NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement – Dosing Regimen
Application Number(s)	BLA 761306 / S-006
Priority or Standard	Standard
Submit Date(s)	August 12, 2025
Received Date(s)	August 12, 2025
PDUFA Goal Date	June 12, 2026
Division/Office	DDD/OII
Review Completion Date	TBD
Established/Proper Name	lebrikizumab
(Proposed) Trade Name	EBGLYSS
Pharmacologic Class	anti-Interleukin-13 (IL-13) monoclonal antibody
Code name	TNX-650/MILR1444A/LY3650150
Applicant	Eli Lilly and Company
Dosage form	Solution for injection
Applicant proposed Dosing Regimen	250 mg every 4 weeks or every 8 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of adults and pediatric patients 12 years of age and older who weigh at least 40 kg 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	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adults and pediatric patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	24079001 |Atopic dermatitis (disorder)|
Recommended Dosing Regimen	500 mg (two 250 mg injections) at Week 0 and Week 2, followed by 250 mg (one injection) every 2 weeks until Week 16 or later, when adequate clinical response is achieved. The maintenance dose of EBGLYSS is 250 mg every 4 weeks or 250 mg every 8 weeks.

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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 (EBGYLSS) is an immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that binds to interleukin (IL)-13 and inhibits IL-13 signaling. It received FDA approval on September 13, 2024 for the treatment of adult and pediatric patients 12 years of age and older who weigh at least 40 kg with moderate to severe atopic dermatitis (AD) and whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. EBGLYSS can be used with or without topical corticosteroids. 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 (Q2W) until Week 16 or later, when adequate clinical response is achieved. The maintenance dose is EBGLYSS 250 mg every 4 weeks (Q4W).

With this supplement, the Applicant proposes to update subsection 2.2 Recommended Dosage of the EBGLYSS United States Prescribing Information (USPI) to include an additional maintenance dosing option of lebrikizumab 250 mg every 8 weeks (Q8W):

> The recommended dosage of EBGLYSS is an initial dose of 500 mg (two 250 mg injections) at Week 0 and Week 2, followed by 250 mg every two weeks until Week 16 or later, when adequate clinical response is achieved. The maintenance dosage of EBGLYSS is 250 mg every four weeks *or every eight weeks*.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Through exposure-efficacy response modeling and supportive clinical data from 103 subjects (adults [n = 63] and adolescents [n = 40]), the Applicant provided evidence that a maintenance dose of lebrikizumab (EBGYLSS) 250 mg Q8W will have similar effects in adult and adolescent subjects who weigh at least 40 kg with moderate to severe AD who receive a 250 mg Q4W maintenance dose.

The Applicant demonstrated that the lebrikizumab maintenance dosing option of lebrikizumab 250 mg every 8 weeks is effective for its intended use in the target population, and met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Lebrikizumab (EBGYLSS) is an immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that binds to interleukin (IL)-13 and inhibits IL-13 signaling. 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. Other clinical features of AD include erythema, oozing and crusting, and lichenification. Pruritus is a hallmark of the condition and responsible for much of the disease burden for patients and their families.

Through the Model-Informed Drug Development (MIDD) program, the Applicant developed pharmacokinetic/pharmacodynamic (PK/PD) models and conducted comprehensive exposure-efficacy response modeling and simulations using both EASI and IGA endpoints to provide primary efficacy evidence for the 250 mg every 8 week (Q8W) maintenance dosing. To support these models and exposure-response analyses, observed clinical data from Study J2T-DM-KGAA Addendum 11 (Addendum 11) were submitted.

Study J2T-DM-KGAA (KGAA) was a 100-week, randomized, open-label, 2-arm, parallel-group, multicenter, phase 3 trial to assess the long-term safety and efficacy of lebrikizumab 250 mg every 2 weeks (Q2W) and lebrikizumab 250 mg every 4 weeks (Q4W) in adult and adolescent subjects ages 12 to <18 years who weigh ≥40kg, with moderate to severe AD. Subjects could directly enter Study KGAA, or those who completed one of the lebrikizumab parent trials were offered the opportunity to enroll in Study KGAA.

KGAA Addendum 11 extended the treatment period by an additional 32 weeks to allow for assessment of the lebrikizumab 250 mg Q8W maintenance dosing regimen. Subjects in Study KGAA who completed treatment with open-label lebrikizumab 250 mg Q2W or 250 mg Q4W had the opportunity to continue in Addendum 11 where they were randomized 1:1 to open-label lebrikizumab 250 mg Q4W or Q8W. The observed clinical data were used as a comparison for simulated steady state Q8W concentrations to support the prediction from the exposure-response analyses.

Through the exposure-efficacy response modeling and supportive clinical data from 103 subjects (adults [n = 63] and adolescents [n = 40]) who enrolled in KGAA Addendum 11, the Applicant demonstrated that the lebrikizumab maintenance dosing option of lebrikizumab 250 mg every 8 weeks is effective for its intended use in the target population and that the Q8W dosing option appears to have a safety profile that is consistent with the known safety profile of lebrikizumab 250 mg Q2W and 250 mg Q4W which was based on a large integrated safety database from two replicate adequate and well-controlled monotherapy trials plus one TCS-combination trial (refer to multidiscipline review under BLA 761306).

A maintenance dose of lebrikizumab (EBGYLSS) 250 mg Q8W does not appear to change the benefit-risk profile of lebrikizumab in the treatment of adults and pediatric patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Therefore, approval is recommended for BLA 761306/S-006 to add an additional maintenance dose option of 250 mg Q8W for the treatment of moderate to severe atopic dermatitis in adults and pediatric patients 12 years of age and older who weigh at least 40 kg and whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

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 phototherapy may vary according to the type of phototherapy and can include actinic	Lebrikizumab was 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 represents an alternative to dupilumab and tralokinumab for systemic treatment of moderate-to-severe AD, especially in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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).	adolescents, as JAK inhibitors are reserved for more refractory cases. Corticosteroids, although approved, are not generally recommended for longer term use in this indication.
Benefit	• Through exposure-efficacy response modeling and supportive clinical data from 103 subjects (adults [n = 63] and adolescents [n = 40]) enrolled in Study KGAA Addendum 11, the Applicant provided evidence that a maintenance dose of lebrikizumab (EBGYLSS) 250 mg Q8W will have similar effects in adult and adolescent subjects who weigh at least 40 kg with moderate to severe AD who receive a 250 mg Q4W maintenance dose.	The Applicant demonstrated that the lebrikizumab maintenance dosing option of lebrikizumab 250 mg every 8 weeks is effective for its intended use in the target population, and met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval. At the individual patient level, an additional maintenance dosing option of lebrikizumab 250 mg

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		Q8W may allow for tailoring of posology to maintain clinical response with a less burdensome dosing regimen.
Risk and Risk Management	• The safety profile of lebrikizumab 250 ng Q8W observed in KGAA Addendum 11 was consistent with the known safety profile of lebrikizumab. No new safety risks have been identified.	No new risk mitigation measures beyond labeling and routine pharmacovigilance are recommended to manage the risk of this product.

