholic steatohepatitis	1	(0.1)	0	(0.0)	1	(0.1)
Bilirubin conjugated increased	0	(0.0)	0	(0.0)	1	(0.1)
Bilirubinuria	0	(0.0)	0	(0.0)	1	(0.1)
Blood bilirubin increased	0	(0.0)	0	(0.0)	1	(0.1)
Cholecystitis	0	(0.0)	2	(0.8)	2	(0.1)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "Any LEB250Q2W" and SAFFL = "Y" (Any LEB250Q2W); TRTNEW = "Any LEB250Q4W" and SAFFL = "Y" (Any LEB250Q4W); TRTNEW = "Any LEB" and SAFFL = "Y" (Any LEB); TEFLNEW = "Y" (Adverse Events).

Two subjects discontinued from treatment (one due to Hepatic enzyme increased, and another due to ALT increased and AST increased).

One subject met laboratory criteria for potential Hy's law. His case is summarized below:

KGAA- (b) (6)**:** a 61-year-old white male subject with medical history of obesity (BMI 29.9 kg/m^2 at screening), hypertension, peripheral venous disease, transient ischemic attack, knee surgery due to osteoarthritis, bilateral deafness, depression, and anxiety was enrolled into open-label period of long-term extension trial and treated with LEB 250 mg Q2W until Study Day 199. Concomitant medication included naproxen, cholecalciferol, and calcium. The subject reported drinking once per week, but quantity was not provided. Baseline potassium was 3.5 mmol/L and hepatic enzymes values were GGT 305 U/L (4.7x ULN), AST 95 U/L (2.3x ULN) with AST:ALT ratio of 4:1, TBL 22.2 umol/L (1.1x ULN), and platelets 63 x 10^9/L. He reported a serious and severe AE of low blood potassium (potassium 2.6 mmol/L, with range 3.5 to 5.3 mmol/L) and a severe nonserious AE of jaundice on Study Day 213. Study drug was withheld, and due to hypokalemia, he was discontinued from the study on the same day and laboratories were obtained. There was an increase in hepatic laboratory values, with GGT 325 U/L (5x ULN), AST 153 (3.7x ULN), and TBL 92.3 umol/L (4.5x ULN). ALP and ALT remained normal throughout the study. The subject reported drinking alcohol prior to laboratory draw. The subject reported no other symptoms and was referred to the emergency room, where he refused follow-up care. Based on AST and TBL elevation, he met laboratory criteria for potential Hy's law.

This event triggered an internal review by the study team and hepatologist. Based on review, this subject with baseline elevation in GGT, AST with AST:ALT ratio of 4:1, and decreased platelets who confirmed drinking alcohol prior to laboratory draw had a severe acute elevation in TBL, leading to jaundice and AST elevation. The pattern of liver injury is consistent with advanced alcohol related liver disease that may be complicated by portal hypertension and does not represent DILI. On Study Day 220, his blood potassium returned to baseline, 3.4 mmol/L. On Study Day 239, hepatic enzymes normalized (GGT 66 U/L, AST 33, and TBL 18.1 umol/L). Etiology of low potassium was not known but may have been related to alcohol use. Event of low potassium was assessed as not related by the investigator.

<u>120-Day Safety Update</u>
No subjects met criteria for potential hepatocellular or cholestatic DILI.

Reviewer Comment: *This reviewer agrees that the subject who met laboratory criteria for Hy's Law likely experienced livery injury due to alcohol-related liver disease rather than DILI. Although the frequency of hepatic-related TEAEs was higher for lebrikizumab-treated subjects compared to those who received placebo, the events were reported by subjects with baseline hepatic enzyme elevation, hepatic past medical history, other confounding factors, or were single point elevations that resolved. The data do not suggest a hepatic safety concern associated with lebrikizumab.*

8.2.5.7. Suicide/Self-Injury

Placebo-Controlled Induction Period (Weeks 0 to 16)
The percentage of subjects that reported at least 1 suicidal ideation/self-injury SMQ event in the placebo-controlled induction period was

- 1 (0.1%) in the LEB 250 mg Q2W group, and
- no events in the placebo group.

A 44-year-old female subject (KGAF-(b) (6)) with history of anxiety and depression and treated with lebrikizumab during induction period reported a non-serious moderate event of suicidal ideation on Study Day 66. Patient recovered on the same day. The event did not lead to treatment discontinuation.

Maintenance Period (AD Mono PC Weeks 16 to 52)
There were no additional events of suicidal ideation/self-injury reported during the maintenance period.

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)
There were no additional events of suicidal ideation/self-injury reported.

Any AD lebrikizumab exposure (AD All LEB)
A 25-year-old female (KGAC-(b) (6)) with no medical history of depression reported a SAE of major depression with suicidal ideation following a major traumatic life event on Study Day 449 during the long-term extension period. She was treated with escitalopram and therapy visits. The event recovered on Study Day 503 and did not lead to study discontinuation.

120-Day Safety Update
Since the initial BLA submission, no additional participants reported events within the Suicide/Self-Injury SMQ.

Reviewer Comment: *Data from subjects in the lebrikizumab AD clinical program do not suggest an increased risk of suicide/self-injury among those treated with lebrikizumab.*

8.2.5.8. Malignancies

Placebo-Controlled Induction Period (Weeks 0 to 16)

There were no malignancy events other than nonmelanoma skin cancer (NMSC) reported during the placebo-controlled induction period. The frequencies of NMSC were low in lebrikizumab-treated participants and comparable to placebo.

Table 8083. Summary of Malignancies from the Induction Period Placebo-Controlled Analysis Sets

Preferred Term	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (ADhere)	
	PBO	LEB 250 mg Q2W	PBO	LEB 250 mg Q2W	PBO + TCS	LEB 250 mg Q2W + TCS
	N=417	N=805	N=342	N=652	N = 75	N=153
	n (%)		n (%)		n (%)	
Keratoacanthoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Squamous cell carcinoma	1 (0.2)	1 (0.1)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)
Bowen's disease	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "PQ2W" and ALLPCFL = "Y" and SAFFL = "Y" (PBO); TRT01A = "L250Q2W" and ALLPCFL = "Y" and SAFFL = "Y" (LEB 250 mg Q2W); TRTEMFL = "Y" and ANL02FL = "Y" and TEMONDFL = "Y" and AEBODSYS = "Neoplasms benign, malignant and unspecified (incl cysts and polyps" (Adverse Events).

Maintenance Period (AD Mono PC Weeks 16 to 52)

No malignancies were reported during the Weeks 16 to 52 maintenance period.

Combined Induction and Maintenance Period (AD Mono/TCS Weeks 0 to 52/56)

One death was reported for a lebrikizumab-treated 74-year-old male study participant who reported events of pancreatic carcinoma with metastasis to the bone and metastasis to the liver. The narrative for this event is provided in section 8.2.4.

Table 8184. Summary of Malignancies for the Combined Induction and Maintenance Periods Analysis Set (Studies KGAB, KGAC, KGAD, and KGAA)

Preferred Term	LEB250Q2W only		LEB250Q2W/ Q4W only		All LEB250Q2W		All LEB250Q2W/ Q4W		PBO	
	(N=872)		(N=151)		(N=1023)		(N=1023)		(N=365)	
	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)
Malignancy	**6**	**(0.7)**	**0**	**(0.0)**	**6**	**(0.6)**	**2**	**(0.2)**	**1**	**(0.3)**
Basal cell carcinoma	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Cutaneous t-cell lymphoma	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)
Metastases to bone	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Metastases to liver	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)

Ovarian germ cell teratoma	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0 (0.0)
Pancreatic carcinoma metastatic	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0 (0.0)
Penile squamous cell carcinoma	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0 (0.0)
Squamous cell carcinoma	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	1 (0.3)
Squamous cell carcinoma of skin	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "LEB250Q2W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W only); TRTNEW = "LEB250Q2W/Q4W only" and COMBIMFL = "Y" and SAFFL = "Y" (LEB250Q2W/Q4W only); TRTNEW = "All LEB250Q2W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W); TRTNEW = "All LEB250Q2W/Q4W" and COMBIMFL = "Y" and SAFFL = "Y" (All LEB250Q2W/Q4W); TRTNEW = "PBO" and COMBIMFL = "Y" and SAFFL = "Y" (PBO); TEFLNEW = "Y" (Adverse Events).

Any AD lebrikizumab exposure (AD All LEB)

In the AD ALL LEB integrated analysis set, there were 7 additional lebrikizumab-treated participants reporting events of malignancy other than NMSC. Four of these events were serious. Brief narratives of these malignancy events are provided below:

A 30-year-old female (KGAA (b) (6)) with no pertinent medical history reported a neuroendocrine tumor of the appendix on Study Day 245 in the open-label arm of Study KGAA and received lebrikizumab 250 mg Q2W. The SAE was not resolved during the study period and led to study discontinuation on Study Day 282. No other AEs were reported.

A 71-year-old male (KGAB (b) (6)) with a medical history of squamous cell carcinoma of the skin and prostate enlargement was randomly assigned to lebrikizumab 250 mg Q2W on Study Day 1. He was then then randomly assigned to placebo Q2W on Study Day 114 and received lebrikizumab 250 mg Q2W in Study KGAA on Study Day 365. He reported prostate cancer on Study Day 644, 14 days since his last exposure to lebrikizumab. The SAE was not resolved during the long-term extension study and led to study discontinuation on Study Day 728.

A 64-year-old post-menopausal female (KGAB (b) (6)) with no pertinent past medical history was randomly assigned to lebrikizumab 250 mg Q2W on Study Day 1 in Study KGAB and continued to receive lebrikizumab 250 mg Q2W during the maintenance period. She rolled into Study KGAA on Study Day 365 and continued to receive lebrikizumab 250 mg Q2W. She reported an AE of mild post-menopausal vaginal hemorrhage that began on Study Day 335, was evaluated, and underwent an endometrial biopsy which confirmed a diagnosis of high-grade serous adenocarcinoma of endometrium. An SAE of endometrial adenocarcinoma was reported on Study Day 405, 11 days after last exposure to lebrikizumab. The participant had a hysterectomy on Study Day 463 and the event was reported as recovered on Study Day 465. The SAE led to study discontinuation.

An 85-year-old post-menopausal female (KGAC (b) (6)) with medical history of skin cancer and breast cancer was treated with breast conservation therapy and left partial mastectomy with sentinel node biopsy in (b) (6). The participant's mother had breast cancer. She was randomly assigned to the placebo arm on Study Day 1, then escaped to lebrikizumab 250 mg

Q2W on Study Day 114 and continued on lebrikizumab 250 mg Q2W on Study Day 366 in Study KGAA. On Study Day 376, she reported a breast mass after a routine mammogram. An ultrasound and breast biopsy were performed and confirmed invasive ductal carcinoma of the right breast. This was reported as an SAE on Study Day 438, 8 days after last exposure to lebrikizumab. She underwent segmental mastectomy and sentinel lymph node biopsy. The last dose of lebrikizumab treatment was on Study Day 450. The SAE was recovered on Study Day 502 and led to study discontinuation on Study Day 555.

KGAE-(b) (6) (Cutaneous T-cell Lymphoma)
A 17-year-old male with a history of AD and lower lip epidermoid cysts treated with LEB 250 mg Q2W on Study Day 1 reported a mild nonserious event of cutaneous T-cell lymphoma (mycosis fungoides) on the left abdomen. Participant underwent a single biopsy at a single site and histological findings from a biopsy raised the possibility of mycosis fungoides. Investigator could not confirm the diagnosis of mycosis fungoides due to the participant's age and pathology as only a single sample from single biopsy site was available. Immunohistochemical stains required for a definitive diagnosis was pending and no further follow-up was obtained. Participant discontinued from the study.

KGAB-(b) (6) (Cutaneous T-cell Lymphoma)
A 22-year-old male participant reported a moderate nonserious event of cutaneous T-cell lymphoma during the maintenance period on Study Day 149. The event was not recovered. Participant discontinued from the study due to physician decision.

KGAC-(b) (6) (Ovarian Germ Cell Teratoma)
A 22-year-old female reported a moderate and nonserious event of left ovarian teratoma. The event recovered and did not lead to treatment discontinuation.

Overall, 13 lebrikizumab-treated participants (0.8%) reported 20 malignancy events. Eight subjects reported malignancies other than NMSC in the any AD lebrikizumab exposure analysis set. NMSC events were generally unremarkable, localized, and a similar frequency was reported across treatment groups. All NMSC events were nonserious, mild or moderate in severity, and did not lead to treatment discontinuation.

<u>120-Day Safety Update</u>
Since the initial BLA submission, no additional NMSC was reported in the safety update. An additional 3 subjects reported malignancies other than NMSC:

- KGAD-(b) (6): Pancreatic carcinoma metastatic
- KGAC-(b) (6): Prostate cancer, and
- KGAL-(b) (6): Hodgkin's disease.

Reviewer Comment: *The data do not suggest an increased risk of malignancy among those treated with lebrikizumab.*

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No COA analyses were conducted to inform safety/tolerability in the AD studies.

8.2.7. Safety Analyses by Demographic Subgroups

Age

In the placebo-controlled induction period, the frequency of adolescents reporting at least 1 TEAE (36.2%) in the lebrikizumab group was lower compared to placebo (55.8%), and similar in lebrikizumab-treated adults (51.9%) compared to placebo (53.2%).

The most common TEAEs in adults occurring more frequently in the lebrikizumab-treated adults compared to placebo were

- Conjunctivitis
- Nasopharyngitis
- Headache,
- Oral herpes, and
- Conjunctivitis allergic.

Adolescents

The most common TEAEs in adolescents (ages 12 to less than 18 years old) occurring more frequently in the lebrikizumab-treated adolescents compared to placebo were

- Conjunctivitis
- Nasopharyngitis
- dry eye, and
- rhinitis allergic

Although the sample size was small and frequencies were low, the reported numbers of the following PTs were numerically higher in the lebrikizumab-treated adolescent population compared to the lebrikizumab-treated adult population (at least 18 years of age):

- Dry eye (2.9% vs 1.3%)
- Pruritis (1.9% vs 1%),
- Nasopharyngitis (4.8% vs 4.3%), and
- Rhinitis allergic (1.9% vs 0.9%)

All other PTs were reported with similar or numerically higher frequency in the adult population.

Open-label adolescent Study KGAE included subjects aged 12 to 18 years old. This 52-week study evaluated subjects with a longer duration of exposure, so the frequencies are not directly comparable between Study KGAE and the analyses above. In Study KGAE, the most frequently reported TEAEs were

- AD (n = 27, 13.1%)
- Nasopharyngitis (n = 20, 9.7%)
- COVID-19 (n = 19, 9.2%)
- Upper respiratory tract infection (n = 13, 6.3%),
- Headache (n = 12, 5.8%)
- Oral herpes (n = 11, 5.3%),
- Conjunctivitis (n = 10, 4.9%), and
- Eosinophilia (n = 8, 3.9%).

Age Subgroups for Adults

The frequency of subjects with at least 1 TEAE in the adult population was similar across age subgroups (adolescent, adult, etc.), although the sample size for those older than 75 years of age was limited. Although numerical differences for individual PTs may show some variability across age groups, no treatment by age group interaction was identified.

Table 8285. Treatment-Emergent Adverse Events Occurring in at Least 1% of Subjects from the Placebo-Controlled Induction Period Stratified by Age Group

	PBO				LEB 250 mg Q2W			
	Adolescents (12<18) years (N=52)	Adults >=18 - < 65 years (N=331)	Adults >= 65 - < 75 years (N=28)	Adults >= 75 years (N=6)	Adolescents (12<18) years (N=105)	Adults >=18 - < 65 years (N=632)	Adults >= 65 - < 75 years (N=53)	Adults >= 75 years (N=15)
Number of Subjects with at least 1 TEAE	29 (55.8)	176 (53.2)	11 (39.3)	5 (83.3)	38 (36.2)	328 (51.9)	19 (35.8)	9 (60.0)
Preferred Terms								
Conjunctivitis	1 (1.9)	5 (1.5)	0	1 (16.7)	4 (3.8)	47 (7.4)	0	0
Dermatitis atopic	11 (21.2)	58 (17.5)	2 (7.1)	3 (50.0)	5 (4.8)	36 (5.7)	3 (5.7)	3 (20.0)
Headache	3 (5.8)	10 (3.0)	0	1 (16.7)	3 (2.9)	30 (4.7)	2 (3.8)	0
Nasopharyngitis	2 (3.8)	12 (3.6)	0	0	5 (4.8)	29 (4.6)	1 (1.9)	0
Oral herpes	1 (1.9)	6 (1.8)	1 (3.6)	1 (16.7)	1 (1.0)	14 (2.2)	0	0
Conjunctivitis allergic	1 (1.9)	2 (0.6)	0	0	2 (1.9)	12 (1.9)	0	0
COVID-19	1 (1.9)	4 (1.2)	0	0	0	8 (1.3)	1 (1.9)	0

Dry eye	0	4 (1.2)	0	0	3 (2.9)	8 (1.3)	0	0
Hypertension	0	3 (0.9)	1 (3.6)	0	0	7 (1.1)	2 (3.8)	0
Pruritus	2 (3.8)	5 (1.5)	0	0	2 (1.9)	6 (0.9)	1 (1.9)	0
Rhinitis allergic	0	1 (0.3)	0	0	2 (1.9)	6 (0.9)	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: ALLPCFL = 'Y', SAFFL = 'Y'.
Number of Subjects with at least 1 TEAE - Dataset: Adverse Events; Filter: ANL02FL = 'Y', TEMONDFL = 'Y'.
Preferred Terms - Dataset: Adverse Events; Filter: ANL02FL = 'Y', TEMONDFL = 'Y', AEDECOD = 'Conjunctivitis' or 'Dermatitis atopic' or 'Nasopharyngitis' or 'Headache' or 'Oral herpes' or 'Conjunctivitis allergic' or 'Dry eye' or 'Pruritus' or 'COVID-19' or 'Hypertension' or 'Rhinitis allergic'; Percent Threshold: >= 1%.

Sex

There were no clinically relevant imbalances in TEAEs between males and females during the placebo-controlled induction period.

Table 8386. Treatment-Emergent Adverse Events Occurring in at Least 1% of Subjects from the Placebo-Controlled Induction Period Stratified by Sex

	PBO		LEB 250 mg Q2W	
	Female (N=212)	**Male (N=205)**	**Female (N=412)**	**Male (N=393)**
Number of Subjects with at least 1 TEAE	111 (52.4)	110 (53.7)	202 (49.0)	192 (48.9)
Preferred Terms				
Conjunctivitis	2 (0.9)	5 (2.4)	22 (5.3)	29 (7.4)
Dermatitis atopic	34 (16.0)	40 (19.5)	23 (5.6)	24 (6.1)
Nasopharyngitis	7 (3.3)	7 (3.4)	15 (3.6)	20 (5.1)
Headache	10 (4.7)	4 (2.0)	18 (4.4)	17 (4.3)
Conjunctivitis allergic	2 (0.9)	1 (0.5)	5 (1.2)	9 (2.3)
Dry eye	2 (0.9)	2 (1.0)	3 (0.7)	8 (2.0)
Oral herpes	6 (2.8)	3 (1.5)	7 (1.7)	8 (2.0)
Hypertension	2 (0.9)	2 (1.0)	5 (1.2)	4 (1.0)
Rhinitis allergic	0	1 (0.5)	4 (1.0)	4 (1.0)
COVID-19	5 (2.4)	0	8 (1.9)	1 (0.3)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: ALLPCFL = 'Y', SAFFL = 'Y'.
Number of Subjects with at least 1 TEAE - Dataset: Adverse Events; Filter: ANL02FL = 'Y', TEMONDFL = 'Y'.
Preferred Terms - Dataset: Adverse Events; Filter: ANL02FL = 'Y', TEMONDFL = 'Y', AEDECOD = 'Conjunctivitis' or 'Dermatitis atopic' or 'Nasopharyngitis' or 'Headache' or 'Oral herpes' or 'Conjunctivitis allergic' or 'Dry eye' or 'COVID-19' or 'Hypertension' or 'Rhinitis allergic'.

Weight

There was no consistent pattern or trend for the types of TEAEs by BMI or weight groups during the placebo-controlled induction period.

Table 8487. Treatment-Emergent Adverse Events Occurring in at Least 1% of Subjects from the Placebo-Controlled Induction Period Stratified by Weight Category

	PBO			LEB 250 mg Q2W		
	<60 (N=90)	**>=60 to <100 (N=268)**	**>=100 (N=59)**	**<60 (N=176)**	**>=60 to <100 (N=527)**	**>=100 (N=102)**

Number of Subjects with at least 1 TEAE	49 (54.4)	143 (53.4)	29 (49.2)	85 (48.3)	255 (48.4)	54 (52.9)
Preferred Terms						
Conjunctivitis	1 (1.1)	6 (2.2)	0	15 (8.5)	30 (5.7)	6 (5.9)
Conjunctivitis allergic	1 (1.1)	2 (0.7)	0	2 (1.1)	11 (2.1)	1 (1.0)
COVID-19	2 (2.2)	2 (0.7)	1 (1.7)	1 (0.6)	8 (1.5)	0
Dermatitis atopic	20 (22.2)	47 (17.5)	7 (11.9)	11 (6.2)	33 (6.3)	3 (2.9)
Dry eye	0	4 (1.5)	0	3 (1.7)	4 (0.8)	4 (3.9)
Headache	3 (3.3)	10 (3.7)	1 (1.7)	3 (1.7)	26 (4.9)	6 (5.9)
Hypertension	0	3 (1.1)	1 (1.7)	1 (0.6)	5 (0.9)	3 (2.9)
Nasopharyngitis	4 (4.4)	6 (2.2)	4 (6.8)	8 (4.5)	18 (3.4)	9 (8.8)
Oral herpes	3 (3.3)	5 (1.9)	1 (1.7)	4 (2.3)	11 (2.1)	0
Rhinitis allergic	0	1 (0.4)	0	2 (1.1)	4 (0.8)	2 (2.0)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: ALLPCFL = 'Y', SAFFL = 'Y'.
Number of Subjects with at least 1 TEAE - Dataset: Adverse Events; Filter: ANL02FL = 'Y', TEMONDFL = 'Y'.
Preferred Terms - Dataset: Adverse Events; Filter: ANL02FL = 'Y', TEMONDFL = 'Y', AEDECOD = 'Conjunctivitis' or 'Dermatitis atopic' or 'Nasopharyngitis' or 'Headache' or 'Oral herpes' or 'Conjunctivitis allergic' or 'Dry eye' or 'COVID-19' or 'Hypertension' or 'Rhinitis allergic'.

Race

There were no consistent patterns of differences in the rates of TEAEs between whites and non-whites.

Reviewer Comment: *This reviewer agrees that, although there may have been small imbalances in TEAEs between subgroups of sex, weight, race, and ethnicity, there were too few events to draw any conclusions. The small numerical differences are unlikely to be clinically meaningful.*

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant is conducting Study KGAK (ADopt-VA), a phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the impact of lebrikizumab on vaccine responses in adult subjects with moderate-to-severe atopic dermatitis. The study was ongoing at the time of BLA submission and could not be incorporated into this review.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No clinical studies were completed specifically for human carcinogenicity or tumor development.

Human Reproduction and Pregnancy

As of June 6, 2022, there have been 27 pregnancies across all lebrikizumab indications. Of these, 10 pregnancies were reported in the AD clinical development program and 17 pregnancies occurred during the asthma interventional studies. A total of 21 women became pregnant during their lebrikizumab study participation, and 6 partners of male subjects became pregnant during the male subject's lebrikizumab study participation.

Within the 27 pregnancies, 21 cases reported pregnancy outcomes, and 6 cases were still in-utero or lost to follow-up. Eight (29.6%) cases reported neonate/fetal outcome. For the 8 pregnancies followed up to delivery across the lebrikizumab clinical development program, no congenital anomaly of the neonate has been reported. Perinatal complications (fetal growth restriction and neonatal jaundice) were reported in 2 neonates from the asthma development program. The neonate birth type and neonate/fetal outcome by indication across all lebrikizumab clinical trials are included in the tables below.

Table 85**88**. Neonate Birth Type in Lebrikizumab Clinical Trials by Indication

Neonate Birth Type	Asthma Clinical Trials	Atopic Dermatitis Clinical Trials	All Lebrikizumab Clinical Trials
Elective termination	2	4	6
Full-term	5	3	8
In-utero[a]	3	3	6
Spontaneous abortion	7	0	7
Total	**17**	**10**	**27**

[a] Some cases reported as in-utero have been lost to follow-up.
Note: Elective termination = a pregnancy that was electively terminated; Full-term = an infant born between 37 and 42 weeks of gestation; In-utero = in the uterus, unborn; Spontaneous abortion = failure of embryonic development and expulsion of all or any part of the product of conception before 20 weeks gestation or expulsion of a fetus weighing less than 500 grams.

Source: Regulatory Response Document dated August 11, 2023

Table 8689. Neonate/Fetal Outcome in Lebrikizumab Clinical Trials by Indication

Neonatal Fetal Outcome	Asthma Clinical Trials	Atopic Dermatitis Clinical Trials	All Lebrikizumab Clinical Trials
Normal	3	3	6

Perinatal complication	2	0	2
Total	**5**	**3**	**8**

Note: Perinatal complication = an infant adverse event within the first 28 days of life.

Source: Regulatory Response Document dated August 11, 2023

Trimester of exposure was reported for 20 (74.1%) pregnancies. In 18 of the 27 pregnancies, exposure occurred in the first trimester of gestation. The 2 cases who reported exposure during all trimesters had full-term delivery with normal neonate/fetal outcome.

For the 8 pregnancies followed up to delivery across the lebrikizumab clinical development program, no congenital anomaly of the neonate has been reported. Perinatal complications were reported in 2 neonates detailed in the table below.

Table 8790. Perinatal Complications Reported in Infants with In-utero Lebrikizumab Exposure

System Organ Class and Preferred Term	Total Number of Events
Pregnancy, puerperium and perinatal conditions	
Fetal growth restriction	1
Jaundice neonatal	1
Total	**2**

Source: Clinical Summary of Safety, Table 2.7.4.35

The table below summarizes the AEs reported by pregnant participants with lebrikizumab exposure. Event count is used in the table below as the same event could occur multiple times throughout a pregnancy.

Table 8891. Adverse Events Reported by Pregnant Participants with Lebrikizumab Exposure

System Organ Class and Preferred Term	Total Number of Events
Pregnancy, puerperium and perinatal conditions	
Cervical incompetence	1
Ectopic pregnancy	1
Imminent abortion	1
Gestational hypertension	1
Reproductive system and breast disorders	
Ovarian cyst	1
Pelvic pain	1
Gastrointestinal disorders	
Abdominal pain lower	1
Infections and infestations	
Staphylococcal skin infection	1
Injury, poisoning and procedural complications	
Procedural complication	1
Total	**9**

Source: Clinical Summary of Safety, Table 2.7.4.36

Because of the limited information regarding pregnancy impact, pregnancy registries will be recommended as postmarketing requirements, consistent with the Division of Pediatric and Maternal Health consultative review.

Lactation

There are no data on the presence of lebrikizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG4 is known to be excreted in breast milk. Therefore, lebrikizumab may be transmitted from the mother to the breastfed infant.

Cumulatively as of 06 June 2022, there has been no cases of exposure to lebrikizumab during lactation. The current data are too limited to draw conclusions about the effect of lebrikizumab exposure during lactation in humans. Label language will recommend administering lebrikizumab to nursing women only if the potential benefit to the mother justifies the potential risk to the infant.

Pediatrics and Assessment of Effects on Growth

Results suggest no meaningful differences in growth parameters of weight, height, and BMI between the adolescent placebo and LEB 250 mg Q2W treatment groups. Similar mean increases were observed from baseline to Week 16 for weight, height, and BMI between placebo and LEB 250 mg Q2W for the adolescent population.

Mean changes in the Any LEB group for Z-score were near zero (-0.1) for all growth parameters. Zero change in mean Z-score is interpreted as the group on average, maintained a growth velocity consistent with the average baseline growth velocity. The average growth percentile, compared to age and sex matched peers, is maintained from baseline to Week 52. Mean changes in all growth parameters percentiles show that until Week 52, percentiles were similar to baseline percentiles (±1.8 percentile change) across Any LEB group.

Due to the small sample size, the interpretation of the results after Week 52 is limited.

Treatment with lebrikizumab did not have a clinically meaningful impact on growth (weight,

height, and BMI) for the adolescent population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
Single intravenous doses up to 10 mg/kg and multiple subcutaneous doses up to 500 mg have been administered to humans in clinical trials without dose-limiting toxicity. There are no available data for doses higher than these and there is no known antidote for lebrikizumab overdose.

In the AD All LEB analysis set, 7 lebrikizumab-treated participants reported 8 AEs of overdose (PT). All events were mild or moderate in severity. The majority of events were due to unintentional dosing mistakes when sites continued to administer a loading dose of 500 mg beyond Week 2. All AE outcomes were considered recovered/resolved. There were no overdose-related clinical AEs reported at the time of the overdose event. No subjects discontinued due to overdose.

As each injection device only holds a single dose and additional injections would be required for a lebrikizumab overdose, the potential for an accidental overdose is not considered a significant risk. The potential for harm from an overdose of lebrikizumab is low based on the observed tolerability in clinical studies and the margin of safety data from preclinical studies.

Drug Abuse Potential
Lebrikizumab is not expected to cross the blood-brain barrier based on its molecular structure and no potential for misuse is anticipated based on its mode of action. Therefore, no drug-dependence study in animals or in drug-abused patients has been conducted. In clinical studies to date, there have been no findings indicating that lebrikizumab causes physical or mental dependency.

Withdrawal and Rebound
In the AD integrated analysis set, there were no AEs in the Drug abuse, dependence, and withdrawal SMQ that suggested withdrawal or rebound symptoms associated with lebrikizumab.

Studies KGAB (ADvocate 1) and KGAC (ADvocate 2) were 52-week studies that randomized lebrikizumab responders from the 16-week placebo-controlled induction period to receive lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, or placebo (LEB withdrawal). Subjects who were rerandomized to placebo (LEB withdrawal) during Weeks 16 to 52 did not report symptoms suggestive of withdrawal and/or rebound.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No postmarketing data exist for lebrikizumab, as it is not marketed in the United States or other countries.

Expectations on Safety in the Postmarket Setting

The review identified no apparent potentially important differences in how lebrikizumab was administered and used in the clinical trial versus its expected use in the postmarketing setting that could lead to increased risk.

8.2.11. Integrated Assessment of Safety

The safety profile of lebrikizumab was adequately characterized during the drug development program, whose safety database consisted of 1756 subjects exposed to lebrikizumab across 8 studies. This clinical review primarily focused on the data from the 3 pivotal phase 3 studies (ADvocate 1, ADvocate 2, and ADhere). The monotherapy trials (ADvocate 1 and 2) enrolled 1,222 subjects (805 in the lebrikizumab treatment group and 417 in the placebo group), and the concomitant TCS trial (ADhere) enrolled 228 subjects (153 in the lebrikizumab + TCS group and 75 in the placebo + TCS group). In all 3 trials, subjects underwent treatment for an initial 16-week induction period, and in studies ADvocate 1 and 2, they continued treatment for an additional 36-week maintenance period.

Additionally, the Applicant submitted supportive safety data from

- Study ADore (KGAE): a phase 3, open-label, single arm safety study in adolescents
- Study ADjoin (KGAA): a phase 3, long-term extension study for subjects who either met inclusion criteria or who completed a parent study (e.g., ADvocate 1 or 2, ADhere, or ADore) – still ongoing at the time of BLA submission
- 3 phase 2 studies in subjects with atopic dermatitis (studies KGAG, KGAH, and KGAF)

The safety profile of lebrikizumab was comparable when used with or without TCS, in adolescents or adults, and with a Q2W or Q4W treatment regimen. The most frequently reported adverse reactions in the pivotal trials were conjunctivitis, injection site reactions, and herpes zoster infections. Longer exposure to lebrikizumab did not result in an increased incidence rate for treatment-emergent adverse events, with the exception of COVID-19; this was likely due to trial conduct during the pandemic, the delta variant expansion, and the duration of the pandemic.

Five deaths were reported in the AD development program, 4 of which occurred in subjects treated with lebrikizumab. Of the 4 deaths reported among subjects receiving lebrikizumab, 1 occurred during the maintenance escape period, 2 occurred during the long-term extension study, and 1 occurred during the open-label adolescent study. None were likely related to the study drug.

The available data from the phase 3 trials demonstrated that lebrikizumab was safe in the treatment of subjects ≥12 years of age with moderate-to-severe atopic dermatitis.

Postmarketing risk management will include labeling and routine pharmacovigilance. Additionally, due to the limited information regarding pregnancy impacts, pregnancy registries will be recommended as postmarketing requirements.

120-Day Safety Update

Per 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a 120-Day Safety Update Report (SDN 6, dated January 12, 2023). The review team identified no new safety signals in the safety update report.

8.3. Statistical Issues

Study KGAD is considered to be a supportive study (b) (4)

During the analyses, the Applicant identified implausible homogeneity of efficacy results on one investigator in which all subjects at the site were IGA responders at Week 16 on both treatment groups. After auditing the site, the Applicant defined a modified intent to treat (mITT) analysis population that excluded 18 participants in Study KGAC and 17 participants in Study KGAD. Additional details can be found in the 8.1.2. Study Results - Compliance with Good Clinical Practices section and the Applicant's IR response. The site exclusion has very little impact on the Study KGAC because the proportion of the impacted data was small and the overall efficacy results in the mITT and ITT populations were consistent across primary and key secondary endpoints. However, in Study KGAD, because the site at issue had very high placebo response rates, the inclusion or exclusion of the site determines whether the study is statistically significant. In addition to that, there were 33 investigators in Study KGAD who participated in multiple studies. To minimize the impact of the common investigators as well as site exclusion, Study KGAD is considered to be a supportive study.

No other significant statistical issues were identified.

8.4. Conclusions and Recommendations

To establish the efficacy and safety of lebrikizumab, the Applicant submitted data from 2 adequate and well-controlled trials (Studies KGAB and KGAC) and 1 supportive trial (Study KGAD) that evaluated lebrikizumab for treatment of adult and adolescent subjects 12 years of age and older with moderate-to-severe atopic dermatitis whose disease was not adequately controlled with topical prescription therapies or when those therapies were not advisable. Studies KGAB and KGAC evaluated lebrikizumab as a monotherapy, and the supportive Study KGAD evaluated lebrikizumab with protocol-specified, concomitant use of topical corticosteroids (TCS).

Lebrikizumab was statistically superior to placebo in Studies KGAB and KGAC in the target AD population for the primary endpoint of IGA success (defined as scoring 0 or 1 with ≥2-point

reduction from Baseline) and EASI-75 (≥75% reduction from Baseline), which is one of the key secondary endpoints, at Week 16. The proportions of IGA responders in the 250 mg Q2W regimen recommended for approval were 43.1% and 33.2% in the monotherapy trials, compared with 12.7% and 10.8% in the respective placebo groups. The proportion of EASI-75 responders in the 250 mg Q2W regimen recommended for approval were 58.8% and 52.1% in the monotherapy trials, compared with 16.2% and 18.1% in the respective placebo groups. Lebrikizumab was also statistically superior to placebo for EASI-90 and pruritus NRS score (i.e., at least a 4-point reduction from Baseline in Worst Daily Pruritus NRS score), which are the key secondary endpoints, at Week 16 in the monotherapy trials.

The Applicant adequately characterized the safety profile of lebrikizumab through analyses of data from the safety database of 1756 subjects, including 382 adolescents, across 8 clinical studies. The size of the safety database and the safety evaluation were adequate to identify local and systemic treatment-emergent adverse reactions. The safety profiles were similar whether lebrikizumab was administered as monotherapy or whether with concomitant topical corticosteroids. The most frequently reported adverse reactions conjunctivitis, injection site reactions, and herpes zoster infections.

In the opinion of the reviewer, the Applicant has provided adequate evidence of safety and efficacy for the use of lebrikizumab in adults and adolescents at least 12 years of age with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Pending resolution of the CMC manufacturing site inspection issues, this reviewer recommends approval for the proposed dosing regimen of 500 mg initially, followed by 250 mg Q2W, in adults and adolescents with moderate-to-severe atopic dermatitis, with a maintenance dose of 250 mg Q4W once adequate clinical response is achieved.

9 Advisory Committee Meeting and Other External Consultations

The Agency did not hold an Advisory Committee Meeting for this application, because there were no efficacy, safety, or novel/complex regulatory issues that required input from an Advisory Committee.

10 Pediatrics

The Applicant submitted an initial pediatric study plan (iPSP) on November 7, 2016, requesting a partial waiver for lebrikizumab for the treatment of AD in children younger than (b) (4) of age based on the rationale that (b) (4) ". The Applicant also requested a deferral of pediatric studies in patients aged (b) (4).

On January 11, 2017, the Division presented the initial Pediatric Study Plan (iPSP) to the Pediatric Review Committee (PeRC). At the time of the iPSP submission, the Division did not agree with (b) (4) the Division advised the Applicant to study subjects down to 6 months of age. The Division agreed to a deferral of all pediatric AD studies, pending the availability of safety and efficacy data from adults that would sufficiently support the initiation of pediatric studies.

The PeRC agreed with the Division's recommendation to plan for a partial waiver down to 6 months and deferral in 6 months to <17 years of age. Additionally, the PeRC recommended that the Applicant conduct a PK, efficacy and safety study (b) (4). The PeRC and the Division agreed that the Applicant should obtain long-term safety data for all pediatric age groups studied. The Division conveyed these recommendations to the Applicant on January 25, 2017, and on April 6, 2017, the Applicant withdrew the iPSP without prejudice for a future PSP submission.

On April 30, 2019, the Applicant submitted a new iPSP, requesting a partial waiver for studies in infants from 0 to 6 months of age, based on the rationale that " (b) (4)

[redacted]" The Applicant also requested a deferral of pediatric studies in patients 6 months to < 12 years of age. The Applicant planned to include pediatric patients 12 to less than 18 years of age weighing greater than 40kg in the adult studies.

On July 24, 2019, the Division presented the iPSP to the PeRC. The Division and the PeRC agreed with the Applicant's plan to request a partial waiver for evaluation of subjects from 0 to 6 months of age, although the Division clarified that the rationale should be because studies in this age group would be impossible or highly impractical. The Division and the PeRC agreed with the Applicant's proposal to request a deferral of studies in pediatric patients 6 months to less than 12 years of age, as well as with the plan to include pediatric patients 12 to 18 years of age weighing more than 40 kg in the adult phase 3 trials. The Division conveyed these responses to the iPSP on August 13, 2019 The Applicant submitted an Agreed iPSP on November 11, 2019; however, the revised iPSP did not reflect the appropriate rationale for the waiver in pediatric subjects less than 6 months of age. The Division agreed with the Agreed iPSP on December 3, 2019.

On March 24, 2021, the Applicant submitted an amendment to the Agreed iPSP, [redacted] the trial in 6 months to 6 years with [redacted] in 6-12 year olds. The Division presented the amendment to the Agreed iPSP to the PeRC on May 25, 2021, and the PeRC agreed with the Applicant's proposal, provided that [redacted] On November 10, 2021, the Division agreed with the Amended Agreed iPSP.

The Division presented the Application to the PeRC on August 15, 2023. The PeRC agreed with the Division to grant a partial waiver because studies would be impossible or highly impracticable. The PeRC also agreed with the Division to grant a deferral in patients 6 months to 11 years of age. The PeRC agreed with the plan for assessment and labeling of the product in patients 12 to less than 18 years of age.

The following Pediatric Research Equity Act (PREA) PMR studies will be recommended once the Applicant is able to address the deficiencies identified by the OQ review team:

- [redacted]:
  Randomized, double-blind, placebo-controlled, [redacted] and safety study in pediatric patients 6 months to <6 years, 6 years to < 12 years and ≥12 years to <18 years weighing <40 kg:
  - Estimated protocol submission date: completed (protocol submitted to IND119866 on April 13, 2022; SN0199)
  - [redacted]
- [redacted]:

Open-label, long-term safety study in pediatric patients 6 months to < 12 years and ≥12 years to <18 years weighing <40 kg:

- Estimated protocol submission date: completed (protocol submitted to IND 119866 on January 27, 2023; SN0227)
- (b) (4)
-
-

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
The Applicant submitted proposed Patient Package Insert (PPI), Prescribing Information (PI) and carton/container labels for Ebglyss. The review team provided recommendations regarding the PI, and these comments are reflected in the labeling received in response by the Applicant.

Corwin D. Howard, PharmD, RPh, from the Division of Medication Error Prevention and Analysis reviewed the proposed container label, carton labeling, PPI, and PI and provided comments. Dr. Howard identified several medication error issues and proposed recommendations to minimize the risk for medication errors (see review dated April 28, 2023).

David Foss, PharmD, MPH, BCPS, RAC, from the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PI, PPI/Instructions for Use (IFU), and carton and container labeling. OPDP had no comments regarding the carton/container labeling (see review dated April 27, 2023).

Other Prescription Drug Labeling
The Applicant submitted a proposed PPI for Ebglyss. Ruth Mayrosh, PharmD, from the Division of Medical Policy Programs and David Foss, PharmD, MPH, BCPS, RAC, from OPDP reviewed and provided comments regarding the PPI and IFU (see review dated May 1, 2023). The final labeling will reflect their recommendations.

12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond labeling and standard postmarketing surveillance are not warranted at this time.

13 Postmarketing Requirements and Commitment

Should the Applicant adequately address the deficiencies identified by the OPQ review team, the team recommends the following are post-marketing requirements, based on the currently available data:

PMR1:
Conduct or participate in a relevant Pregnancy Exposure Registry, a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to lebrikizumab during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, neonatal deaths, and infections, will be assessed through at least the first year of life.

PMR2:
Conduct an additional pregnancy study that uses a different design from the Pregnancy Exposure Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to lebrikizumab during pregnancy compared to an unexposed control population.