1.4. Patient Experience Data

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

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	8.1 (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. Pruritus 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-4Ra. IL-13 receptor alpha 1 (IL-13Ra1) may then be recruited to form a signaling complex. IL-13 mediates its biological activity via binding to IL-13Ra1 and subsequent recruitment of IL-4Ra, 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). 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 pruritus, 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 adults and pediatric patients 12 years of age and older 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.

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 and ointments. 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

On September 13, 2024, Ebglyss received FDA approval for the treatment of moderate to severe atopic dermatitis (AD) in adult and pediatric patients 12 years of age and older who weigh at least 40 kg with and whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

3.2. Summary of Presubmission/Submission Regulatory Activity

During the original BLA review cycle, the Applicant had proposed, based on modeling and simulation, that some patients may maintain adequate clinical response with a maintenance dose of lebrikizumab 250 mg Q8W. However, this lower dosing regimen was not recommended for approval given the lack of clinical experience to support the reduced exposure.

Post-approval, through the Model-Informed Drug Development (MIDD) paired meeting program, the Applicant developed pharmacokinetic/pharmacodynamic (PK/PD) models.
Both meetings were conducted under IND 119866.

On May 15, 2024, MIDD Meeting #1 took place.
Key takeaways during this initial MIDD meeting, which focused on the development of the Eczema Area and Severity Index (EASI) and Investigator Global Assessment (IGA) models, included the following:

1. In the EASI75 model, the predicted response of the placebo withdrawal arm appeared to be lower than the observed data, and the treatment differences between Q2W and Q4W was larger than observed data. The Applicant (Sponsor at the time) stated that the differences were likely due to various factors such as the differences in the use of high potency topical corticosteroids (TCS) between three study arms. That current model did take into account general topical corticosteroid use; however, it did not include the range in potency.
   As an action plan, the Sponsor planned to refine the EASI and PK-IGA modeling and incorporate range in potencies for TCS with updated clinical data.

2. The Agency recommended that the Applicant explore the utility of Quantitative Systems Pharmacology (QSP) modeling in identifying the characteristics of the patient population who would benefit from Q8W dosing. Further, the QSP model may mechanistically represent the disease progression and the mechanism of action of lebrikizumab, providing mechanistic evidence to support the Q8W dosing.
   The Sponsor explained that they would explore these mechanisms with QSP approaches and provide updates to the QSP models.

3. The Agency agreed with the importance of obtaining comparative clinical data on the 250 mg Q8W maintenance regimen. An approach that combines clinical findings with modeling and simulation outcomes to support alternative dosing would be reasonable.

   To support the models and exposure-response analyses, the Applicant proposed to submit observed clinical data from Study J2T-DM-KGAA Addendum 11, a 32-week treatment period that was added to Study J2T-DM-KGAA (hereafter referred to as KGAA). KGAA was, at the time, an ongoing long-term, 100-week, randomized, open-label, 2-arm, parallel-group, multicenter, phase 3 trial to assess the long-term safety and efficacy of

lebrikizumab 250 mg Q2W and lebrikizumab 250 mg Q4W in adult and adolescent subjects ages 12 to <18 years who weigh ≥40kg, with moderate to severe AD. KGAA Addendum 11 allowed for assessment of the lebrikizumab 250 mg Q8W maintenance dosing regimen in subjects who completed treatment with open-label lebrikizumab 250 mg Q2W or 250 mg Q4W during Study KGAA and were subsequently randomized 1:1 to open-label lebrikizumab 250 mg Q4W or 250 mg Q8W.

However, for the proposed clinical data, one potential concern was that the patient population randomized may not be representative of the proposed population who would receive a maintenance regimen, as subjects in KGAA addendum would have completed 100 weeks or more of lebrikizumab treatment.

The Agency commented that the subjects from the original parent studies may be dropping out due to various reasons such as lack of efficacy or tolerability issues; therefore, the addendum population may not be the same responders after 16 weeks of lebrikizumab. The Agency recommended the Sponsor further characterize the patient population.

The Agency also recommended the Sponsor explore and review the topical steroid use between the two randomized arms (and investigate if high potency TCS has an impact on the observed clinical data of Q2W versus Q4W maintenance arms in the pivotal/parent phase 3 trials).

Additionally, the Sponsor may consider looking at the impact of difference in the populations between KGAA addendum and phase trials and stratify the output modeling data and overlay with the observed data.

The Applicant acknowledged the patient population that was randomized may not be representative of the proposed population who would receive the maintenance regimen as the subjects in the addendum have completed 100 weeks or more of lebrikizumab treatment. In designing the KGAA addendum, there was a longer duration of the lebrikizumab treatment that may be a limitation as patients were on lebrikizumab Q2W for 16 weeks before moving to maintenance treatment.

The Applicant pointed out that the patient population in the addendum is the same as the phase 3 trial population with respect to eligibility criteria and treatment. Once the addendum is fully enrolled, the Sponsor planned to compare the characteristics of patients who enter the addendum versus those who entered the maintenance in the phase 3 trials. They would also conduct simulations for PKPD models and QSP models using a population that matches the dosing history in the addendum to compare the results to the observed data.

4. The Agency pointed out that the open label nature of the KGAA addendum trial may limit the interpretability of the efficacy results and the ability of it to lend needed support of the modeling and simulation evidence. The Agency asked for any relevant information that supports the applicability of the findings generated in the KGAA addendum.