PREA Requirements
Lebrikizumab triggers the Pediatric Research Equity Act (PREA) as a new active ingredient.
The following studies in the pediatric population age 6 months to less than 12 years of age were Included in the Agreed iPSP and will be deferred:

(b) (4):

- Randomized, double-blind, placebo-controlled, (b) (4) and safety study in pediatric patients 6 months to <6 years, 6 years to < 12 years and ≥ 12 years to <18 years weighing <40 kg:
    - Estimated protocol submission date: completed (protocol submitted to

IND119866 on April 13, 2022; SN0199)

- (b) (4)

(b) (4):

- Open-label, long-term safety study in pediatric patients 6 months to < 12 years and ≥ 12 years to <18 years weighing <40 kg:
  - Estimated protocol submission date: completed (protocol submitted to IND 119866 on January 27, 2023; SN0227)
  - (b) (4)

REQUIRED PEDIATRIC ASSESSMENTS: Pediatric Research Equity Act (PREA) (21 U.S.C. 355c)

Should the Applicant adequately address the deficiencies identified by the OPQ review team, we will be waiving the pediatric study requirement for ages 0 to less than 6 months because necessary studies are impossible or highly impracticable.

14 **Division Director (DHOT) Comments**

APPEARS THIS WAY ON ORIGINAL

15 Division Director (OCP) Comments

APPEARS THIS WAY ON ORIGINAL

16 Division Director (OB) Comments

APPEARS THIS WAY ON ORIGINAL

17 Division Director (Clinical) Comments

I concur with the review team's recommendation for complete response of BLA 761306, because of unresolved facility inspection deficiencies.

Lebrikizumab injection, a new molecular entity, is an interleukin-13 antagonist, proposed for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Lebrikizumab is an IgG monoclonal antibody that binds to IL-13 and selectively inhibits IL-13 signaling, blocking the downstream effects of IL-13. The proposed administration is by subcutaneous (SC) injection, with or without topical corticosteroids (TCS), at the recommended initial dose of 500 mg (two 250 mg injections) at Weeks 0 and 2, followed by 250 mg given every other week (Q2W) beginning at Week 4 and every four weeks [Q4W] for patients who achieve clear or almost clear skin after 16 weeks of treatment. Lebrikizumab will be presented as a prefilled pen or prefilled syringe with needle shield.

Substantial evidence of effectiveness was adequately demonstrated via two monotherapy clinical trials KGAB and KGAC and one supportive trial (KGAD, protocol-specified background topical corticosteroids). KGAB and KGAC met their primary endpoint of IGA success (scoring 0 or 1 with at least 2-point reduction from baseline) and key secondary endpoint of EASI-75 (at least 75% reduction from baseline in EASI score) at Week 16. The review team considered KGAD to be supportive, as this trial did not meet the IGA success primary endpoint; when the applicant excluded one site with unusual results (e.g., high placebo success rate), post-hoc analysis on the modified study population led to nominal statistical significance.

The safety database was adequate to assess risks and outcomes. Across the AD development program, 1756 subjects were treated with subcutaneous injections of

lebrikizumab with or without concomitant TCS and a total of 903 subjects was treated with lebrikizumab for ≥1 year. The most frequently reported adverse reactions in the lebrikizumab 250 mg Q2W treatment groups compared to placebo were conjunctivitis, injection site reactions and herpes zoster infections. These risks can be appropriately communicated in labeling. If approved, post-marketing requirements include additional pediatric assessments and evaluation of exposures during pregnancy.

18 Office Director (or designated signatory authority) Comments

Eli Lilly and Company (Applicant) submitted a biologics licensing application (BLA) for lebrikizumab (tradename Ebglyss), seeking approval of this interleukin-13 (IL-13) antagonist for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Atopic dermatitis is one of the most common dermatologic diseases, characterized by lichenified plaques and intense pruritis that can disrupt sleep, psychosocial function, and health-related quality of life. The pathophysiology of atopic dermatitis is marked by the complex interplay of genetic polymorphisms, environmental exposures, IgE sensitization, epidermal barrier dysfunction, and immune dysregulation. Multiple lines of evidence suggest that IL-13 plays a central role in the pathogenesis of atopic dermatitis: certain IL-13 polymorphisms are associated with an increased risk of developing atopic dermatitis, IL-13 is overexpressed in lesional skin biopsies from patients with atopic dermatitis, and IL-13 down-regulates production of key skin barrier components such as filaggrin, loricrin, and involucrin. Lebrikizumab is an IgG4 monoclonal antibody that binds with high affinity to IL-13 and inhibits signaling through the IL-4Rα/IL-13Rα1 receptor complex, thus reducing production of Type 2 pro-inflammatory cytokines, chemokines, and IgE that are canonical mediators in the pathophysiology of atopic dermatitis.

Substantial evidence of effectiveness for lebrikizumab was established based on data from two adequate and well-controlled trials that demonstrated statistically significant and clinically meaningful improvements in the severity and extent of skin lesions and a corresponding reduction in pruritis. A higher proportion of participants randomized to lebrikizumab achieved at least a two point improvement on a five point scale for investigator global assessment of disease severity (43% and 33% in the lebrikizumab arms, compared with 13% and 11% in the respective placebo groups). Similar magnitudes of effect were observed on key secondary endpoints that included both clinician and patient reported outcome measures.

The available safety data show that lebrikizumab is safe for its intended use, and that the identified safety risks can be adequately mitigated through labeling and routine pharmacovigilance. Common adverse reactions included conjunctivitis, injection site reactions, and herpes zoster infections. Hypersensitivity reactions, including angioedema and urticaria, were reported with use of lebrikizumab. Conjunctivitis and keratitis were observed more frequently in subjects who received lebrikizumab. These can be addressed in product labeling with Warnings and Precautions, along with class warnings for parasitic infections and risk of infection with live vaccines.

The BLA was reviewed by a multidisciplinary review team. The toxicology, pharmacology, statistical, and clinical reviewers advised that the application is approvable from each of their discipline's perspectives. The OPQ team recommended a complete response action due to unresolved facility deficiencies that raise concerns about comparability between the material used in the clinical studies and commercial material. The signatory authority for this application concurs with the recommendation from the OPQ team for a complete response action.

If the quality issues are satisfactorily addressed upon resubmission, we conclude that the improvements in the severity and extent of skin lesions along with a reduction in pruritis outweigh the risks when lebrikizumab is used according to the recommendations in the agreed labeling. Based on the data available in this submission, and pending review of an updated safety database upon resubmission, postmarketing studies are recommended to evaluate the effects of lebrikizumab during pregnancy and in pediatric patients ages 6 months to < 12 years.

19 Appendices

19.1. References

The majority of the references are included in the footnotes.

19.2. Financial Disclosure

[Insert text here]

Covered Clinical Study (KGAB, KGAC, KGAD): Three (3) Covered Clinical Studies

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 718		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 24		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 24 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

Labeling

Multiple of Human Exposure Calculations

The multiples of human exposure values contained in the proposed label provided by the applicant are based on $C_{avg,ss}$ comparisons.

The multiples of human exposure based on $C_{avg,ss}$ comparisons between the NOAELs identified in pivotal toxicology studies and the maximum recommended human dose (MRHD) are provided in the following table. One set of human exposure multiples, i.e., exposure multiples for adolescents, will be used in the label because the data are fairly indistinguishable in both adolescent and adult populations.

Table 89**92**. Multiples of Human Exposure for NOAELs Identified in Pivotal Toxicology Studies Contained in Labeling

Study	Route	NOAEL (mg/kg)	$C_{avg,ss}$ (µg/mL)	Exposure multiples for adolescents[a]	Exposure multiples for adults[b]
Embryofetal development study	SC	150/50	2041	18	22
Prenatal and postnatal development study	SC	150/50	2041[c]	18	22
13-week male fertility study	SC	25	1230	11	13
9-month female fertility study	IV	25	1640	15	18

[a] Compared with a $C_{avg,ss}$ of 111 µg/mL for human adolescents at the MRHD.
[b] Compared with $C_{avg,ss}$ of 92 µg/mL for human adults at MRHD.
[c] A C_{avg} of 2041 µg/mL from the EFD study was used as a surrogate for the PPND study.

A $C_{avg,ss}$ of 111 (63.9 – 183) µg/mL for human adolescents and 92.0 (52.6 – 164) µg/mL for human adults at the maximum recommended human dose (MRHD, a loading dose of 500 mg SC W0 and W2, then a maintenence dose of 250 mg SC Q2W), expressed as median (5th, 95th confidence intervals), were obtained from simulations of 500 virtual participants in each maintenance period regimen/population based on body weight distributions of phase 3 adolescent and adult participants.

A $C_{avg,ss}$ of 1640 µg/mL was calculated using the Day 57 through Day 267 concentration values at steady-state in a 9-month female intravenous fertility study. A $C_{avg,ss}$ of 1230 µg/mL is calculated using the Day 57 through Day 87 concentration values at steady-state in a 13-week

male subcutanoues fertility study. This value is similar to $C_{avg,ss}$ values calculable from the reported AUC_{tau} values: 1269 µg/mL (8880 µg•day/mL /7 days) for the dosing interval Days 78-85 and 1383 µg/mL (9680 µg•day/mL /7 days) for the dosing interval Days 85-92. These values are between 77% and 84% of the $C_{avg,ss}$ of 1640 µg/mL from the female fertility study and likely reflect SC bioavailability.

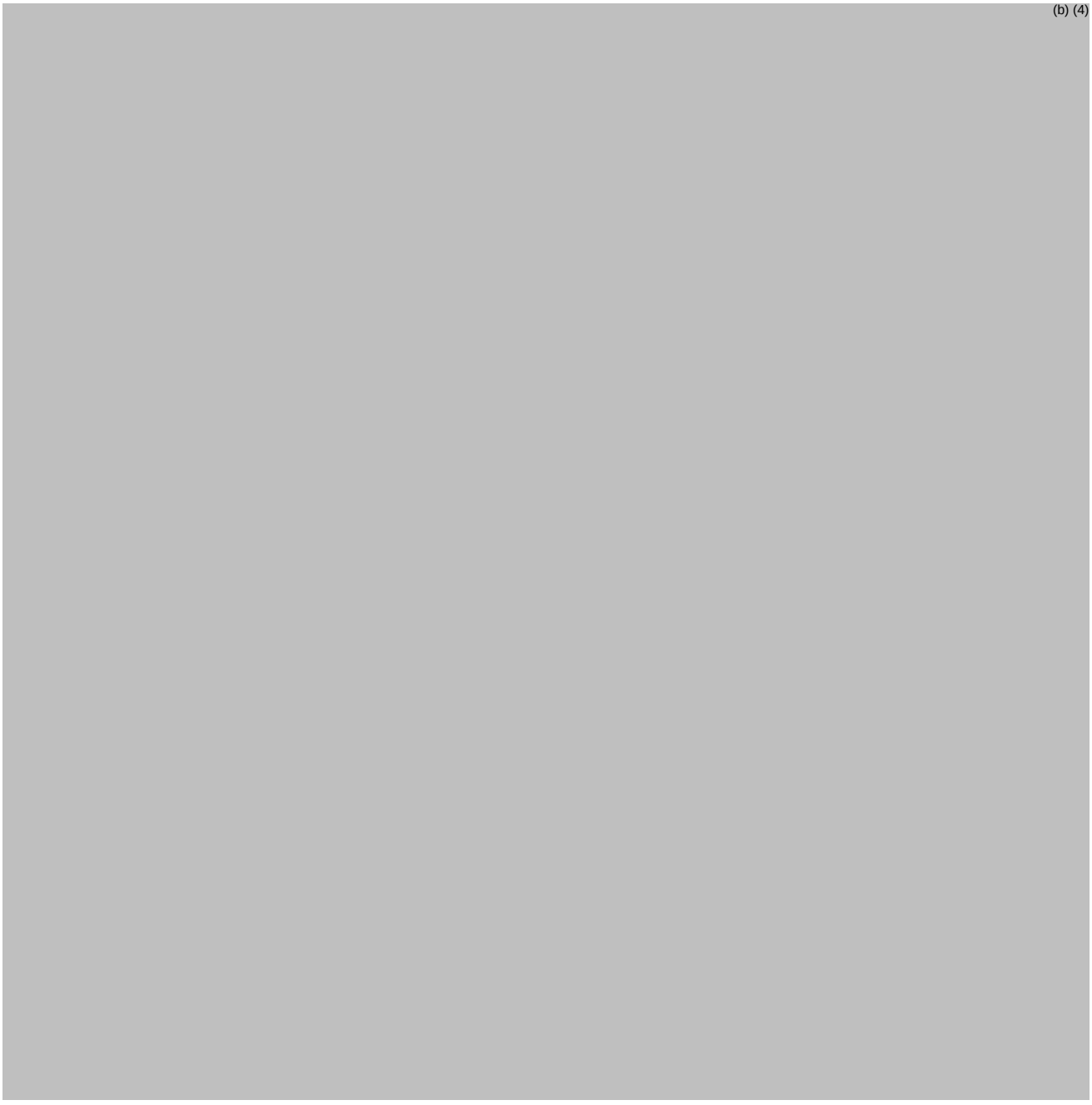
Exposure multiples for both the EFD (Study 07-1269) and PPND (Study 12-3365) studies are based on exposure data from the EFD study (Study 07-1269) compared to human population PK data. In both studies, the NOAEL was the highest dose regimen, 150 mg/kg followed by 50 mg/kg/week. A mean (C_{avg}) of 2041 µg/mL was calculated using all concentration values in the EFD study since there was no discernable change in the peak concentrations over time during the dosing period in the study. Given the concentration data in the PPND study are limited to trough data, the EFD C_{avg} concentration value of 2041 µg/mL was used to calculate exposure multiples for the PPND study. Trough concentrations were generally similar in the EFD and PPND studies and increased only slightly over time during the dosing periods; trough concentrations in the latter part of the PPND study (GD 133 and 168) were highly comparable to trough concentrations in the EFD study. These trough concentration data indicated it was reasonable to use the more comprehensive exposure assessment in the EFD study as a surrogate for the PPND study.

Recommended Revision to the Nonclinical Portions of Labeling

Revisions to the applicant's proposed wording for the nonclinical and related sections of the label are provided below. It is recommended that the underlined wording be inserted into and the strikethrough wording be deleted from the EBGLYSS™ label text.

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Bioanalytical Method Validation

Serum samples in clinical studies were analyzed for lebrikizumab using validated ELISAs. The Tanox ELISA method was designed to detect and quantify lebrikizumab in human serum. In this assay, standards, controls, and test (serum) samples were incubated with saturating IL-13 on a microtiter plate. After incubation, standards, controls, and samples were transferred to a

microtiter plate coated with a mouse monoclonal anti-IL-13 antibody. Following incubation, unbound material was washed away and lebrikizumab was detected using mouse anti-human IgG4 conjugated to HRP and visualized using TMB peroxidase substrate solution. The color development was stopped by adding 0.2 N sulfuric acid and the intensity of the color was measured at 450 nm with a wavelength correction set to 590 nm. The concentration of the samples was proportional to the optical density and obtained from a cubic polynomial curve fit of the standard curve. The validated LLOQ was 20 ng/mL and ULOQ was 1000 ng/mL.

The Genentech ELISA method (4.AIL13.4.AVR_0) was also designed to detect and quantify lebrikizumab in human serum. In this assay, streptavidin-coated microtiter plates were incubated with IL-13 conjugated to biotin to capture lebrikizumab. After washing, diluted standards, controls, and test (serum) samples were added to the plate and incubated. After incubation, unbound material was washed away and lebrikizumab was detected using mouse anti-human IgG4 conjugated to HRP and visualized using TMB peroxidase substrate solution. The color development was stopped by adding 1 M phosphoric acid and the intensity of the color was measured at 450 nm with a wavelength correction set to 620 or 630 nm. The concentration of the samples was obtained from a 4-parameter logistic curve fit of the standard curve, using a weighting factor of $1/F^2$. The validated LLOQ and ULOQ were 90 ng/mL and 3000 ng/mL, respectively, after correction for the 1:100 MRD. Dilutional linearity was demonstrated through up to 1:400000-fold final dilution (after correction for the 1:100 MRD). Intra-assay precision (expressed as % CV) ranged from 1% CV to 5% CV. Accuracy (expressed as % bias) was -9% at the LLOQ and ranged from -8% to -12% at other concentrations. The inter-assay precision during validation ranged from 9% CV to 13% CV (**Table 91)**.

Table 9093. Clinical Studies with PK Evaluating SC lebrikizumab

Study	Phase	Abbreviated Study Description	Dosing Regimen	Study Population/ PK Population
J2T-DMKGBA (ILR4456g)	1	Single dose, safety, tolerability, PK	Group 1: Lebrikizumab 1 mg/kg administered IV bolus infusion over ~15 min[a] Group 2: Lebrikizumab 1 mg/kg administered SC by syringe[b]	Healthy participants (N=22)
J2T-DMKGAZ (GB25741)	1	Single dose, safety, tolerability, PK	Group 1: 125 mg (1 SC injection of 125 mg lebrikizumab) or placebo Group 2: 250 mg (2 SC injections of 125 mg lebrikizumab) or placebo Group 3: 375 mg (3 SC injections of 125 mg lebrikizumab) or placebo	Healthy Japanese and Caucasian participants (N=60)
J2T-DMKGAY (GP29651)	1	Single dose, safety, tolerability, PK	Group 1: 37.5 mg (0.3 mL of 125 mg/mL) administered SC by a needle and syringe Group 2: 37.5 mg (1 mL of 37.5 mg/mL) administered SC by PFS-NSD	Healthy participants (N=176)
J2T-DMKGAM (DRM06-	1	Single dose safety, tolerability, PK	Group 1: Lebrikizumab 250 mg administered SC by two 1-mL	Healthy participants

AD03)			(125 mg) syringes Group 2: Lebrikizumab 250 mg administered SC by one 2-mL (250 mg) syringe	(N=41)
J2T-DMKGAG (GS29250, TREBLE)	2	Efficacy when used as adjunctive therapy with TCS compared with TCS, safety, PK, biomarkers	Weeks 0–12 Dosing Group 1: Lebrikizumab 250 mg single-dose SC injection + TCS Group 2: Lebrikizumab 125 mg single-dose SC injection + TCS Group 3: Lebrikizumab 125 mg Q4W × 3 SC injection + TCS Group 4: Placebo Q4W SC injection + TCS	Adult patients with moderate-to-severe AD (N=212)
J2T-DMKGAH (GS29735, ARBAN)	2	Safety when used as monotherapy compared with TCS, PK	Weeks 0–12 Dosing Group 1: Lebrikizumab 125 mg SC injection Q4W × 3 (monotherapy) Group 2: TCS cream (triamcinolone acetonide 0.1% cream, hydrocortisone 2.5% cream, or both) twice daily	Adult patients with moderate-to-severe AD (N=55)
J2T-DMKGAF (DRM06-AD01)	2	Safety and efficacy compared with placebo, PK	Weeks 0–16 Dosing Group 1: Lebrikizumab 250 mg SC at baseline, followed by 125 mg SC injection Q4W × 3 Group 2: Lebrikizumab 500 mg SC at baseline, followed by 250 mg SC injection Q4W × 3 Group 3: Lebrikizumab 500 mg SC at baseline and Week 2, followed by 250 mg SC injection Q2W × 6 Group 4: Placebo Q2W	Adult patients with moderate-to-severe AD (N=280)
J2T-DMKGAB - Advocate 1 (DRM06- AD04)	3	Efficacy, safety compared with placebo, PK	Weeks 0–16 Dosing Lebrikizumab 250 mg SC with a loading dose of 500 mg at Week 0 and Week 2 followed by 250 mg Q2W × 6, or placebo Q2W Weeks 16-52 Dosing (maintenance period) Maintenance blinded period: responders were reassigned in 2:2:1 ratio to lebrikizumab Q2W, lebrikizumab Q4W, and placebo Q2W. Maintenance escape period: non-responders received openlabel lebrikizumab 250 mg Q2W through Week 52, maintenance period data not included in PopPK or E-R analyses	Adolescent patients (≥12 to <18 years, weighing ≥40 kg) and adult patients with moderate-to-severe AD (N=424)
J2T-DMKGAC - Advocate 2 (DRM06- AD05)	3	Efficacy, safety compared with placebo, PK	Weeks 0–16 Dosing Lebrikizumab 250 mg SC with a loading dose of 500 mg at Week 0 and Week 2 followed by 250 mg Q2W × 6, or placebo Q2W Weeks 16-52 Dosing (maintenance period) Maintenance blinded period: responders were reassigned in 2:2:1 ratio to lebrikizumab Q2W, lebrikizumab Q4W, and	Adolescent patients (≥12 to <18 years, weighing ≥40 kg) and adult patients with moderate-to-severe AD (N=445)

			placebo Q2W. Maintenance escape period: non-responders received openlabel lebrikizumab 250 mg Q2W through Week 52, maintenance period data not included in PopPK or E-R analyses.	
J2T-DMKGAD Adhere (DRM06- AD06)	3	Efficacy, safety when used in combination with TCS compared with placebo, PK	Weeks 0–16 Dosing Lebrikizumab 500 mg SC at baseline and Week 2, followed by 250 mg Q2W × 6, or placebo Q2W TCS initiated at baseline; could be tapered or stopped as warranted	Adolescent patients (≥12 to <18 years, weighing ≥40 kg) and adult patients with moderate-to-severe AD (N=228)
J2T-DMKGAE (DRM06- AD17)	3	Safety, efficacy, PK	Weeks 0–52 Dosing Lebrikizumab 500 mg SC at baseline and Week 2, then 250 mg SC (2 mL injection of 125 mg/mL) Q2W through Week 52	Adolescent patients (≥12 to <18 years, weighing ≥40 kg) with moderate-to-severe AD (N=206[c])

Abbreviations: AD = atopic dermatitis; E-R = exposure-response; IV = intravenous; PFS-NSD = prefilled syringe with needle safety device; PK = pharmacokinetic(s); PopPK = population pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; TCS = topical corticosteroid.
a Each vial of IV formulation contained 2 mL of lebrikizumab at 25.0 ± (b) (4), for a total of 50.0 ± (b) (4) of lebrikizumab per vial.
b Each vial of SC formulation contained 1 mL of lebrikizumab at 125.0 ± (b) (4), for a total of 125.0 ± (b) (4) lebrikizumab per vial.
c Since J2T-DM-KGAE was not a randomized study, the number of participants who received study treatment is shown.