<u>On May 14, 2025, MIDD Meeting #2 took place</u>.
The Applicant addressed the aforementioned issues identified during the first MIDD meeting.
Additionally, since the first MIDD meeting, the Applicant further evaluated the models with data up to Week 100 from the Study KGAA.
Both models were used to simulate EASI and IGA responses over time under less-frequent dosing regimens, including a regimen with a Q2W Induction period followed by Q8W dosing.

Trial simulations were designed to reflect, as closely as possible, the study designs of the phase 3 ADvocate study, KGAA, and KGAA Addendum 11 to predict the expected response and provide evidence supporting an optional lebrikizumab Q8W dosing regimen.
Each simulation included the following:

- 16-week Induction period (250 mg Q2W)
- Maintenance period through Week 52
  - Placebo (PBO)
  - lebrikizumab 250 Q2W
  - lebrikizumab 250 mg Q4W
- "KGAA 100 Week" period from Week 52 through Week 152
  - PBO during maintenance →250 mg Q2W
  - non-PBO during maintenance → remained on dose
- 32-week "KGAA Addendum 11" period from Week 152 through Week 184
  - Q4W and Q8W dose intervals were simulated to predict the expected response from KGAA Addendum 11

Hence, the simulated regimens were as follows:

Regimen	Maintenance	KGAA 100 Weeks	KGAA Addendum 11
q2w.pbo.q2w.q8w	Placebo	Q2W	Q8W
q2w.q2w.q2w.q4w	Q2W	Q2W	Q4W
q2w.q2w.q2w.q8w	Q2W	Q2W	Q8W
q2w.q4w.q4w.q4w	Q4W	Q4W	Q4W
q2w.q4w.q4w.q8w	Q4W	Q4W	Q8W
q2w.q8w.q8w.q8w	Q8W	Q8W	Q8W

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

4.1. Office of Scientific Investigations (OSI)

The team recommended no OSI were needed for this supplement.

4.2. Product Quality

No new CMC information was submitted. Module 3 Sections 3.2.P.2.2 and 3.2.P.5.4 were updated with information for lots used for clinical study J2T-DM-KGAA. According to product quality assessors, Katherine Lukonin, Ph.D. and Kathryn King, Ph.D., all lots met batch release specifications, and no CMC issues were identified for these lots. These are routine lot release data; therefore, no action is indicated from a CMC perspective. See the CMC review uploaded to Panorama on February 23, 2026.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

Additional nonclinical studies were not needed to support this new supplement. No nonclinical information was submitted with this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking the approval of EBGLYSS [generic name: lebrikizumab (LY3650150)] for a newly proposed additional optional maintenance dosage of lebrikizumab 250 mg Q8W 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 previous submission in 2022 when it was initially submitted, which included a total of 13 clinical trials (six phase 1, three phase 2, and 4 phase 3 trials), and efficacy and safety were evaluated in 3 pivotal phase 3 trials which included adults and adolescents (aged 12 to less than 18 years who weigh at least 40 kg), while the phase 1 and 2 trials included adults only.

The proposed Q8W maintenance dosing regimen is primarily supported by comprehensive exposure-efficacy response models which were discussed and planned out in collaboration with FDA within the MIDD Paired Meeting Program. Supportive clinical data for Q8W maintenance dosing specifically comes from the Study J2T-DM-KGAA (Study KGAA) Addendum 11. Study KGAA Addendum 11 also provides supportive safety and immunogenicity data for this application.

Study KGAA was a 100-week, randomized, open-label, 2-arm, parallel-group, multicenter, phase 3 trial to assess the long-term safety and efficacy of lebrikizumab 250 mg Q2W and lebrikizumab 250 mg Q4W in adult and adolescent subjects ages 12 to <18 years who weigh ≥40kg, with moderate to severe AD.

KGAA Addendum 11 extended the treatment period by an additional 32 weeks to allow for assessment of the lebrikizumab 250 mg Q8W maintenance dosing regimen. Subjects in Study KGAA who completed treatment with open-label lebrikizumab 250 mg Q2W or Q4W had the opportunity to continue in Addendum 11 where they were randomized 1:1 to open-label lebrikizumab 250 mg Q4W or Q8W. The observed clinical data were used as a comparison for simulated steady state Q8W concentrations to support the prediction from the exposure-response analyses.

The clinical pharmacology program provided model informed drug development (MIDD) evidence to support the inclusion of the proposed Q8W posology in the lebrikizumab label. Overall, it established validated PK/PD modeling of the efficacy of Q2W and Q4W dosing regimens, using both EASI and IGA endpoints, based on the population PK database and this model was used to predict the efficacy of Q8W maintenance dosing.

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

Overall, the simulations produced by the exposure-efficacy response models indicate that lebrikizumab 250 mg Q8W dosing would provide clinically comparable maintenance of EASI 75 and IGA 0,1 response to Q4W dosing after 36 weeks of treatment. The Q8W modeling predictions are corroborated by the supportive clinical data from Study KGAA Addendum 11, which shows that after 32 weeks of treatment, participants achieved or maintained efficacy as measured by EASI 75 or IGA 0,1, with similar results between Q8W and Q4W treatment groups.

Recommendations
The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology information submitted under BLA 761306 S006 and finds the BLA approvable. The Applicant proposed maintenance dose of 250 mg every Q8W is recommended for approval.

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

The effectiveness of the maintenance dosage of EBGLYSS 250 mg every 8 weeks was established using longitudinal exposure-response modeling. Longitudinal exposure-response modeling predicted a maintenance dose of EBGLYSS 250 mg every 8 weeks consistent with EBGLYSS 250 mg every 4 weeks.

Lebrikizumab steady-state exposure following either a subcutaneous dose of 250 mg every 2 weeks, every 4 weeks, or every 8 weeks in patients with atopic dermatitis are presented in Table 1. Lebrikizumab exposure increases dose-proportionally over a subcutaneous dose range of 37.5 to 500 mg. The systemic exposures were at steady state at Week 4 following the approved recommended loading doses.

Table 1: Lebrikizumab Steady-State Exposure Following Subcutaneous Administration in Patients with Atopic Dermatitis

Lebrikizumab 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
250 mg every 8 weeks	43 mcg/mL	26 mcg/mL	11 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.

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 is 24.5 days and clearance is 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, as a monoclonal antibody, 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
The 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 through Week 16 or later, when adequate clinical response is achieved. The maintenance dose is EBGLYSS 250 mg every 4 weeks or 250 mg every 8 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 exposure	In clinical pharmacology studies under the original BLA submission, the PK of 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. A comprehensive MIDD approach was undertaken to establish exposure-response relationship models capable of reliably predicting clinical outcomes under various dosing regimens, including Q8W maintenance dosing.