(Source: Summary of clinical pharmacology, Table 2.7.2.1, pages 15-18.)

The ELISA method 4.AIL13.4.AVR_0 developed by Genentech was transferred to and validated by (b) (4). The assay format did not change and is the same as described for Genentech 4.AIL13.4.AVR_0.

The validated LLOQ and ULOQ were 90 ng/mL and 3000 ng/mL, respectively, after correction for the 1:100 MRD. Dilutional linearity was demonstrated through up to 1:800000-fold dilution after correction for the 1:100 MRD. Intra-assay precision (expressed as % CV) was less than or equal to 11.5%. Intra-assay accuracy (expressed as % RE) was greater than or equal to 14.1% at the LLOQ, and greater than or equal to -24.4% at other concentrations. The inter-assay accuracy during validation ranged from -4.7% RE to -1.3% RE. The inter-assay precision during validation ranged from 6.3% CV to 18.3% CV (**Table 91)**

Reviewer's Comments:

(b) (4) *Validation Report 8257531 did not meet FDA current guidelines for testing of accuracy, precision, selectivity, bench top stability at ambient room temperature, and freeze/thaw stability. To bring the validation data package for this method to current guidance expectations, a partial validation was performed (* (b) (4) *Report 8399391). The assay format did not change and is the same as described for* (b) (4) *Method 8257531. The validated LLOQ and ULOQ were 90 ng/mL and 3000 ng/mL, respectively, after correction for the 1:100 MRD. System suitability (calibration curve performance) met the requirements stated in the validation protocol. The targeted acceptance criteria for precision and accuracy as stated in the protocol (%Bias: ±20 [±25*

at LLOQ and ULOQ]; and %CV: less than or equal to 20 [less than or equal to 25 at LLOQ and ULOQ]) were met for all 5 control levels. The inter-assay precision during validation ranged from 5.1% CV to 5.4% CV. Inter-assay accuracy ranged from -8.7% bias to 5.1% bias.
Additional parameters evaluated in the partial validation were selectivity, bench top stability at ambient room temperature, and freeze/thaw stability. Performance of the additional parameters demonstrated that human serum samples met target specifications for selectivity in normal, diseased (atopic dermatitis), lipemic, and hemolyzed matrix at LLOQ (90.0 ng/mL) and high quality control (2200 ng/mL). Stability samples at the low quality control (150 ng/mL) and high quality control concentrations were assessed. Room temperature stability was acceptable for at least 85 hours and 39 minutes and freeze/thaw stability was acceptable for up to 8 freeze/thaw cycles at -60°C to -80°C. Given that the additional validation parameters demonstrated acceptable performance, there was no negative impact on the ability to use the bioanalytical dataset.

The summary from validation reports of the analytical methods used in the clinical pharmacokinetic studies for the determination of lebrikizumab in human serum is described in following Table 91.

Table 9194. Summary of Bioanalytical Assay Validation for Lebrikizumab in Clinical Pharmacology Studies

CRO/Assay	**4AIL13.4.AVR_0 – Genentech 2012**		**8257531-** (b) (4) **2012**		**8399391 –** (b) (4) **2019**	
Method description	Lebrikizumab Lot LNT1111-105		Lebrikizumab Lot: 74872-3		Lebrikizumab Lot: 627463	
Materials used for standard calibration curve and concentration	4.AIL13.4 Anti-IL13 (MILR1444A) Human Antigen ELISA		Validation of an ELISA Method for the Quantification of Lebrikizumab in Human Serum		Method Validation of Lebrikizumab in Human Serum using ELISA	
Lower limit of quantification	0.9 ng/mL		0.9 ng/mL		0.9 ng/mL	
Upper limit of quantification	30 ng/mL		30 ng/mL		30 ng/mL	
Minimum required dilutions (MRDs)	1:100		1:100		1:100	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7	Number of standard calibrators from LLOQ to ULOQ	5	Number of standard calibrators from LLOQ to ULOQ	8
	Cumulative accuracy (%bias) from LLOQ to ULOQ	Not determined	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.0% to 2.6%	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.4% to 6.5%
	Cumulative precision (%CV) from LLOQ to ULOQ	Not determined	Cumulative precision (%CV) from LLOQ to ULOQ	≤2.9% CV	Cumulative precision (%CV) from LLOQ to ULOQ	≤2.9% CV

Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 3 QCs	-12% to -8%	Cumulative accuracy (%bias) in 3 QCs	-4.7% to -1.3%	Cumulative accuracy (%bias) in 3 QCs	-9.5% to -4.2%
	Inter-batch %CV	≤ 12% CV	Inter-batch %CV	≤12.5% CV	Inter-batch %CV	≤5.5% CV
	Total Error (TE)	≤ 23%	Total Error (TE)	NA	Total Error (TE)	NA
Dilution linearity & hook Effect	Dilution linearity determined up to 400000-fold. No hook effect observed.		Dilution linearity determined up to 800000-fold (after MRD correction)		Dilution linearity up to 800000-fold (after MRD correction)[a]	
Short Term Stability: Benchtop stability at Room temperature	7 h		22 h		85.65 h	
Short Term Stability: Freeze -thaw cycles	6 freeze–thaw cycles at -60°C		6 freeze–thaw cycles at -70°C		8 freeze–thaw cycles -60 °C to -80°C	
Long Term Stability	Not determined		4.75 years at -70°C and 36 months at -20°C		4.75 years at -70°C[a]	
Study sample analysis/ Stability	Samples were stored for up to 377 days at -60°C		Samples were kept at -70°C for up to 170 days. Stability was established for 4.75 years at -70°C		Samples were kept at -70°C for up to 1095 days. Stability was established for 4.75 years at -70°C	

Abbreviations: CV = coefficient of variation; ELISA = enzyme-linked immunosorbent assay; IL = interleukin; LLOQ = lower limit of quantitation; NA = not applicable; ULOQ = upper limit of quantitation
a Determined as part of Validation 8257531.
b These studies also used the full Validation 8257531 in the analysis of the samples.
(Source: Appendix to the Summary of Biopharmaceutic Studies and Associated Analytical Methods (section 2.7.1.4) Table APP.2.7.1.2., pages 8 to 16)

19.4.2. Population PK and PK-PD Analysis

The Applicant conducted a population pharmacokinetic (PopPK) and subsequently pharmacokinetic-pharmacodynamic (PK-PD) analysis to support the proposed dosing regimens of lebrikizumab for the treatment of adolescent and adult patients with moderate-to-severe atopic dermatitis (AD). Initially, a popPK model was developed to characterize the pharmacokinetics of lebrikizumab in patients and healthy and identify patient and laboratory factors significantly affecting its PK. PopPK analysis included data from 11 clinical studies that evaluated a dose range of 37.5 to 500 mg and involved 1607 subjects (healthy and patients) with a total of 6860 measurable concentrations. Both adult and adolescent patients were included with a body weight range of 40 to 192 kg.

The final PopPK model was a 2-compartment model with first-order absorption and linear elimination that adequately described concentration-time profiles of lebrikizumab. The steady state exposures (median Cmax, Ctrough, Cavg) were 2-fold higher following 250 mg Q2W regimen than those of Q4W, implying the linear PK characteristics of lebrikizumab. The steady state was attained after dose at Week 4. No covariates other than body weight (BW) were found to have significant impact on the lebrikizumab PK. The median Cavg,ss following 250 mg

Q2W dosing was 24% lower for the highest BW quartile while 33% higher for the lowest BW quartile compared to the population median. The impact of BW on lebrikizumab exposure is not clinically significant given the lack of dose-response relationship over a wider exposure range resulting from Q2W and Q4W treatment. PopPK estimated 17 - 21% higher exposure in adolescents than that of adults, which can be attributed to lower body weight distribution for adolescents. The PopPK model-estimated mean t1/2 was 24.5 days and bioavailability after SC dosing was 86.1%.

Subsequently, a PK-PD model based on the data from phase 2 and phase 3 studies was developed with an intent to support the clinical dose selection of lebrikizumab for the treatment of adult and adolescent patients with moderate-to-severe AD. This PK-PD analysis was conducted in two steps: i) development of a PopPK model to characterize the PK of lebrikizumab (described above) and ii) development of a PD model based on the exposures derived from the PopPK model in step 1 to describe the relationship between lebrikizumab exposure and Eczema Area and Severity Index (EASI) response. The combined population PK-PD model was also intended to understand and quantify patient factors which may affect EASI response.

The final PK-PD model was an indirect effect model that well described the longitudinal EASI response to lebrikizumab with or without topical corticosteroids (TCS) usage. The maximum effect (Emax) was estimated to be 0.831 (95% CI, 0.761 – 0.883) and the half maximal effective concentration (EC50) was 16.5 µg/mL (95% CI, 9.84 – 27.6 µg/mL). There was a small effect of TCS use on the percentage change in EASI score from baseline. The model was adequate and validated to describe the observed EASI score, hence suitable to perform simulations in support of different dosing regimens. No covariates were identified as significant to impact exposure-response (E-R) relationship.

Simulations demonstrated that two loading doses of 500 mg lebrikizumab at Week 0 and 2 followed by 250 mg every two weeks (Q2W) up to Week 16 (induction period, last dose was at Week 14) produced rapid and greater responses compared to other dosing regimens with different loading doses. The response reached plateau after Week 16 for all dosing regimens. There was only a 3-4% higher response rate seen between Week 16 and 24 for 250 mg Q2W regimen compared to that of Week 16. Simulations of responders at Week 16 switching to maintenance regimens of 250 mg Q2W, Q4W, or placebo up to Week 52 indicated that the efficacy rates were comparable between Q2W and Q4W treatment regimen with a small numerically higher response rate gained from Q2W. The placebo withdrawal group maintained efficacy for long-term with a gradual and smaller decline over time. Overall, the (b) (4) dosing regimens of 500 mg lebrikizumab at Week 0 and 2 followed by 250 mg Q2W up to Week 16 (induction treatment) and thereafter either 250 mg Q2W or Q4W maintenance regimen for responders at Week 16 are supported by the PK-PD analysis.

Table 9295. Summary of PopPK analyses

General Information		
Objectives of PopPK analysis	• To characterize the pharmacokinetics (PK) of lebrikizumab in adult and adolescent participants with atopic dermatitis (AD) and healthy participants • To identify patient factors and laboratory parameters that may influence lebrikizumab disposition in this population, and • To derive individual PK parameters/exposure metrics for the future assessment of exposure-response relationships.	
Study and population included	The PopPK analysis dataset contained data from 11 studies: 4 were in healthy participants and 7 were in participants with AD. The dataset includes a total of 1607 subjects from phase 1, 2, and 3 studies. Both adults and adolescents (12 to <18 years, ≥40 kg) were included in the phase 3 studies and included in the analysis. See **Table 93** for details.	
Dose(s) included	Single SC doses: 37.5 – 375 mg Single IV or SC dose: 1 mg/kg Multiple SC dose: 250 mg Q2W or Q4W preceded by 250 – 500 mg loading doses. In phase 3 studies, the following doses and dosing regimen ((b) (4) in the target patient population) were evaluated in adult and adolescent patients (12 to <18 years weighing at least 40 kg): • Loading doses – 500 mg at Week 0 and Week 2 • Induction doses – 250 mg every 2 weeks (Q2W) starting at Week 4 and continuing to Week 16 • Maintenance doses – 250 mg Q2W or 250 mg every 4 weeks (Q4W) starting at Week 16 and continuing to Week 52 Refer to **Table 93** for dosing regimen of individual study included in PopPK analysis.	
PopPK analysis dataset	The source data from 11 studies contained 8050 post-baseline observations from 2015 participants. Based on criteria outlined in the analysis plan, 1190 observations were excluded from the source data.	
No. of patients, PK samples, and BLQ	Healthy subjects: 281 Patients with AD: 1326 Number of PK samples: 6860 Total BLQs: None (All BLQs [N = 122] were excluded from the PopPK dataset) See **Figure 12** for PK sample distribution.	
Population Characteristics	See **Table 94**	
Final Model	**Summary**	**Acceptability [FDA's Comments]**
Software and version	• Nonlinear mixed effects modeling (NONMEM) (Version 7.4.2; ICON Development Systems, Gaithersburg, MD, USA) • R (Versions 4.1.2; R Foundation for Statistical Computing, Vienna, Austria)	**Acceptable**
Model Structure	This model was a two-compartment disposition model with first-order absorption and linear elimination. Inter-	**Acceptable**

	individual variability (IIV) terms were included on Ka, CL, V2, and bioavailability (F1) parameters with omega blocks on CL-Ka and Ka-V2 terms and a logit transformation on F1 to restrict the estimate of bioavailability to between 0 and 1. Body weight was included as a fixed exponent of 0.8 on clearance parameters (CL and Q) and a fixed exponent of 1 on volume parameters (V2 and V3).	
Base Model Parameters	Body weight was included as a covariate on CL, V2, V3, and Q in base model consistent with the previous modeling. See **Table 95** for final parameter estimates as the base and final model are the same. The precision in parameter estimates is good. The 95% CI of parameter estimates obtained from bootstrap analysis also supports the precision of final parameter estimates.	**Acceptable**
Final Model Parameters	**See Table 95 for parameter estimates.** An assessment of covariate effects was conducted using the Stepwise Covariate Modeling (SCM) procedure in PsN per the criteria outlined in the analysis plan. The covariates evaluated in the analysis are age, body weight, sex, race, disease state, injection location, markers of hepatic and renal function. As noted, body weight was already included as a covariate on CL, V2, V3, and Q. Hence, BW was formally tested on absorption rate constant (Ka) only as a part of the SCM procedure.	**Acceptable**
GOF, VPC plots	The goodness-of-fit plots and prediction-corrected VPC plots of the final population PK model are shown in **Figure 13, and 14,** respectively.	**Acceptable**
Effect of Covariates	No covariates except body weight was found significant in PopPK model. Though BW was identified as a significant covariate, its effect on the PK is not clinically significant given the lack of dose-response relationship. Hence, no dose adjustment on the basis of body weight is needed for the adolescent (weight at least 40 kg) and adult patients with AD.	**Acceptable**

Table 9396. Clinical Studies included in the PopPK dataset

Study ID	Objectives	Study design	Study treatment	Remarks
J2T-DM-KGBA	Safety, tolerability, PK	Phase 1, R, PG, OL single-dose study in healthy subject (N = 22). PK sampling: Day 1 (pre-dose and 30 min post-dose, and Days 2, 4, 8, 11, 15, 22, 36, 57, 78, and 92 and at ET (early termination)	Lebrikizumab 1 mg/kg IV (N=11) or SC (N=11) administration	Bioavailability: 85%; mean t1/2: 24.7 days

J2T-DM-KGAZ	Safety, tolerability, PK	Phase 1, R, DB, PC, PG, and single-ascending dose study in healthy Japanese and Caucasian subjects (N = 60). PK sampling: Day 1 (pre-dose and 4, 12 hours post-dose), and Days 2, 5, 8, 15, 29, 50, 71, 99, and 120.	Lebrikizumab 125, 250, 375 mg or placebo	Exposure was dose proportional. CL/F, t1/2 appeared to be dose-independent
J2T-DM-KGAY	Safety, tolerability, PK and BE evaluation	Phase 1, R, OL, 2-arm, PG, MC, single-dose study in healthy subjects (N = 176).	**Arm 1**: single 0.3 mL SC inj of 125 mg/mL lebrikizumab using needle and syringe **Arm 2**: single 1 mL SC inj of 37.5 mg/mL lebrikizumab using PFS-NSD	PK exposure (Cmax and AUC) was similar and bioequivalent between two presentations
J2T-DM-KGAM	Safety, tolerability, PK	Phase 1, R, PG, SC, 2-arm single-dose study in healthy subjects (N = 41).	250 mg using 2 × 1-mL (125 mg/mL) injections or 250 mg using 1 × 2-mL injection	Overall PK was similar. Cmax, AUCinf were a little out of 90% CI limit
J2T-DM-KGAG	Efficacy as adjunctive therapy with TCS and PK, Safety	Phase 2, R, DB, PC, multiple-dose study in patients with persistent moderate-to-severe AD that is inadequately controlled by TCS (N = 212).	LEB 250 mg single dose (SD) + TCS LEB 125 mg SD + TCS LEB 125 mg Q4W + TCS. Duration: 12 weeks	Statistically significant treatment effect was observed on EASI-50 (82.4% vs 62.3%) as primary endpoint.
J2T-DM-KGAH	Safety and PK for monotherapy compared with TCS	Phase 2, R, OL, PC study in adult patients with persistent moderate-to-severe AD (N = 55).	LEB 125 mg Q4W (N=28) or TCS (N=27). Duration: 12 weeks	Mean Ctrough: 1.6-fold higher at 12-Week than after first dose. Clinically meaningful but not statistically significant effects on EASI was showed.
J2T-DM-KGAF	Dose-ranging. Safety, efficacy, and PK	Phase 2b, R, DB, PC, PG dose-ranging trial in adult patients with moderate-to-severe AD (N = 280, in a 3:3:3:2 ratio).	Arm 1: Loading 250 mg then LEB 125 mg Q4W; Arm 2: Loading 500 mg, then 250 mg Q4W; Arm 3: Loading 500 mg at W-0, 2, and then 250 mg Q2W; Arm 4: Placebo Q2W. Duration: 16 Weeks	Dose-response was observed.

J2T-DM-KGAB	Efficacy, safety compared with placebo, PK (monotherapy)	Phase 3, R, DB, PC study in adolescent patients (12 to <18y weighing ≥40 kg) with moderate-to-severe AD (N = 424).	Induction period (16-Week): LEB 500 mg loading at W-0, 2, then 250 mg Q2W up to W-14 or matching placebo in 2:1 Maintenance period (W-16 to 52): For LEB responders during induction: LEB 250 mg Q2W or LEB 250 mg Q4W or placebo Q2W in 2:2:1 up to W-50 (blinded) Placebo-responders (N=24) during induction: 500mg loading then 250mg Q4W, or 2 loading dose of 500 mg, then 250 mg Q2W Escape OL arm for non-responders during induction: Q2W up to W-52	Statistically significant and clinically meaningful effect was achieved on primary endpoints (IGA, EASI 75) at Week 16
J2T-DM-KGAC	Efficacy, safety compared with placebo, PK	Phase 3, R, DB, PC, PG study in adolescent (12 to <18y weighing ≥40 kg) and adult patients with moderate-to-severe AD (N = 445).	Induction: W-0 to 16 Dosing: LEB 500 mg loading at W-0, 2 and then 250 mg Q2W up to W-14, or placebo Q2W in a 2:1 ratio. Maintenance (W-16 to 52 Dosing): Blinded: responder during induction period were reassigned to LEB 250 mg Q2W or Q4W or placebo Q2W in 2:2:1 ratio [note: placebo-responders also received either Q2W or Q4W) Escape OL: Non-responders randomized to LEB 250 mg Q2W	Statistically significant and clinically meaningful effect was achieved on primary endpoints (IGA, EASI 75) at Week 16
J2T-DM-KGAD	Efficacy, safety when used in combination with TCS compared with placebo, PK	Phase 3, R, DB, PC, PG study in adolescent (12 to <18yo weighing ≥40 kg) and adult patients with moderate-to-severe AD (N = 228).	Induction: W-0 to 16 Dosing: LEB 500 mg loading at W-0, 2 and then 250 mg Q2W + TCS or Placebo Q2W + TCS up to W-14, in a 2:1 ratio. TCS initiated at baseline; could be tapered or stopped as warranted.	Placebo response was higher compared to KGAB, KGAC study, due to allowed TCS. However, it met primary and key secondary endpoints.
J2T-DM-KGAE	Safety, efficacy, PK	Phase 3, non-randomized, OL, single-arm study in adolescent (12 to <18y weighing ≥40 kg) and adult	LEB 500 mg at W-0, 2, and then 250 mg Q2W through Week 52	

		patients with moderate-to-severe AD (N = 206).		

R: randomized; PG: parallel-group; OL: open-label, LEB: Lebrikizumab. Doses were administered subcutaneously if not implied otherwise.

Table 9497. Summary of Demographics and Baseline Characteristics for Participants Included in the Population Pharmacokinetic Analyses

	Continuous Characteristics			
	Mean ± SD (Minimum-Maximum)			
	Phase 1 (Healthy subjects)	Phase 2 and 3 (subjects with AD)		Total
		Adult (≥18 y)	Adolescent (12 to <18 y, ≥40 kg)	
N	281	1022	304	1607
Age (years)	36.1 ± 11.2 (18-64)	39.4 ± 16.4 (18-93)	14.6 ± 1.74 (12-17)	29.6 ± 17.5 (12-93)
Body weight (kg)	73.3 ± 12.8 (39.9-103.8)	78.5 ± 20.6 (39.6-192.1)	65.9 ± 20.0 (39.8-158.5)	73.4 ± 21.1 (39.6-192.1)
ALT (IU/L)	19.5 ± 10.9 (6-95)	23.9 ± 15.1 (5-178)	19.1 ± 13.2 (6-98)	22.2 ± 14.2 (5-178)
AST (IU/L)	20.6 ± 5.7 (10-45)	23.7 ± 10.1 (6-105)	22.1 ± 7.5 (8-63)	22.9 ± 9.1 (6-105)
eGFR by MDRD (mL/min/1.73 m²)	97.5 ± 18.5 (61.4-180.5)	97.9 ± 22.8 (27.4-198)	150.7 ± 40.7 (87.4-335)	108 ± 33.6 (27.4-335)
	Categorical Characteristics			
	N (%)			
Sex				
Female	150 (53)	504 (49)	160 (53)	814 (51)
Male	131 (47)	518 (51)	144 (47)	793 (49)
Race				
White/Caucasian	175 (62)	648 (63)	198 (65)	1021 (64)
African	57 (20)	151 (15)	34 (11)	242 (15)
Asian	32 (11)	176 (17)	44 (14)	252 (16)
Other/missing	17 (6)	47 (5)	28 (9)	92 (6)

Source: Reviewer's analysis based on data from '*lebri_meta_pk_atopic_derm_final_psn.xpt*'

Table 9598. Pharmacokinetic and Covariate Parameters in Base and Final Population PK Model. Base and Final Model are the Same Model

Model Parameter (Unit)	Population Estimate (%RSE)	Interindividual Variability %CV[a] (%RSE)	95% Confidence Interval from Bootstrap Analysis
Ka (1/day)	0.303 (11)	45.1 (17)	(0.249-0.376)
F	0.861 (4)	119 (24)	(0.802-0.914)

CL (L/day)	0.154 (4)	24.7 (8)	(0.143-0.164)
V2 (L)	3.86 (7)	23.7 (30)	(3.312-4.458)
Q (L/day)	0.525 (11)	-	(0.232-0.690)
V3 (L)	1.28 (27)	-	(0.468-1.897)
Covariates effects			
Covariate for BW on CL[b]	0.8 FIX	-	-
Covariate for BW on V2[c]	1 FIX	-	-
Covariate for BW on Q[d]	0.8 FIX	-	-
Covariate for BW on V3[e]	1 FIX	-	-
Variance			
Covariance for CL-Ka[f]	-	-0.057 (23.5)	-
Covariance for Ka-V2[f]	-	-0.0384(65)	-
Residual error[g]			
Proportional	0.0342 (7)		(0.0297-0.0387)
Additive (µg/mL)	0.00307 (59)		(0.00102-0.00756)

Abbreviations: CL = clearance; CV = coefficient of variation; F = bioavailability; FIX = fixed; ka = absorption rate constant; Q = intercompartmental clearance, SEE = standard error of estimate; V2 = central volume of distribution; V3 = peripheral volume of distribution.

[a] %CV = (SQRT(e^(OMEGA(N))−1))*100%
[b] CL = population CL*(WTE/70)0.8, where WTE is body weight at study entry and 70 is median body weight
[c] V2 = population V2*(WTE/70)1, where WTE is body weight at study entry and 70 is median body weight
[d] Q = population Q*(WTE/70)0.8, where WTE is body weight at study entry and 70 is median body weight
[e] V3 = population V3*(WTE/70)1, where WTE is body weight at study entry and 70 is median body weight
[f] Covariance between ω^2
[g] Reported as σ^2

Source: m5.3.3.5, seq 1: Population PK/PD Report, table 9.1, page 39. Reviewer's independent analysis provides the similar base model parameters.

Figure 12. PK sampling distribution of PopPK dataset

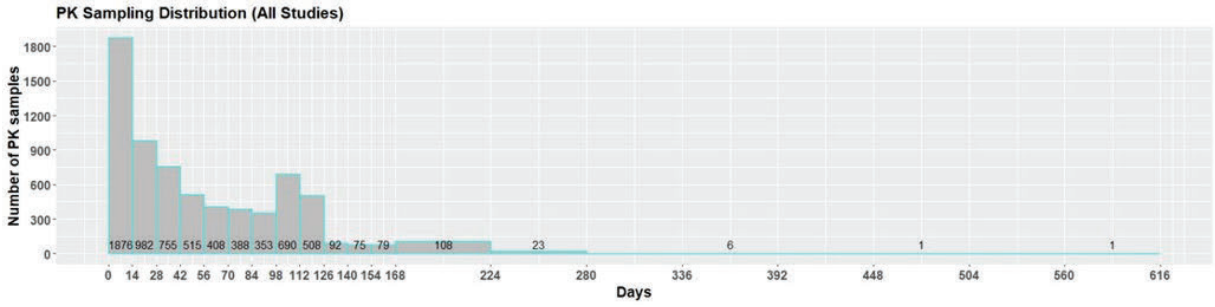


Figure 13. Goodness-of-Fit Plots for the Final Population PK Model

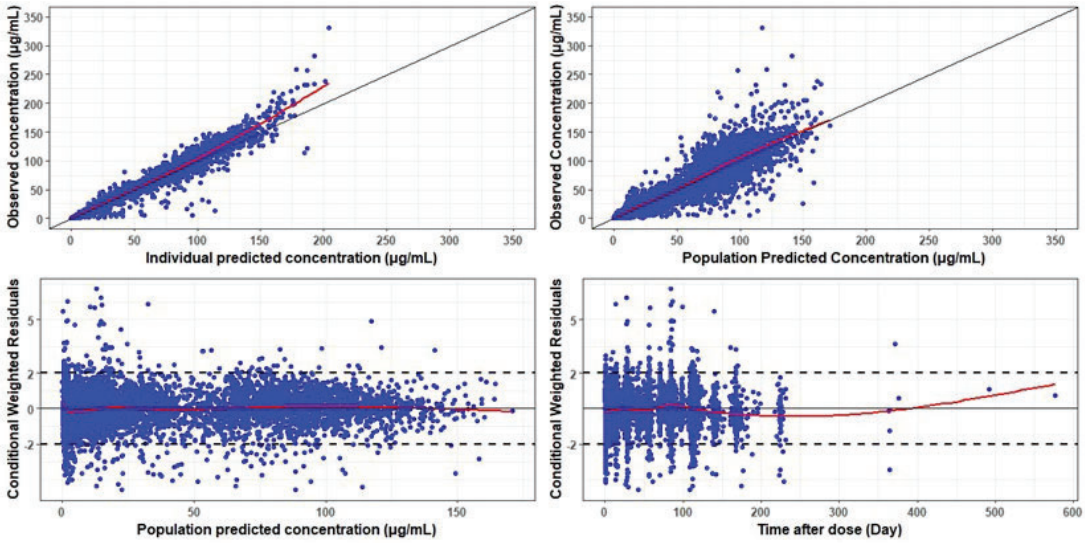
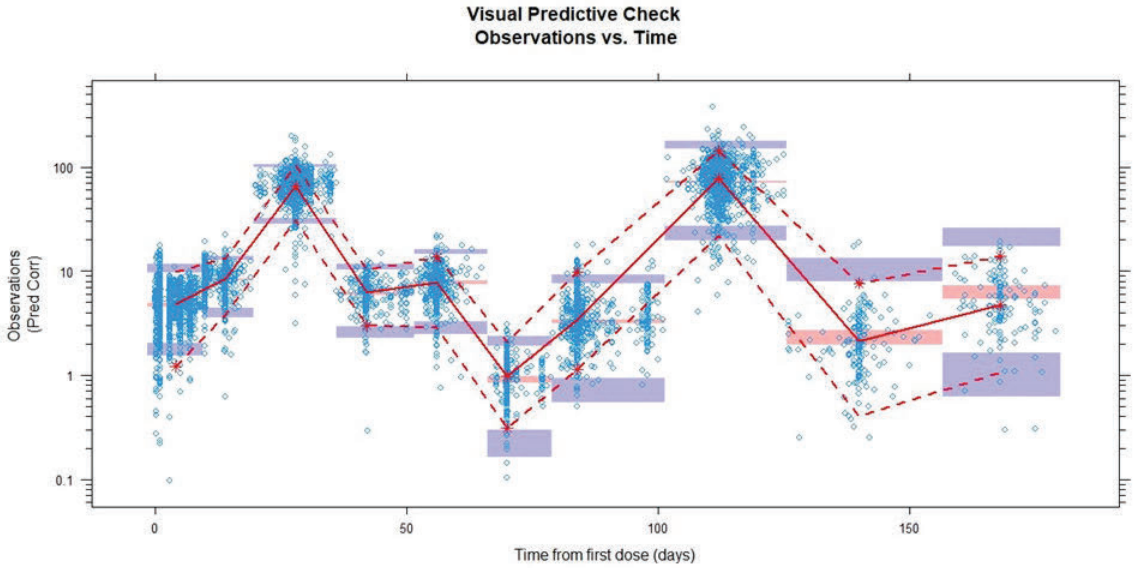
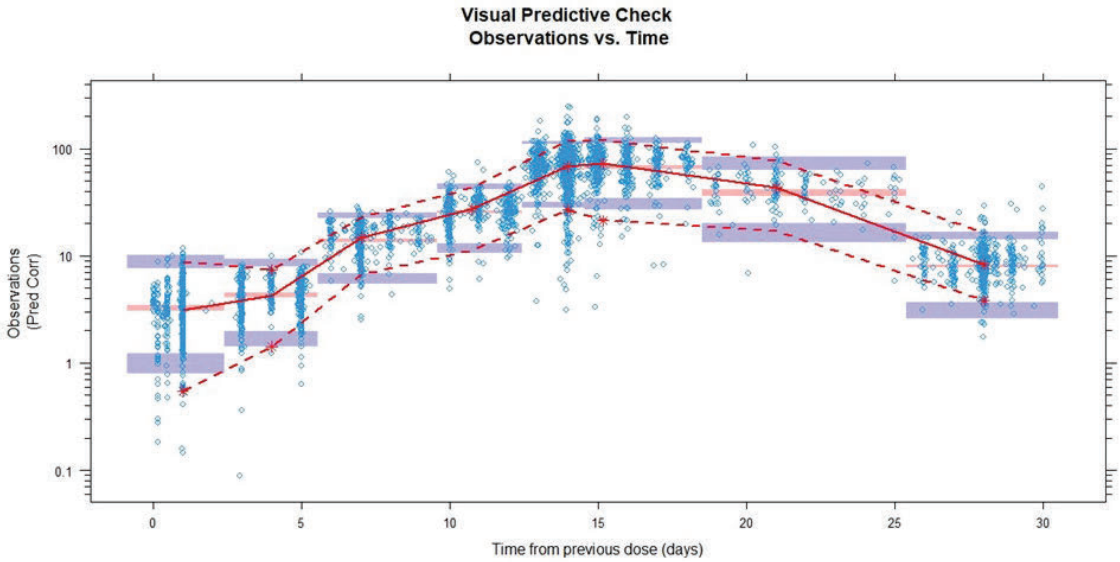


Figure 14. Prediction-Corrected Visual Predictive Check for the Final Population PK model (in Logarithmic Y Scale: time after first dose up to Day 180 [upper panel], and time after previous dose up to Day 30 [lower panel])





Note: Blue dots represent the observed data. The solid red line depicts median observed data, while pink shaded areas define the 95% confidence intervals around the median of the simulated data. Red dashed lines represent the 5th and 95th percentiles of observed data, while blue shaded areas represent the simulated 95% confidence interval of the same.
Source: Based on the reviewer's model output from 039b model run.

Table 9699. Summary of PK-PD analyses

General Information	
Objectives of PopPK analysis	• To characterize the relationship between lebrikizumab exposure and Eczema Area and Severity Index (EASI) response, based on data from the available phase 2 and phase 3 studies • To understand and quantify patient factors which may affect EASI response. • Overall, to support the clinical dose selection for lebrikizumab in adult and adolescent (aged 12 to <18 years, with body weight ≥40 kg) patients with moderate-to-severe AD and to support the dose recommendation for pediatric patients (<12 years) with AD
Study and population included	The PK-PD analysis dataset contained data from 5 studies: KGAH, KGAF (phase 2), KGAB, KGAC, KGAD (phase 3). The dataset includes a total of 1307 subjects. Both adults and adolescents (12 to <18 years, ≥40 kg) were included in the phase 3 studies and included in this analysis (see **Table 93** for details*)*. The study population consisted of 655 males and 652 females with weights ranging from 40 to 192 kg. The age range in the study population was 12 to 93 years, with 131 adolescents and 1176 adults.
Dose(s) included	125 and 250 mg (single or multiple doses)
PK-PD analysis dataset	The analyses included data up to 16 weeks of lebrikizumab treatment (induction dosing) and doses ranging from a single dose of 125 mg to 250 mg every 2 weeks (Q2W).
Covariates evaluated	Age, sex, body weight, race, and baseline IGA were tested on Emax and EC50 parameter. Additionally, all these covariates except baseline IGA were tested on Kout and Epbo.

	Emax: maximal effect, EC50: half maximal effective concentration, Kout: first order rate constant for loss of response, Epbo: placebo effect	
Final Model	**Summary**	**Acceptability [FDA's Comments]**
Software and version	• The PK-PD analysis was carried out using NONMEM (Version 7.4.3, ICON Development Solutions, Elicott City, MD, USA) under Windows 10 and the GNU gfortran compiler (Version 4.6.0). • Post-processing of NONMEM analysis results was carried out in R version 4.0.5 (R Development Core Team, 2008). • NONMEM run execution and visual predictive checks (VPCs) were carried out using Perl-speaks-Nonmem (PsN), version 4.8.1.	**Acceptable**
Model Development	• The PK-PD model was developed in a stepwise approach to assess potential model bias and/or misspecification as more data became available. • Preliminary models were built using phase 2 studies KGAG and KGAF, then redeveloped with the addition of phase 3 studies KGAB, KGAC, and KGAD • Model development was carried out using first order conditional estimation with interaction (FOCE-I), including individual pharmacokinetics (PK) estimates from the previously developed PopPK model • Exploratory analysis showed that there is a difference in baseline EASI score across studies, hence study effect on baseline EASI score was estimated by stratifying the studies into 3 groups: KGAG (mean baseline 25.4), KGAF and KGAD (mean baseline 26.8), and KGAB and KGAD (mean baseline 29.0) • Exploratory analysis also showed that TCS use contributed to a little higher decrease in the percent change of EASI score from baseline compared to that with no TCS use (**Figure 15**). Therefore, the model included a time-varying multiplicative TCS effect on the first-order rate constant for loss of response (Kout). • The model also included a logit fractional placebo effect on the zero-order constant for the production of response (Kin). • Subgroups of interest were explored graphically, including age, sex, body weight, race, and baseline Investigator's Global Assessment (IGA) (e.g., moderate vs severe) and tested as covariates in the PK-PD model as indicated by the results of the graphical analysis.	**Acceptable**

Model Parameters	PK parameters were estimated in a previous PopPK model and combined with the PK-PD analysis dataset. The estimated PD parameters are presented in **Table 97**.	**Acceptable**
GOF, VPC plots	The goodness-of-fit plots and prediction-corrected VPC plots of the final population PK-PD model are shown in **Figure 16 and 17**, respectively. The final EASI model (Run 857) demonstrated good agreement between predicted and observed data. The condition number was low (33.71), and all parameters were well estimated with acceptable precision. Plots of the conditional weighted residuals show that the model is overall unbiased over time and across the concentration range.	**Acceptable**
Significant covariates	The final model only included two covariates to be significant: TCS effect on Kout and study effects on baseline EASI. All other continuous or categorical covariates were found insignificant. Body weight was included in the PopPK model and was re-evaluated for its potential effect on Emax or EC50 in the PK-PD model but was not found significant.	

Table 97100. Parameter estimates of the final PK-PD model (Run 857)

Param	Alias	Estimate	Relative SE (%)	95% CI
θ_1	Baseline EASI (KGAG)	23.9	3.1	(22.4 - 25.3)
θ_2	Baseline EASI (KGAF,KGAD)	26.8	1.9	(25.8 - 27.8)
θ_3	Kout (1/d)	0.0523	.....	(0.0489 - 0.0559)
θ_4	Placebo Effect (Fixed)	0.702	.....	.....
θ_5	TCS on Kout (unitless multiplier)	1.08	.....	(1.06 - 1.10)
θ_6	sigmaE	0.468	.....	(0.463 - 0.474)
θ_7	Emax	0.831	.....	(0.761 - 0.883)
θ_8	EC50 (ug/mL)	16.5	.....	(9.84 - 27.6)
θ_9	Baseline EASI (KGAB,KGAC)	29.5	0.5	(29.3 - 29.8)
$\omega_{1.1}$	ω^2_{E0}	1.74	8.4	(1.45 - 2.03)
$\omega_{2.1}$	$\omega^2_{E0,Kout}$	-0.0599	82.5	(-0.157 - 0.0370)
$\omega_{2.2}$	ω^2_{kout}	0.340	8.2	(0.285 - 0.395)
$\omega_{3.2}$	$\omega^2_{kout,Epbo}$	0.0860	81.8	(-0.0519 - 0.224)
$\omega_{3.3}$	ω^2_{Epbo}	2.46	7.9	(2.08 - 2.84)
$\omega_{5.5}$	ω^2_{EC50}	4.96	32.2	(1.83 - 8.09)

Parameter values for the final PK-PD model. **EASI:** Eczema Area and Severity Index; **TCS:** topical corticosteroid; **E0:** individual baseline EASI estimate; **Epbo:** placebo effect; **sigmaE:** individual variability on baseline; ω^2_X : variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$. $\omega^2_{X,Y}$: covariance of the IIV of parameters X and Y.

Source: m5.3.3.5, seq 1: Population PK/PD Report ((b) (4) Modeling Report), table 9, page 37. Reviewer's independent analysis provides the similar PD model parameters.

Figure 15. Impact of concomitant use of TCS on the percentage change in EASI score from baseline for phase 2 and 3 studies with the available placebo or dose groups. The use of TCS

demonstrated a little more reduction in EASI score from baseline with more pronounced effect in placebo arm (red triangle).