To support these models and exposure-response analyses, observed clinical data from Study KGAA Addendum 11 were also submitted. KGAA Addendum 11 extended the treatment period by an additional 32 weeks to allow for assessment of the lebrikizumab 250 mg Q8W maintenance dosing regimen. Subjects in Study KGAA (long term open label safety and efficacy trial) who completed 100-week treatment with lebrikizumab 250 mg Q2W or Q4W had the opportunity to continue in Addendum 11 where they were randomized 1:1 to open-label lebrikizumab 250 mg Q4W or Q8W. The observed clinical data were used as a comparison for simulated steady state Q8W concentrations to support the prediction from the exposure-response analyses.

Lebrikizumab-treated participants in Study KGAA Addendum 11 achieved or maintained efficacy as measured by EASI 75 or IGA 0,1 at Week 32, with similar results between treatment groups at each visit. The clinical results support the MIDD evidence based on exposure-efficacy response modeling and simulation approaches.

A 2-compartment PopPK model with first-order absorption and linear clearance established previously (Initial BLA, PopPK report). Body weight was the only significant covariate on PK, consistent with the known effect for mAbs.

The model was used to predict individual PK from Study KGAA (100 weeks, Q2W and Q4W) and Study KGAA Addendum 11 (32 weeks, Q4W and Q8W). Predicted concentrations aligned with clinical data in Study KGAA Addendum 11, and individual PK parameters were used for ER analyses.

The model development process was iterative, incorporating feedback from the FDA to enhance overall model performance. Ultimately, 2 modeling approaches were leveraged to characterize the relationship between lebrikizumab exposure and EASI or IGA efficacy endpoints.

- 1st approach: A PK-EASI score model and a PK-IGA 0,1 model, each independently describes the exposure and corresponding efficacy relationship
- 2nd approach: A PK-EASI-IGA combined longitudinal ordered categorical model simultaneously describes the proportion of patients at each EASI category (EASI 100, 75, 50, or <50) or IGA score (0 to 4).

Model development dataset: more than 1300 participants with more than 13,000 EASI observations and more than 15,000 IGA observations from two Phase 2 trials, two monotherapy Phase 3 trials, and one Phase 3 trial with TCS combination therapy.

Model validation dataset: Study KGAA, a long-term 100-week extension study, included patients from the 3 above-mentioned Phase 3 trials, and new patients enrolled directly; Study KGAA Addendum 11 included patients receiving additional 32 weeks of either Q4W or Q8W maintenance dosing.

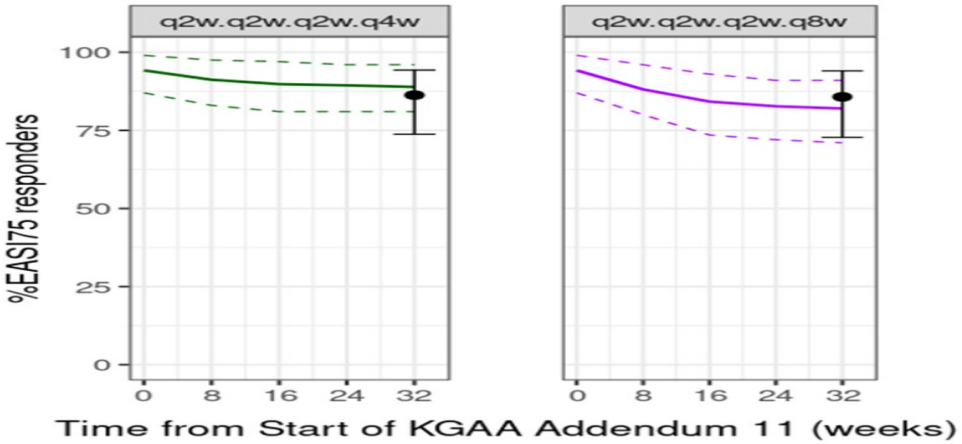
Model outcome: Both approaches consistently demonstrated a predictable EASI 75 and IGA 0,1 response to lebrikizumab in patients with moderate-to-severe AD.

- It is expected that the mean difference between lebrikizumab 250-mg Q4W and 250-mg Q8W maintenance regimens will be within 5% for EASI 75 and 7% for IGA 0,1 response rate.
- TCS or HP-TCS usage at any time during lebrikizumab treatment is not expected to impact EASI 75 or IGA 0,1 response rate.

PK-EASI Model:

Figure 1 provides a visual comparison between simulated and observed clinical Week 32, EASI 75 response from Study KGAA Addendum 11. The observed clinical data aligned with the model prediction, with overlapping 95% PI and 95% CI, supporting PK-EASI model as adequate for generating MIDD evidence to support a Q8W maintenance dosing regimen.

Figure 1: Independent PK-EASI model: simulated and observed clinical EASI 75 response rate at Week 32 following lebrikizumab 250 mg Q4W or Q8W dosing in Study KGAA Addendum 11.