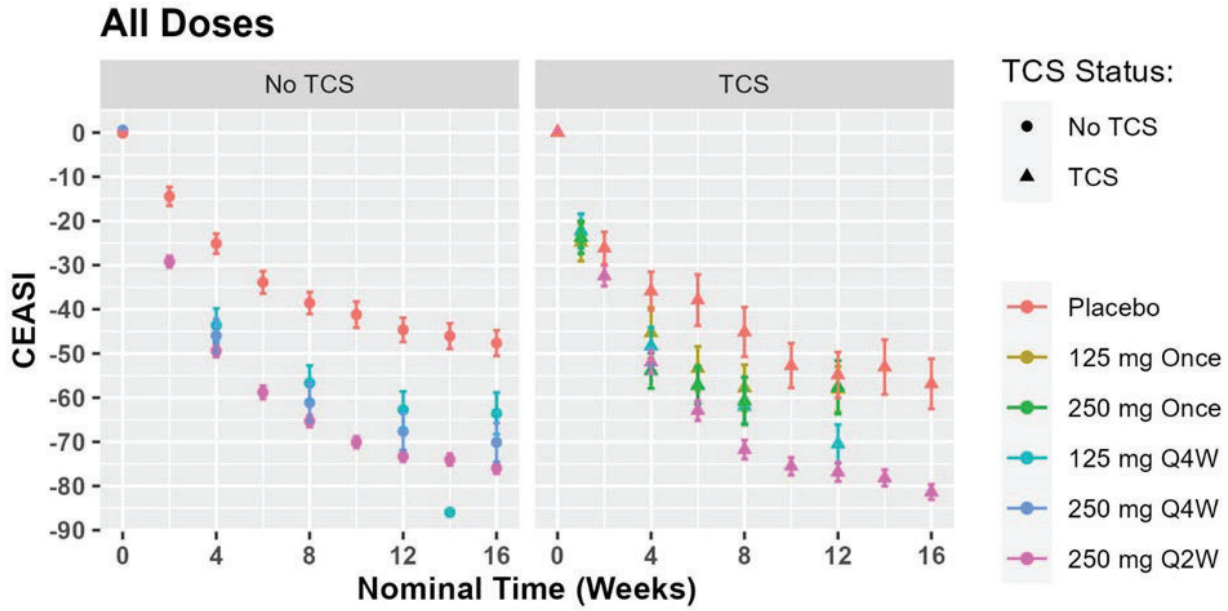
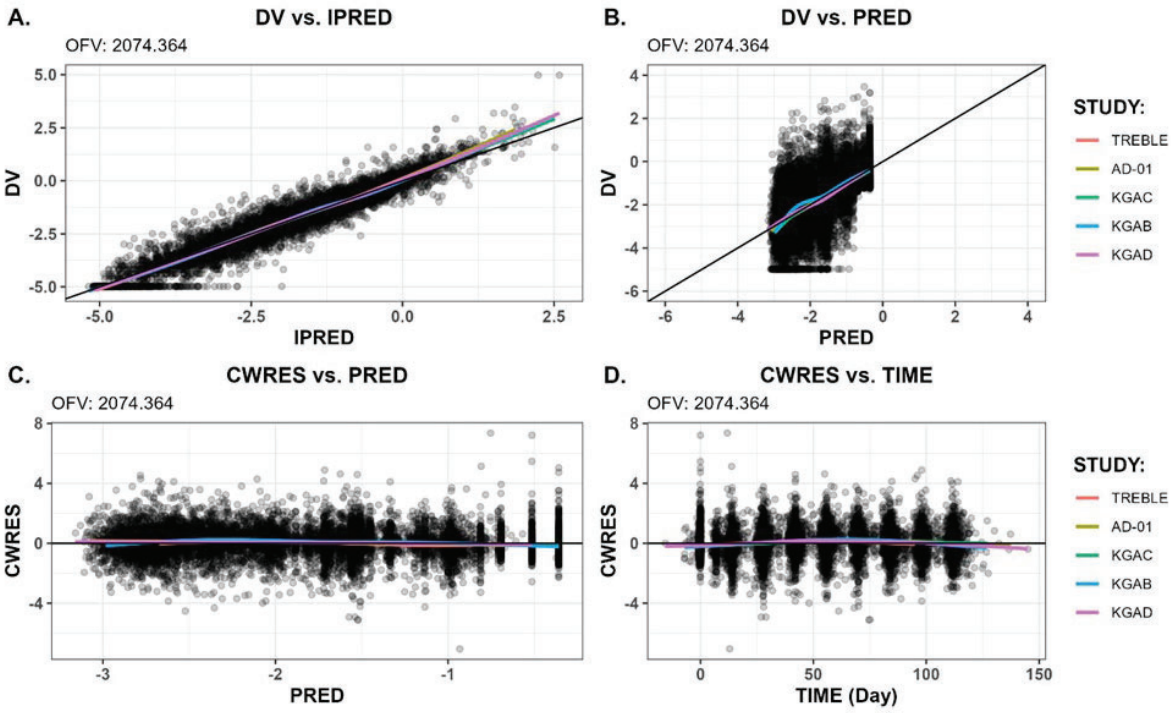
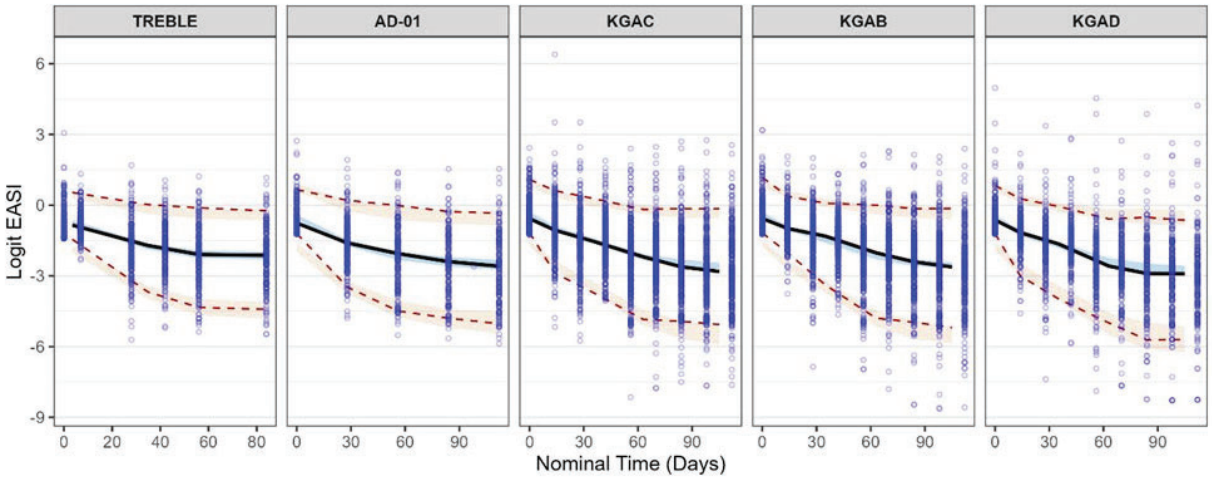


Figure 16. Goodness of fit plots for final PK-PD model: A. Observations (EASI) versus Individual Prediction, B. Observations (EASI) versus Population Prediction, C. Conditional Weighted Residuals (CWRES) versus Population Predictions, and D. Conditional Weighted



Source: Reviewer's plots.

Figure 17. Prediction-corrected VPC of EASI Score over Time by Study - Final Model



Solid Black Line: Median of the observed data; Dashed Red Lines: 5th and 95th percentiles of the observed data; Shaded Area: The shaded areas indicate the 95% CI around the median (blue area) and 5th and 95th percentiles of the simulated response (pink areas). **Source**: reviewer's plot based on final model simulation.

Applicant's Summary of Pharmacokinetic Results

Brief description of the PopPK model results:
The Applicant developed a 2-compartment model with first-order absorption and linear elimination to characterize the PK profile of lebrikizumab based on 11 pooled studies. The model was found adequate and predictive based on GOF and VPC plots, which was supported by the reviewer's independent analysis of the model (see **Table 92** and hyperlinked model results and plots). Only body weight was identified as a significant covariate on lebrikizumab PK. Age, sex, race, injection site location, disease (atopic dermatitis vs healthy), and markers of hepatic and renal function were found as insignificant covariates. Note that base model included BW-based allometric exponents on clearance and volume of parameters. This base model was considered as the final model as all other covariates tested were insignificant.

Note that immunogenicity was not tested as a covariate in the current PopPK model since the Week 52 data were not available at the time of this analysis. Immunogenicity will therefore be evaluated in a separate analysis.

Lebrikizumab concentrations were decreased with increase in BW, which is consistent with the expected PK of a monoclonal antibody. Lebrikizumab bioavailability after subcutaneous administration was 86.1% as estimated in the final model. The mean half-life of lebrikizumab was 24.5 days.

PK results based on PopPK model analyses:

The Applicant conducted simulation using the final PopPK model, which provided the following PK results:

- Steady state lebrikizumab concentrations were rapidly achieved after 250 mg dosing at Week 4, with the 500 mg loading doses at Weeks 0 and 2.
- Maximum concentration over a dosing interval at steady state (Cmax,ss), average concentration over a dosing interval at steady state (Cavg,ss), and minimum concentration over a dosing interval at steady state (Ctrough,ss) following 250 mg every 2 weeks (Q2W) were 108, 100, and 87 µg/mL, respectively. Cmax,ss, Cavg,ss, and Ctrough,ss following 250 mg every 4 weeks (Q4W) were 63, 51, and 36 µg/mL, respectively. These simulated exposure metrics indicate that lebrikizumab concentrations were approximately 50% lower for 250 mg Q4W dosing compared to 250 mg Q2W (**Table 98**).
- The median lebrikizumab Cavg,ss is approximately 50% lower for the 250 mg Q4W dosing group compared to the 250 mg Q2W group in the maintenance period. Overlap in lebrikizumab concentrations was observed between Q2W and Q4W.
- Higher BW resulted in lower overall lebrikizumab concentrations.
- At steady state after 250 mg Q2W dosing, simulations showed that the highest and lowest BW quartiles have median Cavg,ss of 75.7 and 133 µg/mL, compared to the overall population median Cavg,ss of 100 µg/mL (**Table 98** and **Table 99**). Therefore, the Cavg,ss was reduced by about 24% for the highest BW quartile and increased about 33% for the lowest BW quartile.
- At steady state after 250 mg Q4W dosing, simulations showed that the highest and lowest BW quartiles have median Cavg,ss of 37.9 and 64.9 µg/mL, compared to the overall population median Cavg,ss of 51.1 µg/mL (**Table 98** and **Table 99**). Therefore, the Cavg,ss was reduced by about 26% for the highest BW quartile and increased about 27% for the lowest BW quartile.
- The simulated median Ctrough,ss values were above 50 µg/mL for the Q2W regimen for all BW quartiles and generally 25 to 50 µg/mL for the Q4W regimen for all BW quartiles. Therefore, trough concentrations were maintained above the drug concentration that produces 50% of maximum effect (EC50) of 16.5 µg/mL (estimated by exposure-response model), even with the less frequent dosing of Q4W.

Table 98101. Observed (Ctrough,ss at Week 16) and simulated lebrikizumab concentrations from the final population PK model following phase 3 dosing regimens, reported as median (5th percentile, 95th percentile)

Dosing Regimen	500 mg Loading Dose at Weeks 0 and 2, 250 mg Q2W Starting at Weeks 4 to 16, and 250 mg Q2W or 250 mg Q4W Starting at Week 16			
Population	Phase 3 Study Participants (Observed)	Simulations of 500 Virtual Participants Based on Body Weight Distribution of Phase 3 Adolescent and Adult Participants		
PK Parameter	250 mg Q2W Week 16	250 mg Q2W Week 16	250 mg Q2W Week 52	250 mg Q4W Week 52
$C_{max,ss}$ (µg/mL)	NA	109 (61.6-177)	108 (61.7-182)	62.6 (38.2-106)
$C_{avg,ss}$ (µg/mL)	NA	100 (56.3-167)	99.9 (56.1-175)	51.1 (29.4-86.5)
$C_{trough,ss}$ (µg/mL)	94.4[a] (32.6-152)	86.4 (46.4-153)	86.6 (46.0-159)	36.1 (17.6-67.9)

Abbreviations: AD = atopic dermatitis; $C_{avg,ss}$ = average concentration over a dosing interval at steady state; $C_{max,ss}$ = maximum concentration over a dosing interval at steady state; $C_{trough,ss}$ = minimum concentration over a dosing interval at steady state; NA = not applicable; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks

[a] Based on n = 796 participants in the Phase 3 studies with observed concentrations at Week 16.

Source: m5.3.3.5, seq0001: Population PK/PD Report, Table 3.1, page 5.

Table 99102. Summary of lebrikizumab PK exposure parameters simulated at Week 52 by regimen and weight quartile

Simulations of 500 Virtual Participants in Each Maintenance Period Regimen Based on Body Weight Quartiles of Phase 3 Adolescent and Adult Participants. Concentrations Are Expressed as Median (5th, 95th)								
Dosing Regimen	**500 mg Loading Dose at Weeks 0 and 2, 250 mg Q2W from Weeks 4 to 16, and 250 mg Q2W or 250 mg Q4W Starting at Week 16**							
Maintenance Regimen	**Q2W**				**Q4W**			
Body Weight Quartile[a]	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
N (%)[b]	125 (25)	115 (23)	134 (27)	126 (25)	141 (28)	127 (25)	108 (22)	124 (25)
$C_{max,ss}$ (µg/mL)	143 (97.0-219)	114 (83.9-167)	103 (65.3-146)	81.3 (50.1-119)	81.4 (56.9-127)	67.3 (49.4-96.4)	56.2 (41.0-80.4)	45.9 (32.7-63.8)
$C_{avg,ss}$ (µg/mL)	133 (85.1-208)	106 (76.1-159)	95.9 (58.1-138)	75.7 (45.7-113)	64.9 (38.9-108)	54.9 (35.7-83.5)	45.6 (29.6-70.1)	37.9 (25.3-54.5)
$C_{trough,ss}$ (µg/mL)	117 (67.8-191)	93.4 (63.8-147)	83.7 (47.0-127)	67.2 (39.0-103)	43.3 (21.7-82.1)	39.0 (20.6-64.3)	32.0 (16.7-56.3)	26.8 (15.6-45.2)

Abbreviations: $C_{avg,ss}$ = average concentration over a dosing interval at steady state; $C_{max,ss}$ = maximum concentration over a dosing interval at steady state; $C_{trough,ss}$ = minimum concentration over a dosing interval at steady state; N = number of participants; PK = pharmacokinetics; Q1 = 39.6 to ≤58.5 kg; Q2 = 58.5 to ≤71.1 kg; Q3 = 71.1 to ≤85.1 kg; Q4 = 85.1 to 192 kg; Q2W = every 2 weeks; Q4W = every 4 weeks.

[a] Quartiles of body weight were calculated using the observed weight data from Phase 3 adolescent and adult participants.

[b] Simulations of 500 virtual participants are presented, which were sampled from the Phase 3 body weight distribution. Therefore, the number of participants in each quartile vary slightly between simulations.

Source: m5.3.3.5, seq0001: Population PK/PD Report, Table 3.2, page 7.

Reviewer's PopPK analysis

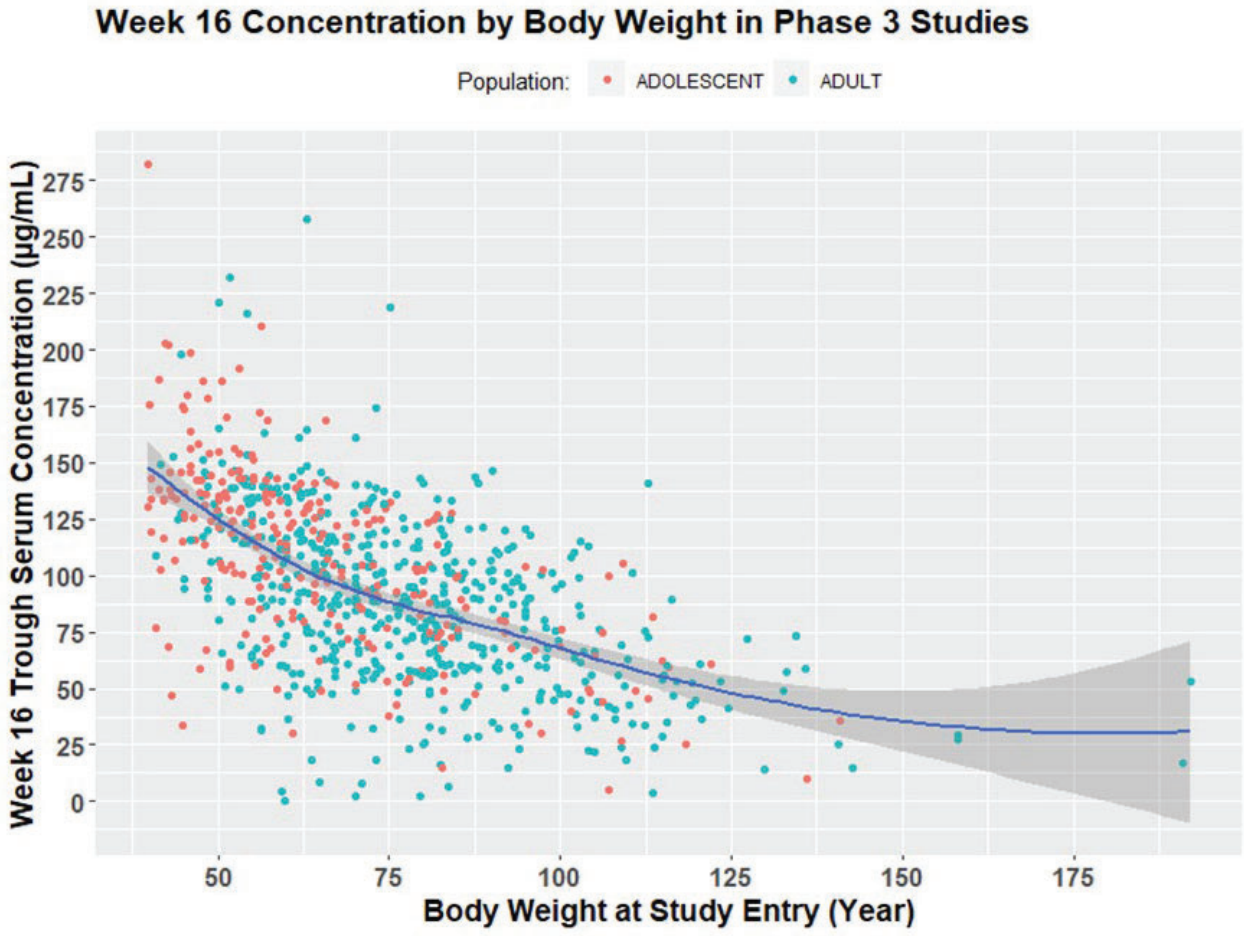
The reviewer's own analysis of the final PopPK model provided similar parameters estimates with similar precision as reported by the Applicant. The adequacy and predictability of the Applicant's PopPK model is supported by the reviewer's independent analysis. The summary results of the final PopPK model were provided in **Table 92**, hence will not be repeated here.

It is noted that body weight was identified as significant covariate. The clearance of lebrikizumab is increased with the increase in BW. This was supported by exploratory analysis of lebrikizumab concentrations-time data derived from phase 3 study. For example, predose concentrations (Ctrough) observed at Week 16 of phase 3 studies were decreased with increase in BW as seen in the **Figure 18**.

On the other hand, evaluation of markers of renal function (defined by estimated glomerular filtration rate, eGFR) as a continuous covariate was not a significant covariate. However, exploratory analysis of renal function indicates that 40 patients with moderate renal function

(30 mL/min/1.73 m^2<eGFR< 60 mL/min/1.73 m^2) were included in phase 2 and 3 studies. Only 21 of 40 patients with moderate renal impairment (RI) were available within phase 3 studies. For these 21 moderate RI patients, the median Ctrough at Week 16 was 73.6 µg/mL, which was approximately 22% lower than that of population median (94.4 µg/mL). However, a 22% decrease in lebrikizumab exposure in patients with moderate RI is unlikely to be clinically significant.

Figure 18. Lebrikizumab observed Week 16 predose (trough) concentrations by baseline body weight: all phase 3 participants (adults and adolescents)



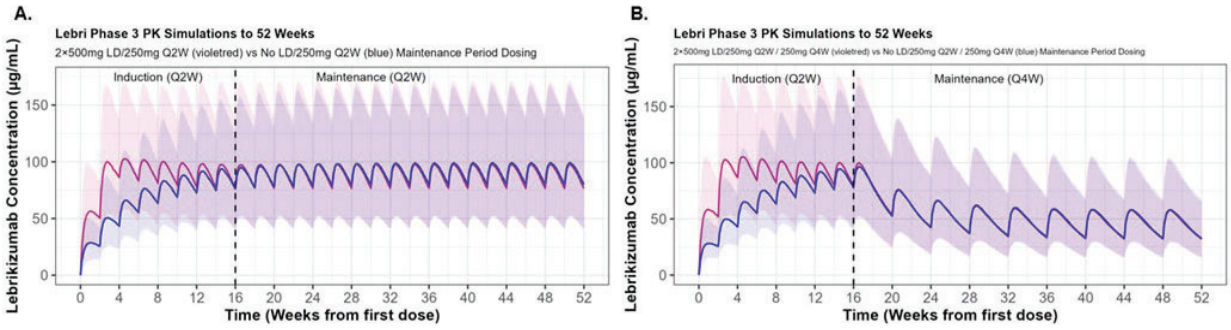
Summary of PK results based on reviewer's simulation

The reviewer has performed simulation using the final PopPK model to describe the PK characteristics of lebrikizumab under different scenarios. For example, the phase 3 dosing regimens, lebrikizumab 250 mg Q2W up to Week 16 (with/without loading doses) followed by 250 mg Q2W, 250 mg Q4W [redacted] (b) (4) up to Week 52 were considered as relevant scenarios to describe the PK parameters of lebrikizumab.

Since BW was a significant covariate, the BW was sampled from the observed baseline BW data of phase 3 studies. The reviewer's simulation-based PK results supported the Applicant's summary of PK results as stated above.

PK simulation shows that steady state is attained rapidly when two loading doses of 500 mg lebrikizumab are used at Week 0 and 2 compared to that with no loading dose. The steady state was achieved after Week 4 dosing (250 mg lebrikizumab) with loading doses while it took more than 12 weeks to reach steady state without loading doses (**Figure 19**).

Figure 19. Virtual patient simulations to 52 weeks, adults + adolescents, 2 x 500 mg loading doses versus no loading (N = 500 each), followed by 250 mg Q2W induction and 250 mg Q2W (plot A) or 250 mg Q4W (plot B) maintenance period dosing



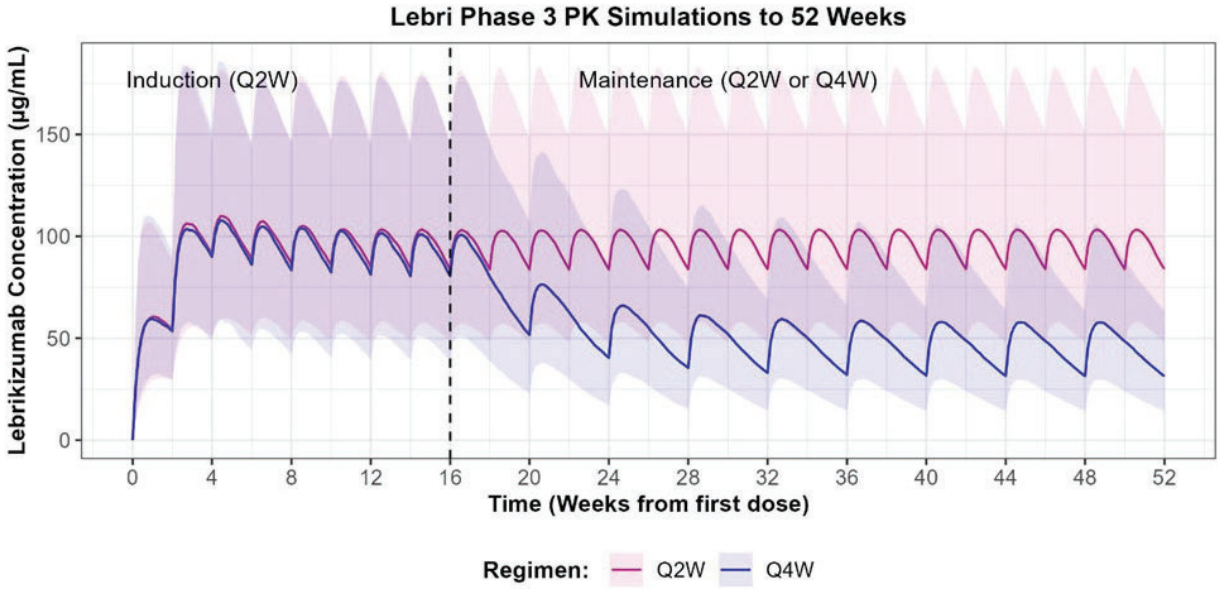
The simulated median Cmax,ss, Cavg,ss, and Ctrough,ss at Week 52 were 103, 97, and 84 µg/mL following 250 mg Q2W regimen and 59, 46, and 32 µg/mL following 250 mg Q4W regimen, respectively. The median lebrikizumab Cavg,ss is approximately 50% lower for the 250 mg Q4W dosing group compared to the 250 mg Q2W group in the maintenance period. There is an overlap in PK exposure between Q2W and Q4W regimen (**Table 100** and **Figure 20**).

Table 100103. Observed (Ctrough,ss at Week 16) and simulated lebrikizumab concentrations from the final population PK model following phase 3 dosing regimens, reported as median (5th percentile, 95th percentile)

Dosing Regimen	**500 mg Loading Dose at Weeks 0 and 2, 250 mg Q2W Starting at Weeks 4 to 16, and 250 mg Q2W or 250 mg Q4W Starting at Week 16**			
Population	**Phase 3 Study Participants (Observed)**	**Simulations of 500 Virtual Participants Based on Body Weight Distribution of Phase 3 Adolescent and Adult Participants**		
PK Parameter	**250 mg Q2W Week 16**	**250 mg Q2W Week 16**	**250 mg Q2W Week 52**	**250 mg Q4W Week 52**
Cmax,ss (µg/mL)	**NA**	103.1 (57.3 – 181.8)	103.4 (58.0 – 183.5)	58.7 (30.6 – 106.0)

Cavg,ss (µg/mL)	**NA**	96.8 (53.9 – 169.3)	96.8 (53.9 – 169.3)	46.2 (23.1 – 85.2)
Ctrough,ss (µg/mL)	94.6[a] (32.3 - 152.0	84.1 (47.9 – 147.1)	84.0 (47.7 – 151.0)	31.5 (14.4 – 63.4)
[a]Based on n = 794 participants in the Phase 3 studies with observed concentrations at Week 16. **Source**: Reviewer's simulation based on the final PopPK model.				

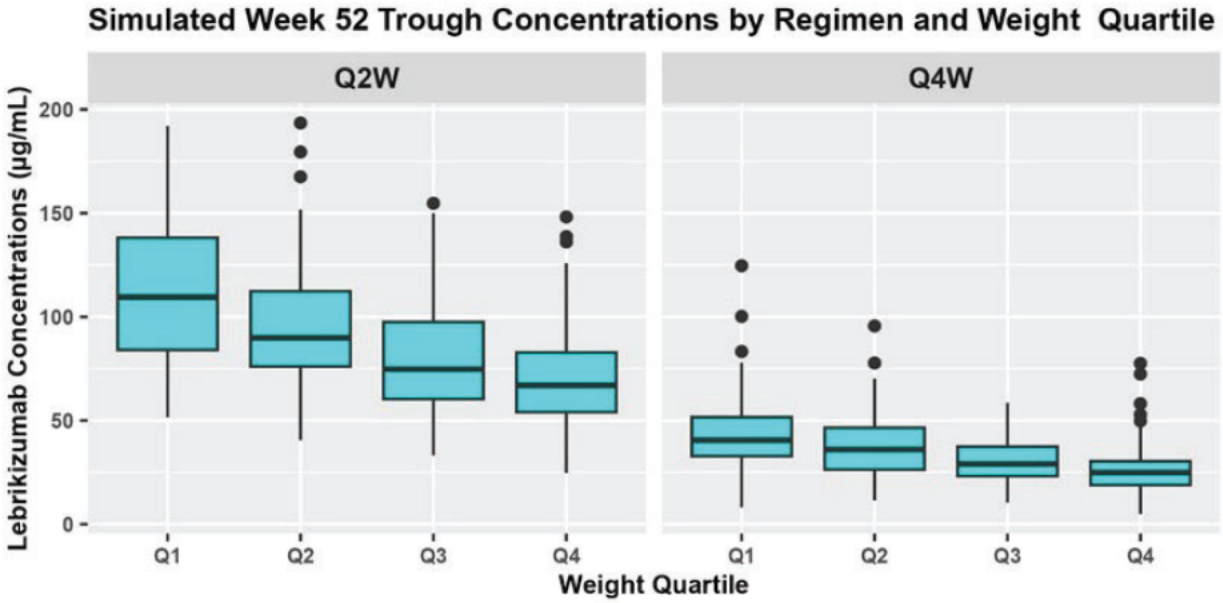
Figure 20. Virtual patient simulations to 52 weeks: phase 3 dosing regimen for loading doses, induction doses to Week 16, then lebrikizumab 250 mg Q2W versus 250 mg Q4W in maintenance period



Notes: Simulated patients received 500 mg loading doses at Weeks 0 and 2, followed by 250 mg Q2W dosing until Week 16. At Week 16, 1 group remained on 250 mg Q2W and 1 group reduced their dose to 250 mg Q4W for remainder of maintenance period to Week 52. N = 500 participants for each dose group in maintenance period. Lines represent medians, and shaded areas represent 5th and 95th percentiles, of simulated values at each time point. **Source**: reviewer's simulation.

Since lebrikizumab concentration was decreased with increase in BW, simulation was performed to compare Ctrough levels of lebrikizumab at Week 52 across all body weight quartiles. The box plots of lebrikizumab concentration vs weight quartiles indicate that concentration was decreased with increase in weight for both regimens (**Figure 21**). However, there was some overlap in the lebrikizumab exposures among the BW quartiles.

Figure 21. Box plots of simulated Week 52 Ctrough,ss concentrations by maintenance-period dosing regimen (250 mg Q2W and Q4W) and phase 3 weight quartile

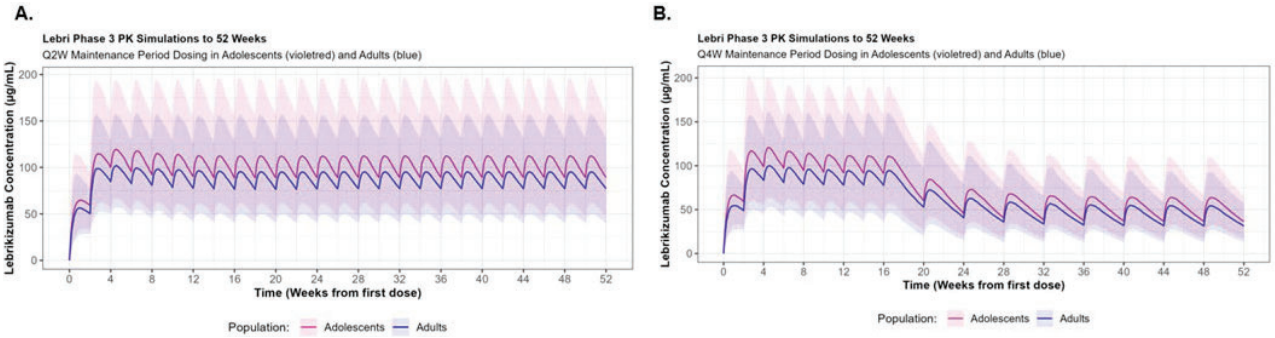


BW was sampled from phase 3 studies. Abbreviations: Q1 = first quartile of body weight (39.8 to ≤56.7 kg); Q2 = second quartile body weight (57 to ≤70.4 kg); Q3 = third quartile of body weight (70.6 to ≤83.7 kg); Q4 = fourth quartile of body weight (83.8 to 192.1 kg). Note: Center line within box represents the median (50th percentile), whereas the lower and upper hinges of box represent the first and third quartiles (25th and 75th percentiles). Whiskers extend from hinges to the smallest and largest values no further than +/-1.5 times the interquartile range (distance between the first and third quartiles). Dots represent individual data points beyond this range.

At steady state, the Q2W regimen resulted in a median Cavg,ss of 74 and 124 µg/mL for highest and lowest BW quartiles, respectively. Conversely, for Q4W regimen, median Cavg,ss were 35 and 60 µg/mL for highest and lowest BW quartiles. When compared with population median of 97 and 46 µg/mL for Q2W, and Q4W, respectively, the Cavg,ss was reduced by about 24% for the highest BW quartile and increased by about 28 - 30% for the lowest BW quartiles regardless of dosing regimen. These data agree with those reported by the Applicant. The change in lebrikizumab exposure in highest and lowest BW quartiles compared to the median exposure of population is not clinically significant, hence BW-based dosing recommendation is not needed.

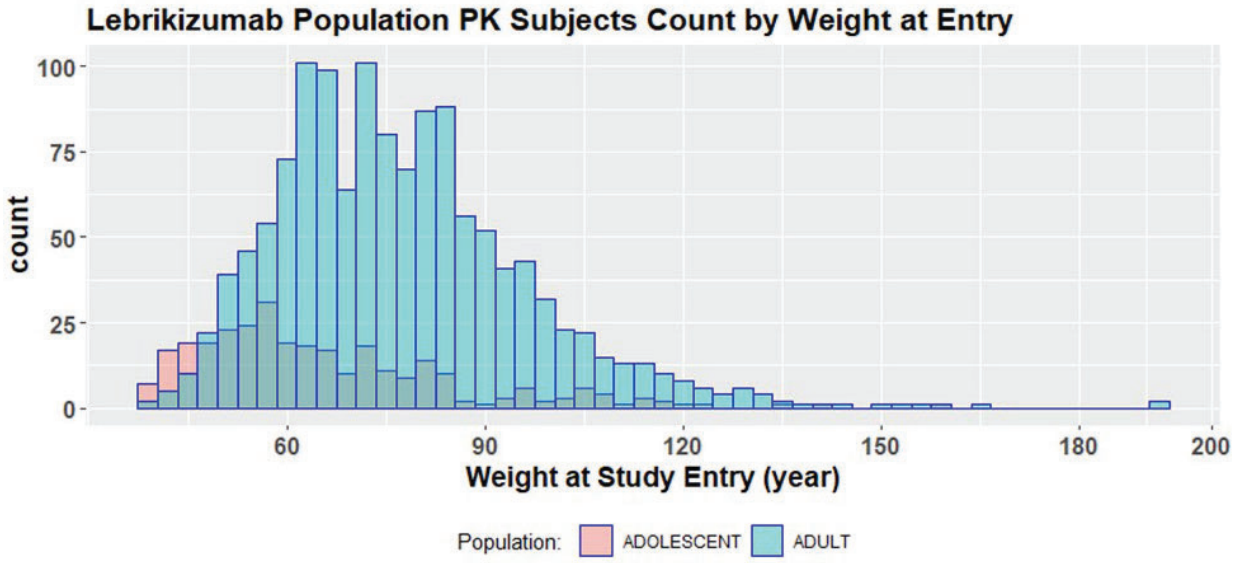
(b) (4)

Figure 23. Virtual patient simulations to 52 weeks, Induction period dosing followed by 250 mg Q2W maintenance-period dosing (plot A) or 250 mg Q4W maintenance-period dosing (plot B), adult versus adolescent participants (N = 500 participants, for each population category and dosing regimen)



Lines represent medians, and shaded areas represent 5th and 95th percentiles, of simulated values at each time point.

Figure 24. Distribution of body weight at baseline for adolescents and adults in the PK population



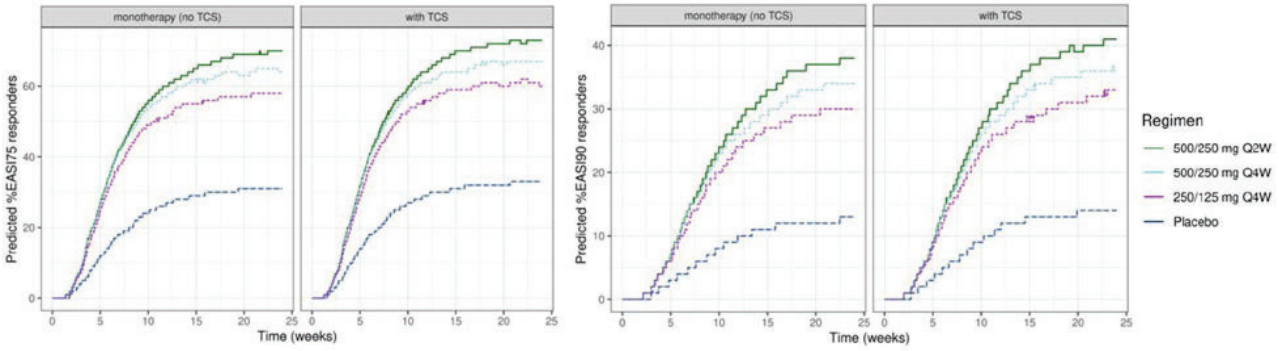
Exposure-Response Analyses

To allow for adequate exposure-response analysis, the Applicant developed a PK-PD model as summarized in **Table 96**. The model was determined as adequate and predictive model. The model's validity was supported by the agreement between observed and simulated EASI response after longer term dosing, even though only data up to Week 16 were used in the model development. Hence, it is reasonable to use the PK-PD model for simulation of E-R relationship for different dosing scenarios. To support the Sponsor's proposed dose recommendations, simulations were performed to describe E-R relationship using various EASI responses as endpoints for different dosing regimen and treatment duration. The Applicant's E-R analysis has been summarized below.

Applicant's summary of E-R analysis based on PK-PD model:

- The longitudinal EASI response to lebrikizumab exposure was well described by the final PK-PD indirect effect model which included a drug effect, placebo effect, and time-varying TCS effect. The model-estimated half maximal effective concentration (EC50) was 16.5 µg/mL (95% CI, 9.84 - 27.6 µg/mL). The effect of TCS usage (whether transitory or consistent) was small. Without TCS, the EASI turnover rate was 19.1 days compared to 17.7 days with TCS usage. The model did not identify any significant covariates affecting E-R relationship; hence no dose adjustment based on extrinsic or intrinsic factors is recommended.
- The typical baseline EASI score varied across five studies with the lowest baseline observed for KGAG (25.4, 95% CI 14.4 - 36.4), the next highest for patients in the KGAF and KGAD studies (26.8, 95% CI 15.8 - 37.8), and the highest baseline in patients in the KGAB and KGAC studies (29.0, 95% CI 18 - 40). A study effect on baseline was stratified into these three groups.
- No significant covariates were identified by the PK-PD model. Note that BW was also reevaluated in the PK-PD model but was not found to be a statistically significant covariate.
- The final PK-PD model was used to simulate different dosing scenarios with or without daily TCS use to illustrate dose-response during induction period and maintenance period up to Week 52 to support the proposed dosing regimens. Eczema Area and Severity Index (EASI) 50, 75, and 90 (EASI 50, EASI 75, EASI 90) and percent change in EASI from baseline were used as the response variables. Simulation showed that induction regimen of 500 mg lebrikizumab at Week 0, 2, then 250 mg Q2W up to Week 16 (last induction dose was at Week 14) predicted to have achieved a high level of efficacy with rapid onset compared to other induction regimens with or without TCS use (**Figure 25**). This induction regimen as proposed by the Applicant is reasonable. Furthermore, simulation up to Week 24 of maintenance treatment with continued induction dosing regimen showed that EASI 75 and 90 curves start to flatten for all regimens after Week 16. Continued 250 mg Q2W regimen would only provide approximately 3 – 4% more patients achieving EASI 75 or 90 between Week 16 and 24. EASI 75 and 90 response rates were numerically higher for Q2W regimen compared to that of Q4W.
- The estimated effect of concomitant use of TCS was small compared to the lebrikizumab effect. At Week 16 for the 250 mg Q2W regimen, the percentage of patients achieving EASI 75 was estimated as 66% for lebrikizumab monotherapy, compared with 70% for lebrikizumab with daily TCS use. The percentage of patients achieving EASI 90 was estimated as 34% for lebrikizumab monotherapy, compared with 37% for lebrikizumab with daily TCS use. Therefore, the incremental effect of daily TCS use was approximately 3% to 4% for EASI 75 and 90 (**Figure 25 and Table 101A-B**).

Figure 25. Simulations using final PK-PD model for various induction dosing regimens to illustrate the lebrikizumab dose-response for EASI 75 and EASI 90, with or without daily use of TCS. Simulations show dosing up to Week 24



Regimen refers to the loading dose followed by the treatment regimen. 500/250 mg Q2W: two loading doses of 500 mg Q2W followed by 250 mg Q2W; 500/250 mg Q4W: single loading dose of 500 mg followed by 250 mg Q4W; 250/125 mg Q2W: single loading dose of 250 mg followed by 125 mg Q4W.

Source: **m2.7.2 Summary of Clinical Pharmacology, page 58.**

Table 101104. Week 16 and 24 simulations using final PK-PD model of various induction dosing regimens, with and without daily use of TCS. Percentage of patients achieving EASI 50, 75, and 90 at week 16 (A) and week 24 (B) from the simulations is shown.

A.

Regimen[a]	TCS	Median EASI	% Achieving EASI-50	% Achieving EASI-75	% Achieving EASI-90	Median Cmin
Placebo	monotherapy (no TCS)	12.30	56	30	12	0.00
Placebo	with TCS	11.40	60	32	13	0.00
250/125 mg Q4W	monotherapy (no TCS)	6.10	82	56	27	17.40
250/125 mg Q4W	with TCS	5.56	83	59	29	17.40
500/250 mg Q4W	monotherapy (no TCS)	5.18	86	61	30	34.70
500/250 mg Q4W	with TCS	4.78	87	64	34	34.70
500/250 mg Q2W	monotherapy (no TCS)	4.66	89	66	34	83.40
500/250 mg Q2W	with TCS	4.24	91	70	37	83.40

B.

Regimen[a]	TCS	Median EASI	% Achieving EASI-50	% Achieving EASI-75	% Achieving EASI-90	Median Cmin
Placebo	monotherapy (no TCS)	11.70	57	31	13	0.00
Placebo	with TCS	10.90	60	33	14	0.00
250/125 mg Q4W	monotherapy (no TCS)	5.69	82	58	30	17.40
250/125 mg Q4W	with TCS	5.23	83	60	33	17.40
500/250 mg Q4W	monotherapy (no TCS)	4.77	85	64	34	34.70
500/250 mg Q4W	with TCS	4.36	87	67	36	34.70
500/250 mg Q2W	monotherapy (no TCS)	4.07	90	70	38	83.40
500/250 mg Q2W	with TCS	3.73	91	73	41	83.40

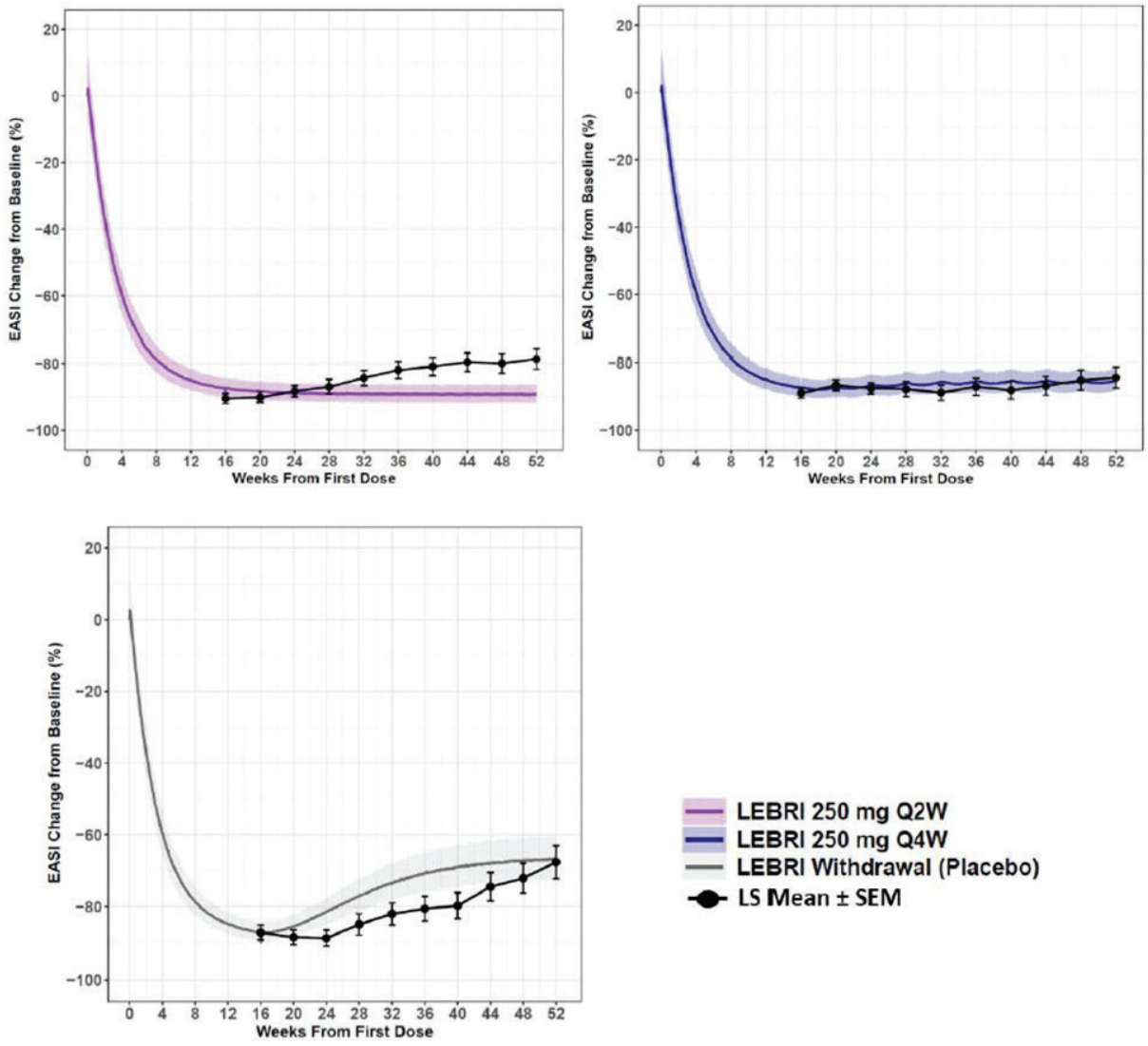
Abbreviations: EASI = Eczema Area and Severity Index; EASI 50 = 50% EASI reduction, EASI 75 = 75% EASI reduction, EASI 90 = 90% EASI reduction, Q4W = every 4 weeks; Q2W = every 2 weeks; TCS = topical corticosteroid.