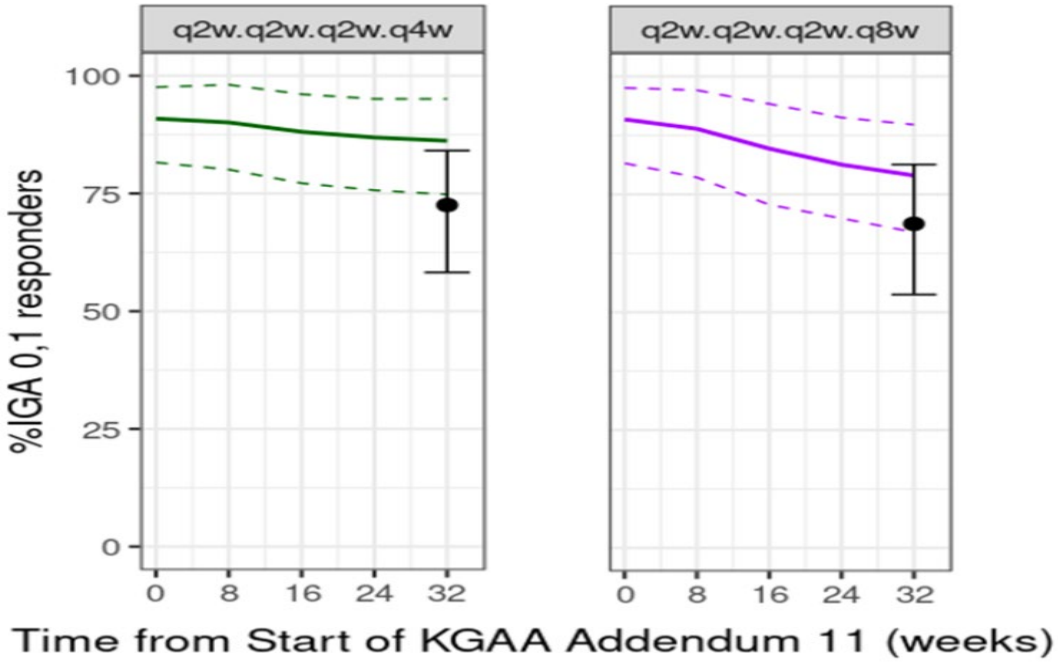


Abbreviations: CI = confidence interval; EASI = Eczema Area and Severity Index; PK = pharmacokinetic(s); Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.
Note: The dosing regimens were simulated starting at induction, including Week 16 responders and nonresponders. Simulation incorporated escape dosing per protocol, in which patients with less than EASI 50 transitioned to lebrikizumab Q2W. Simulated participants that, per-protocol, would have discontinued due to loss of or failure to achieve EASI 50 response were excluded. The solid line shows the mean percentage of responders over the 900 simulated trials. The dashed lines show the 2.5th and 97.5th percentiles over the 900 trials. The circle and whisker show the observed mean and 95% CI.
Source: Summary of Clinical Pharmacology, Figure 2.7.2.9, page 38

Independent PK-IGA 0,1 Model:

The predicted and observed IGA 0,1 response rates are summarized in figure 2 below. It provides a visual comparison between simulated and observed clinical Week 32 IGA 0,1 response from Study KGAA Addendum 11. While mean clinically observed data from Study KGAA Addendum 11 were lower than the predicted value, the 95% CI of observed clinical data overlapped with the 95% PI supporting that the final PK-IGA 0,1 model can be used to generate MIDD evidence to support an optional lebrikizumab 250 mg Q8W maintenance dosing regimen following a 16-week induction period with lebrikizumab 250 mg Q2W.

Figure 2: Independent PK-IGA 0,1 model: model-simulated and observed clinical IGA 0,1 response rate following lebrikizumab 250 mg Q4W or Q8W dosing in Study KGAA Addendum 11.



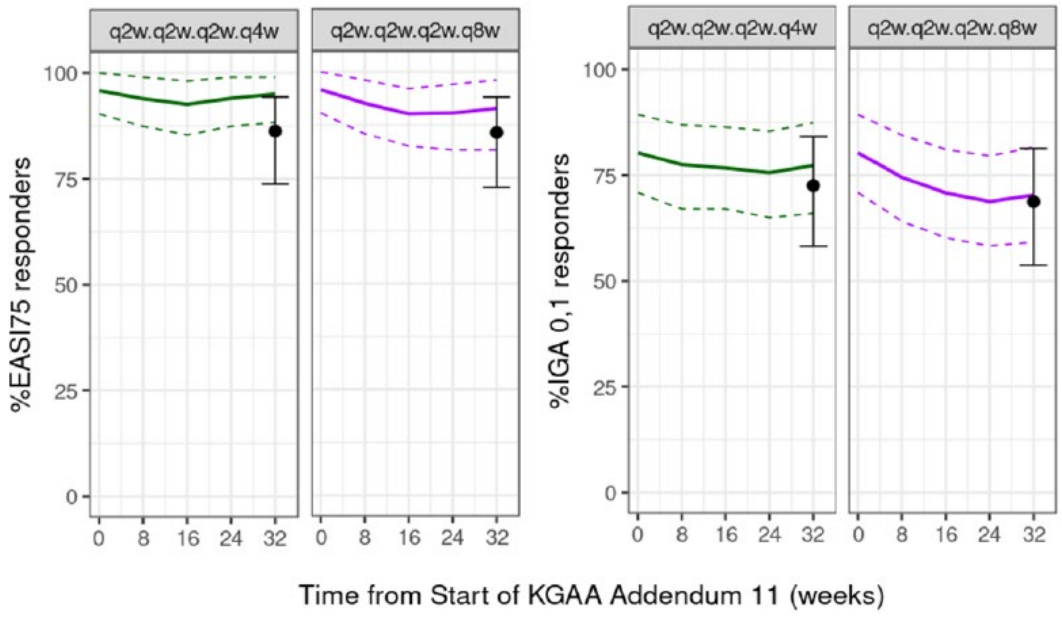
Abbreviations: CI = confidence interval; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; PK = pharmacokinetic(s); Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.
Note: The dosing regimens were simulated starting at induction, including Week 16 IGA 0,1 responders. Simulation did not incorporate escape dosing based on the protocol, in which patients with less than EASI 50 discontinued or transitioned to lebrikizumab Q2W after Week 16. The solid line shows the mean percentage of responders over the 900 simulated trials. The dashed lines show the 2.5th and 97.5th percentiles over the 900 trials. The circle and whisker show the observed mean and 95% CI.
Source: Summary of Clinical Pharmacology, Figure 2.7.2.15, page 50.

The simulated results were used to estimate the expected difference in percentage of responders between Q4W and Q8W dosing regimens at Week 52 (the end of the parent study), following 16-week induction based on the design of Phase 3 Studies KGAB and KGAC. The mean difference (95% PI) in the estimated IGA 0,1 response rate between lebrikizumab 250 mg Q4W and 250 mg Q8W maintenance dosing regimens was predicted to be 7.0% (1.5, 14.5).

PK-EASI-IGA Combined Model:

The PK-EASI-IGA combined model describes EASI response and IGA response in the same patient simultaneously, to allow simulations to reflect the study designs (that is, participants moving to escape arm or discontinuing if EASI 50 was not maintained during the maintenance phase) of the Phase 3 studies, including Studies KGAB, KGAC, KGAA, and KGAA Addendum 11, as closely as possible and to improve the model predictability.

Figure 3: PK-IGA-EASI combined model: overlay of simulated and observed clinical EASI 75 (left panel) or IGA 0,1 (right panel) response rate at Week 32 following lebrikizumab 250 mg Q4W or Q8W dosing for Study KGAA Addendum 11.



Abbreviations: CI = confidence interval; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; PK = pharmacokinetic(s); Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.
Note: The dosing regimens were simulated starting at induction, including Week 16 responders and nonresponders. Simulation incorporated escape per protocol, in which patients with less than EASI 50 discontinued or transitioned to lebrikizumab Q2W. The solid line shows the mean percentage of responders over the 900 simulated trials. The dashed lines show the 2.5th and 97.5th percentiles over the 900 trials. The circle and whisker show the observed mean and 95% CI.

Source: Summary of Clinical Pharmacology, Figure 2.7.2.24, page 69.

The combined model also adequately predicted available clinical observations in a validation dataset containing up to 100 weeks of additional lebrikizumab treatment data from the long-term extension Study KGAA, and the additional 32 weeks of treatment, including Q8W dosing in
Study KGAA.

Participants at Study KGAA Week 100 who entered Study KGAA Addendum 11 were re-randomized to receive open-label lebrikizumab, either 250-mg lebrikizumab Q4W or Q8W, for an additional 32 weeks. Simulation results for lebrikizumab treatment regimens of interest are summarized for Study KGAA Addendum 11 Week 32 in Figure 4 demonstrated the same endpoints over Study KGAA Addendum 11.

The expected difference in percentage responders between Q4W and Q8W dosing regimens at the end of Study KGAA Addendum 11 in participants who received Q2W dosing at the end of Study KGAA Week 100 were 3.75 (0.87, 6.84) for EASI 75 and 5.57 (2.51, 9.36) for IGA 0,1. Similar differences were expected for those who received Q4W before entering Study KGAA
Addendum 11.

The PK-EASI-IGA combined model simulated results were used to estimate the expected difference in percentage of responders between Q4W and Q8W dosing regimens at Week 52 (theend of the parent study), following 16-week induction. These were consistent with independent models, with overlapping PIs.

The mean difference (95% PI) of the estimated EASI 75 response rate between lebrikizumab 250 mg Q4W and 250 mg Q8W maintenance dosing regimens was predicted to be 4.1% (0.95, 7.58). The mean difference (95% PI) of the estimated IGA 0,1 response rate between lebrikizumab 250 mg Q4W and 250 mg Q8W maintenance dosing regimens was predicted to be 5.53% (1.94, 9.35).

Refer to section 8 and pharmacometrics review in Appendix 16.3 for more information.

Supportive clinical evidence:
The rationale for Study KGAA Addendum 11 was to add the Q8W maintenance dosing regimen for lebrikizumab. Hence, Study KGAA extended the study treatment period by an additional 32 weeks beyond the main protocol where Q8W dosing was evaluated. At the time of data cutoff, 86 participants completed the Safety Follow-Up period, and 14 participants were ongoing in the Safety Follow-up Period.

KGAA Addendum 11: Patients achieved or maintained efficacy of IGA or EASI at Week 32, with similar results between Q4W and Q8W dosing at each visit. The percentages of Q8W participants with IGA 0,1 or EASI 75 response at Week 32 were no more than 4% lower than the Addendum 11 baseline, consistent with the 7% and 5% variance predicted by the model.

Studies KGAB and KGAC: The placebo (lebrikizumab withdrawal) arm continued to demonstrate clinically meaningful results until Week 52. Thus, the outcomes of a 250-mg Q8W maintenance dose is expected to fall between the outcomes observed from withdrawal and observed efficacy with the Q4W dosing.

Refer to section 8 and pharmacometrics review in Appendix 16.3 for more information.

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

Yes. The proposed dosage of Week 0 and Week 2, followed by 250 mg (one injection) every 2 weeks until Week 16 or later, when adequate clinical response is achieved. The maintenance dose of EBGLYSS is 250 mg every 4 weeks ***or every 8 weeks***.

The initial induction dosing regimen and Q4W maintenance dosing regimen were approved under BLA 761306. In this submission, the Q8W as a new maintenance dosing regimen was proposed based on MIDD (PopPK and ER modeling and simulation) and supplemental clinical data from Study KGAA Addendum 11.

The model adequately predicts Q8W exposures, which are approximately 50% lower in average steady-state concentration compared to Q4W dosing, as validated against observed data from Study KGAA Addendum 11. The close agreement between predicted and observed concentrations supports the use of this model for generating individual exposure estimates for exposure-response analyses which would provide support to the proposed Q8W dosing as an alternative maintenance dosing option for Week 16 responders following Q2W induction.

Comprehensive population PK/efficacy analyses of lebrikizumab for the treatment of AD, using data from multiple Phase 2 and Phase 3 trials have been conducted through 2 approaches including 2 independent PK-EASI score and PK-IGA 0,1 models, and one PK-EASI-IGA combined model.

The simulations conducted using both approaches closely aligned with observed clinical data, reinforcing the models' reliability. The difference in efficacy between Q4W and Q8W dosing regimens was approximately a 5% mean difference in EASI 75 response rates and 7% mean difference in IGA response rates based on phase 3 trials KGAB and KGAC study design, demonstrating that Q8W dosing is a viable option for patients who are responders following Q2W induction.

Overall, Pop PK and ER modeling support Q8W as an alternative maintenance dosing option for Week 16 responders following Q2W induction.

Please refer to pharmacometrics review in appendix 16.3 for more information.

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 were included on clearance parameters and volume of distribution parameters, respectively, in the PopPK model.

Please refer to pharmacometrics review in appendix 16.3 for more information.

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?

In the original BLA submission, 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.

In the current submission, immunogenicity incidence and associated titers in lebrikizumab-treated participants were low. For Q8W dosing, 1 participant (2.9%) was TE-ADA positive. Due to the low incidence of TE-ADA, no evaluation of the relationship between immunogenicity and efficacy, safety, PK, or PD was done. These results are consistent with the results for Q2W and Q4W dosing presented in the original submission for AD.

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 bioanalytical method which was recently used (in Study KGAA Addendum 11) for the measurement of lebrikizumab serum concentrations has been reviewed earlier in 2023 (see unireview in DARRTS dated 09/28/2023, Reference ID: 5252985).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The primary data for this supplement are the PK-efficacy models (PK-EASI, PK-IGA, and PK-EASI-IGA), which utilized the totality of the lebrikizumab atopic dermatitis clinical development program data, most of which were reviewed as part of the initial BLA.
To support these models and exposure-response analyses, observed clinical data from **Study J2T-DM-KGAA Addendum 11** were submitted.