[a] The induction regimens were: 500/250 mg Q2W: loading doses of 500 mg at Weeks 0 and 2 followed by 250 mg Q2W; 500/250 mg Q4W: single loading dose of 500 mg followed by 250 mg Q4W; 250/125 mg Q2W: single loading dose of 250 mg followed by 125 mg Q4W.

Source: Adapted from population PK/PD report ((b) (4) modeling report), m5.3.3.5, seq0001, page 157-8.

- Though the PK-PD model included data up to Week-16, the simulation of maintenance treatment up to Week 52 was performed using various dosing regimens to predict other clinical trial data. This can also serve as an external validation of the PK-PD model. The simulations of patients who responded at Week-16 after induction period and subsequently received 250 mg Q2W or Q4W or withdrew to placebo during maintenance period well described the observed data as presented in **Figure 26**. However, a slight model underprediction of lebrikizumab efficacy was seen for placebo withdrawal. To note, responders at Week 16 were those who had an IGA score of 0 or 1 or, at least a 75% reduction in EASI score from baseline to Week 16. Additionally, the simulations didn't account for TCS use, which was likely used in placebo withdrawal group, although a relatively small effect on the efficacy is expected from TCS use.

Figure 26. Model-simulated and observed EASI percent change from baseline profiles for Week 16 responders, separated by treatment, from Studies KGAB and KGAC combined



Note: Each maintenance regimen precedes an induction treatment with 500 mg lebrikizumab at Week 0 and 2 followed by 250 mg Q2W up to Week-16 (last dose was administered at Week 14).
Colored lines and shaded regions show median and 95% CI of simulated values, respectively, while black dots and lines represent clinical trial LS means +/- SEM (error bars) with Markov Chain Monte Carlo Multiple Imputation method. LS: least square; SEM: standard error of the mean. **Source**: m2.7.2 Summary of Clinical Pharmacology, page 61.

- Further simulations of patients who were either responders or non-responders at Week 16 for entire treatment period were conducted. For responders, the maintenance dosing regimens of 250 mg Q2W and Q4W predicted to have maintained high levels of response (-89% and -85% in terms of change in EASI) with responses overlapping between regimens. For non-responders, the EASI 75 response rates in maintenance phase were predicted to be numerically higher for Q2W versus Q4W (41% versus 26%), but with substantial overlap in the 95% CI for EASI 75 (**Table 102**).

Table 102105. Simulated Week 52 EASI percent change from baseline and EASI response rates for Week 16 responders and non-responders

Maintenance Dosing Regimen	Model Simulations		
	Mean EASI Change from Baseline % (95% CI)	EASI 75 % (95% CI)	EASI 90 % (95% CI)
Week 16 Responders at 52 Weeks			
250 mg Q2W	-89 (-92, -86)	88 (81, 95)	60 (49, 70)
250 mg Q4W	-85 (-88, -82)	80 (72, 88)	48 (38, 58)
Placebo	-67 (-72, -60)	48 (38, 59)	22 (14, 32)
Week 16 Non-responders at 52 Weeks			
250 mg Q2W	-66 (-72, -60)	41 (27, 56)	8 (0, 19)
250 mg Q4W	-57 (-64, -49)	26 (14, 42)	5 (0, 13)
Placebo	-21 (-32, -6)	5 (0, 12)	0 (0, 5)

Abbreviations: EASI = Eczema Area and Severity Index; CI = confidence interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Source: m2.7.2 Summary of Clinical Pharmacology, page 63.

- (b) (4)

Reviewer's Independent Analyses

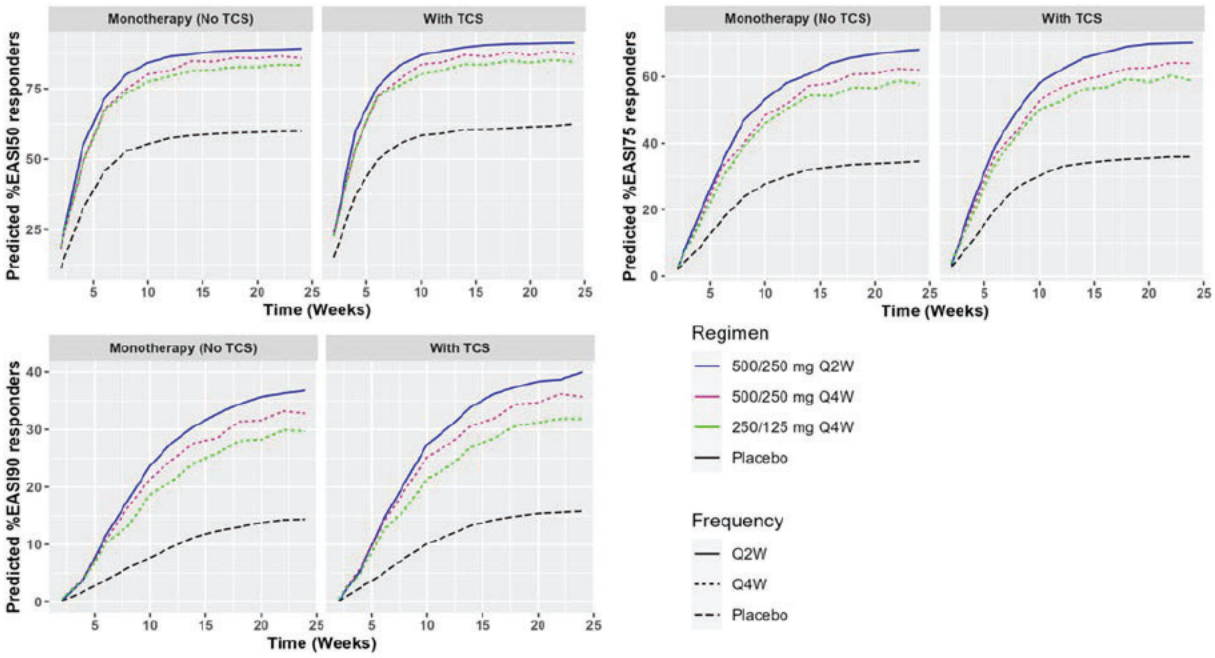
The PK-PD model was independently run by the reviewer. The resultant model parameter estimates are similar to those reported by the Applicant.

As implied in **Table 96**, the final PK-PD model was a well predictive model for the intended purpose. Hence, the reviewer has conducted a number of simulations to support the Applicant's justification of the recommended dosing regimen for the treatment of patients with moderate to severe AD.

Simulations of different dosing regimens with different loading doses were performed up to Week 24 to support the recommended SC dosing regimen of 500 mg lebrikizumab at Week 0 and 2 followed by 250 mg Q2W up to Week 16 for induction period. The simulations provided similar results as reported by the Applicant both for monotherapy and concomitant use of TCS. For 500 mg/250 mg Q2W regimen, a higher level of efficacy was attained rapidly compared to

other regimens, hence a reasonable dosing regimen for induction period. If Q2W regimen was continued beyond Week 16, it would provide 3-4% higher response rates between Week 16 and 24 in terms of EASI 75 and 90. In addition, Q2W regimen showed a marginally higher response rates over Q4W regimen at both Week 16 and 24. There was no apparent dose-response relationship noted between two of these regimens (**Figure 27** and **Table 103-104**). Use of concomitant TCS produced only ≤ 3% more effect compared to the lebrikizumab effect.

Figure 27. Simulated dose-response curves for lebrikizumab for EASI 50, EASI 75, and EASI 90, with and without daily use of TCS. Simulations show dosing up to Week 24



Source: Reviewer's plots based on simulation using the final PK-PD model

Table 103106. Summary of simulation results of Week 24 for EASI-50, EASI-75, and EASI-90 Achievement

Regimen	TCS	Median EASI	%Achieving EASI-50	%Achieving EASI-75	%Achieving EASI-90	Median Cmin
Placebo	monotherapy (no TCS)	11.41	60	33	12	0
Placebo	with TCS	9.91	61	35	14	0
250/125 mg Q4W	monotherapy (no TCS)	6.08	82	54	26	16.81
250/125 mg Q4W	with TCS	5.14	84	57	29	16.81
500/250 mg Q4W	monotherapy (no TCS)	5.55	85	58	29	33.6
500/250 mg Q4W	with TCS	4.64	86	61	32	33.2
500/250 mg Q2W	monotherapy (no TCS)	4.74	88	64	33	83.9
500/250 mg Q2W	with TCS	3.81	91	67	36	83.0

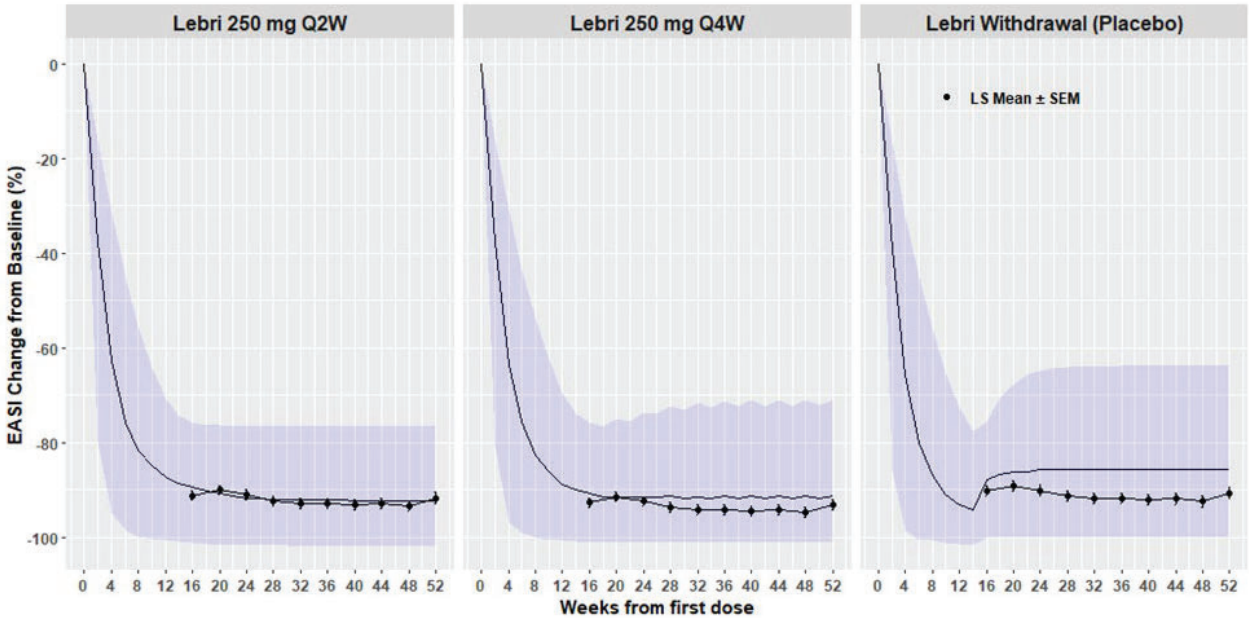
Table 104107. Summary of simulation results of Week 24 for EASI-50, EASI-75, and EASI-90 Achievement

Regimen	TCS	Median EASI	%Achieving EASI-50	%Achieving EASI-75	%Achieving EASI-90	Median Cmin
Placebo	monotherapy (no TCS)	11.2	60	35	14	0
Placebo	with TCS	9.73	63	36	16	0
250/125 mg Q4W	monotherapy (no TCS)	5.52	83	58	30	16.75
250/125 mg Q4W	with TCS	4.75	85	59	32	16.82
500/250 mg Q4W	monotherapy (no TCS)	4.87	86	62	33	33.6
500/250 mg Q4W	with TCS	4.12	87	64	36	33.1
500/250 mg Q2W	monotherapy (no TCS)	4.11	89	68	37	83.8
500/250 mg Q2W	with TCS	3.57	91	70	40	83.0

The reviewer also conducted simulations using different maintenance regimens to assess the model's ability to predict EASI response to Week 52. The induction regimen (500 mg at Week 0, 2, then 250 mg Q2W up to Week 16) was the same proposed by the Applicant. During the maintenance regimen, the patients who responded at Week 16 were either switched to 250 mg Q2W or Q4W or placebo without use of TCS. Simulated percent change in EASI score from baseline versus time profiles for different regimens indicate that predicted % change in EASI score is in agreement with observed data, suggesting the model's adequacy and usefulness to predict data for different clinical trials. However, for Q4W and placebo withdrawal group, a slight model-predicted underestimation was observed (**Figure 28**).

To note that observed data overlaid on the simulated plots are not based on Markov Chain Monte Carlo-Multiple Imputation (MCMC-MI), the approach used by the Applicant. Hence, the difference in the observed data with that of the Applicant is possible. But the predicted EASI score change still adequately describes the observed data over the entire maintenance period which was not included in the PK-PD model. It should also be noted that the 90% CI for simulated data is greatly wider than what was reported by the Applicant, the reason of which is not clear. The reviewer considered a cutoff of lower 2.5 percentiles and upper 97.5 percentiles data to estimate 95% CI, a reasonable approach to present 95% CI limit for simulated data.

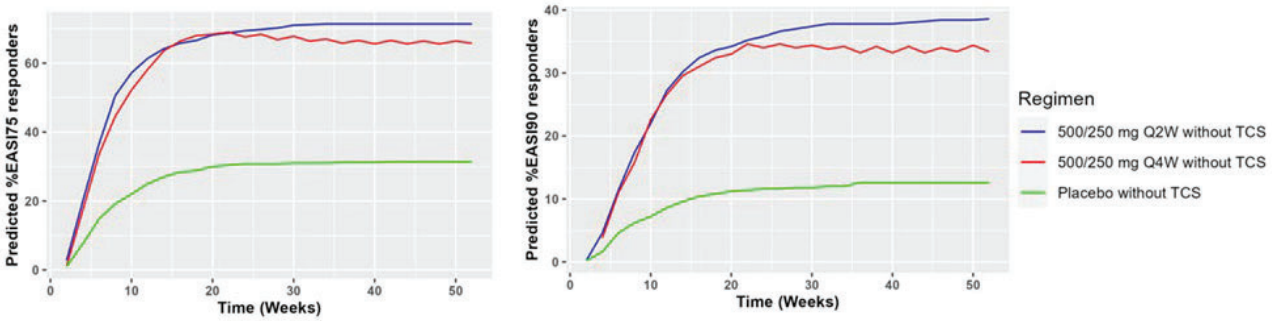
Figure 28. Model-simulated and observed EASI percent change from baseline profiles for Week 16 responders, separated by treatment, from Studies KGAB and KGAC combined



Solid black line indicates median and shaded blue indicates 95% CI for simulated % change of EASI from baseline. The line with dots represents observed LS mean with SEM. Observed data of KGAB and KGAC were sourced from *kgab_pkpd_nm_intrm2_prd_20220622.xpt and kgac_pkpd_nm_intrm2_prd_20220623.xpt*

Though the simulations did not account for TCS use which is likely, its effect is small as presented in **Table 103** and **104**. Further simulations of all patients (non-responders and responders) provided 71% (95% CI: 67 – 75) and 66% (95% CI: 61 – 70) patients achieving EASI 75 at Week 52 for Q2W and Q4W maintenance regimen, respectively (**Figure 29**). This translated lower efficacy is expected as all patients were considered and most of those who were non-responders at Week 16 remained so at Week 52 as well. Nevertheless, the efficacy between Q2W and Q4W regimen is comparable with approximately 5 – 6% more patients achieving the primary endpoint in Q2W arm. This supports the proposed dosing regimen of using both 250 mg Q2W or Q4W during maintenance treatment period for the patients who achieved adequate response during induction period.

Figure 29. Simulations of predicted EASI 75 and 90 in patients receiving 250 mg Q2W or Q4W during maintenance period



Reviewer's Comments

The Applicant's PopPK and PK-PD models were adequate to describe the PK of lebrikizumab and exposure-response relationship, hence suitable for simulating different scenarios. Based on PK-PD simulations, the induction treatment with 500 mg lebrikizumab at Week 0 and 2 (loading doses) followed by 250 mg Q2W up to Week 16 attained higher efficacy with its rapid onset compared to other induction regimens. Subsequent simulations using different maintenance dosing regimens showed comparable effectiveness of 250 mg Q2W and Q4W regimens starting from Week 16. All endpoints (e.g., EASI 50, 75, 90, and percent change in EASI score from baseline) included in the E-R analysis supports both Q2W and Q4W as potential maintenance treatment regimens.

The reviewer noted that the Applicant's predicted percentage change of EASI score versus time plots demonstrated a narrow confidence interval as opposed to the reviewer's CI estimated based on lower 2.5% and upper 97.5% percentiles cutoff of simulated data. The reason for discrepancy is unclear but it does not affect the overall trend of ER relationship.

Conclusion

The final PopPK model adequately described concentration-time profiles of lebrikizumab. The steady state exposures (median Cmax, Ctrough, Cavg) were 2- fold higher following 250 mg Q2W regimen than those of Q4W, implying the linear PK characteristics of lebrikizumab. No covariates other than body weight were found to have significant impact on the lebrikizumab PK. The median Cavg,ss following 250 mg Q2W dosing was 24% lower for the highest BW quartile while 33% higher for the lowest BW quartile compared to the population median. The impact of BW on lebrikizumab exposure is not clinically significant given the lack of dose-response relationship over a wider exposure range resulting from Q2W and Q4W treatment.

PopPK estimated 17 - 21% higher exposure in adolescents than that of adults, which can be attributed to lower body distribution for adolescents. The PopPK model estimated mean t1/2 was 24.5 days and bioavailability after SC dosing was 85%.

The final PK-PD model was an indirect effect model that well described the longitudinal EASI response to lebrikizumab with or without topical corticosteroids (TCS) usage. The maximum effect (Emax) was estimated to be 0.831 (95% CI, 0.761 – 0.883) and the half maximal effective concentration (EC50) was 16.5 µg/mL (95% CI, 9.84 – 27.6 µg/mL). There was a small effect of TCS use on the percentage change in EASI score from baseline. The model was adequate and validated to describe the observed EASI score, hence suitable to perform simulations in support of different dosing regimens. No covariates were identified as significant to impact exposure-response (E-R) relationship.

Simulations demonstrated that two loading doses of 500 mg lebrikizumab at Week 0 and 2 followed by 250 mg every two weeks (Q2W) up to Week 16 (induction period, last dose was at Week 14) produced rapid and greater responses compared to other dosing regimens with different loading doses. The response reached plateau after Week 16 for all dosing regimens. There were only a 3-4% higher response rates seen between Week 16 and 24 for 250 mg Q2W regimen. Simulations of responders at Week 16 switching to maintenance regimens of 250 mg Q2W, Q4W, or placebo up to Week 52 indicated that the efficacy rates were comparable between Q2W and Q4W treatment regimen with a small numerically higher rates in favor of Q2W. The placebo withdrawal group maintained efficacy for long-term with a gradual and smaller decline over time. Overall, the (b) (4) dosing regimens of 500 mg lebrikizumab at Week 0 and 2 followed by 250 mg Q2W up to Week 16 (induction treatment) and thereafter either 250 mg Q2W or Q4W maintenance regimen for responders at Week 16 are supported by the PK-PD analysis.

(b) (4)

19.5. Additional Clinical Outcome Assessment Analyses

[Add Text and Figures/Tables Here]

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