Study J2T-DM-KGAA (KGAA) titled "*A Long-term Study to Assess the Safety and Efficacy of Lebrikizumab in Patients with Moderate-to-Severe Atopic Dermatitis*", was a 100-week, randomized, open-label, 2-arm, parallel-group, multicenter, phase 3 trial to assess the long-term safety and efficacy of lebrikizumab 250 mg Q2W and lebrikizumab 250 mg Q4W in adult and adolescent subjects ages 12 to <18 years who weigh ≥40kg, with moderate to severe AD. Subjects could directly enter Study KGAA or those who completed one of the lebrikizumab parent studies listed below were offered the opportunity to enroll in Study KGAA.

- J2T-DM-KGAB (Study KGAB), a 52-week monotherapy study
- J2T-DM-KGAC (Study KGAC), a 52-week monotherapy study
- J2T-DM-KGAD (Study KGAD), a 16-week TCS combination study
- J2T-DM-KGAE (Study KGAE), a 52-week open-label adolescent safety study
- J2T-DM-KGAK (Study KGAK), a 16-week vaccine study.

Study KGAA subjects who completed a parent study were assigned treatment based on their treatment in their parent study, either lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W. Subjects who were receiving placebo in the parent study received a loading dose of 500 mg lebrikizumab at the time of Study KGAA enrollment (baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W. Placebo injections were used to maintain blinding of loading doses and Q4W dosing until unblinding, as applicable.

Direct entry subjects were assigned open-label treatment of 500 mg lebrikizumab administered at baseline and Week 2 (loading dose) followed by 250 mg lebrikizumab Q2W.

KGAA Addendum 11 extended the treatment period by an additional 32 weeks to allow for assessment of the lebrikizumab 250 mg Q8W maintenance dosing regimen. Subjects in Study KGAA who completed treatment with open-label lebrikizumab 250 mg Q2W or 250 mg Q4W had the opportunity to continue in Addendum 11 where they were randomized 1:1 to open-label lebrikizumab 250 mg Q4W or 250 mg Q8W. The observed clinical data were used as a comparison for simulated steady state Q8W concentrations to support the prediction from the exposure-response analyses.

Table 2: Listing of Clinical Trials Relevant to sBLA 761306/S-006

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	Studies to Support Efficacy and Safety as demonstrations of model predictability							
J2T-DM-KGAA (KGAA)	NCT04392154	Randomized, open-label, 2-arm, parallel-group, multicenter	Lebrikizumab 250 mg; Q2W or Q4W; SC	*Primary*: Proportion of subjects who discontinued from study treatment due to adverse events through the last treatment visit *Secondary*: -Proportion of subjects with a response of IGA 0,1 at each visit -Proportion of subjects achieving EASI-75 from baseline at each visit	110 weeks safety follow-up 12 weeks after the last dose	Randomized 1153 Completed 771 -Q2W: 668 -Q4W: 103	adult and adolescent subjects ages ≥12 to <18 years, who weigh ≥40kg with moderate to severe AD	199 centers that enrolled 1175 subjects in Australia, Bulgaria, Canada, Estonia, France, Germany, Latvia, Lithuania, Mexico, Poland, Singapore, South Korea, Spain, Taiwan, Ukraine, and the United States
J2T-DM-KGAA Adden-dum 11	Same as KGAA	Randomized open-label	Lebrikizumab 250 mg; Q4W or **Q8W**; SC	*Primary*: -Proportion of subjects who achieve IGA 0,1 or EASI-75 (≥75% reduction in EASI	32 weeks safety follow-up 12 weeks after the	Randomized 103 Completed 100 -Q8W: 49		55 centers that enrolled 103 subjects in Australia, Canada, South

				from baseline of parent study) at Week 32 Secondary: -Percent change from baseline in EASI scores, Patient Oriented Eczema Measure (POEM) scores, and body surface area (BSA), and the percentage of subjects achieving IGA 0,1 at each visit.	last dose	-Q4W: 51		Korea, Mexico, Singapore, Taiwan, and the United States

7.2. Review Strategy

The proposed lebrikizumab Q8W maintenance dosing regimen is primarily based on exposure-efficacy response models that were established based on the draft guidance for industry *M15 General Principles for Model-Informed Drug Development* (December 2024) and feedback from the Agency via the MIDD Paired Meeting Program.

Clinical data from Study KGAA were submitted to support the prediction from the exposure-response analyses and assist with validating the reliability of the models. Given model predictions are not being compared with KGAA 100-week responses to make a determination regarding the Q8W regimen, the primary focus of this review will be of the efficacy and safety results for the **KGAA Addendum 11** 32-week treatment period.

The sources of data used for the evaluation of the efficacy and safety for the proposed indication included trial reports and datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] submitted by the Applicant. This application was submitted in electronic common technical document format and entirely electronic. The electronic submission included direct links to protocols, as well as statistical analysis plans (SAPs), clinical trial reports, SAS transport datasets in Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM) format. The datasets were in the following network path:

Original Submission: \\CDSESUB1\evsprod\BLA761306\0157

The Applicant submitted the required certification and disclosure information for participating investigators (Form 3454). Refer to Section 19.2. Financial Disclosure of this review for additional information.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study KGAA Addendum 11

Trial Design

Study KGAA was a 100-week, randomized, open-label, 2-arm, parallel-group, multicenter, phase 3 trial to assess the long-term safety and efficacy of lebrikizumab 250 mg Q2W and lebrikizumab 250 mg Q4W in adult and adolescent subjects ages 12 to <18 years who weigh ≥40kg, with moderate to severe AD. Figure 4 presents the trial design schematic for Study KGAA. Subjects could directly enter Study KGAA or those who completed one of the lebrikizumab parent studies listed below were offered the opportunity to enroll in Study KGAA.

- J2T-DM-KGAB (Study KGAB), a 52-week monotherapy study
- J2T-DM-KGAC (Study KGAC), a 52-week monotherapy study
- J2T-DM-KGAD (Study KGAD), a 16-week TCS combination study
- J2T-DM-KGAE (Study KGAE), a 52-week open-label adolescent safety study
- J2T-DM-KGAK (Study KGAK), a 16-week vaccine study.

Study KGAA subjects who completed a parent study were assigned treatment based on their treatment in their parent study, either lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W. Subjects who were receiving placebo in the parent study received a loading dose of 500 mg lebrikizumab at the time of Study KGAA enrollment (baseline) and at Week 2 followed by 250 mg lebrikizumab Q2W. Placebo injections were used to maintain blinding of loading doses and Q4W dosing until unblinding, as applicable. Direct entry subjects were assigned open-label treatment of 500 mg lebrikizumab administered at baseline and Week 2 (loading dose) followed by 250 mg lebrikizumab Q2W.

KGAA Addendum 11 extended the treatment period by an additional 32 weeks to allow for assessment of the lebrikizumab 250 mg Q8W maintenance dosing regimen. Figure 5 presents the trial design schematic for KGAA Addendum 11. Subjects in Study KGAA who completed treatment with open-label lebrikizumab 250 mg Q2W or Q4W had the opportunity to continue in Addendum 11 where they were randomized 1:1 to open-label lebrikizumab 250 mg Q4W or Q8W. The randomization was stratified at the Addendum 11 baseline by IGA score (0,1 versus >1), and region (US versus non-US).

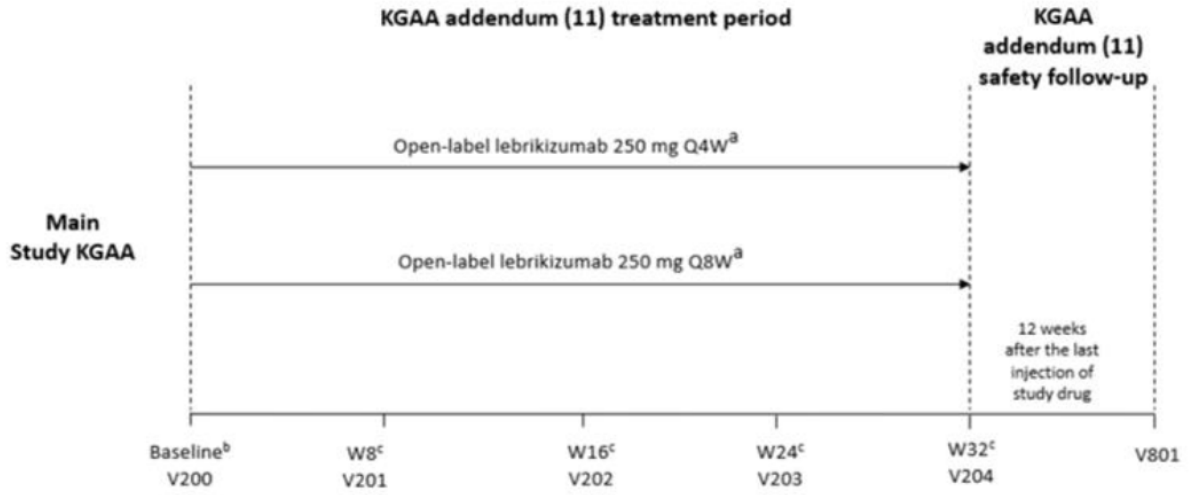
The protocol addendum did not specify any inclusion criteria based on disease severity (e.g., Investigator's Global Assessment [IGA] and Eczema Area and Severity Index [EASI]).

The protocol addendum specified that starting from Visit 201 (i.e., Week 8 of Addendum 11), subjects who do not maintain an EASI-50 response (from parent study baseline) will move to lebrikizumab 250 mg Q2W for the remainder of the addendum.

Figure 4: Trial Design Schematic for Study KGAA

Source: page 52 of the Clinical Study Report for Study KGAA.
Abbreviations: Q2W = every 2 weeks; Q4W = every 4 weeks; V = Visit; W = Week; wks = weeks.
[a] The treatment regimen assignment remained blinded until unblinding, except for participants who received open-label study drug. Placebo injections were used to maintain the blind and ensure all participants received the same number and frequency of injections. Some participants received a loading dose of lebrikizumab 500 mg at baseline and Week 2.
[b] Baseline (Visit 1) = parent study exit visit (excluding direct entry participants).
[c] Last injection of study drug = Week 98 or Week 96 depending on Q2W or Q4W dosing.

Figure 5: Trial Design Schematic for KGAA Addendum 11



Source: page 24 of the Clinical Study Report for Study KGAA Addendum 11.
Abbreviations: EASI = Eczema Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; W = week; V = visit.
[a] Starting at Visit 201 of this addendum, participants who do not maintain an EASI-50 response (from the parent study baseline) will move to lebrikizumab 250 mg Q2W dosing regimen for the remainder of this addendum.
[b] Participants may enter the addendum at Week 100 of Study KGAA, or after Week 100 of Study KGAA provided they have not yet completed the safety follow-up visit for Study KGAA.
[c] From KGAA Addendum (11) baseline.

Study Endpoints

The protocol addendum and statistical analysis plan (SAP) specified the following primary efficacy endpoints:

- Proportion of subjects who achieve IGA 0 or 1 at Week 32
- Proportion of subjects who achieve EASI-75 (≥75% reduction in EASI from baseline of parent study) at Week 32

The protocol addendum did not specify any secondary efficacy endpoints. The SAP specified the following secondary endpoints:

- Proportion of subjects with EASI-90, EASI-75 and EASI-50 (EASI-90, EASI-75 and EASI-50 calculated relative to EASI score from parent study baseline) at each visit
- Proportion of subjects with IGA of 0 or 1 at each visit
- Change and percent change from baseline in EASI score at each visit
- Change from baseline in Patient Oriented Eczema Measure (POEM) scores at each visit
- Change from baseline in Body Surface Area (BSA) at each visit

Statistical Analysis Plan

Analysis Populations:
The SAP specified the following analysis populations:

- Intent-to-Treat (ITT) Population: All subjects randomly assigned to treatment in the Addendum (11), even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Subjects will be analyzed according to the treatment to which they were assigned.
- Safety Population: All subjects who were randomized and received at least one dose of study treatment during the Addendum period will be included in the Safety Population.

Estimands:
The SAP specified the following as the main estimand for the primary efficacy endpoints:

- *Population*: defined through appropriate inclusion criteria to reflect the target patient population.
- *Treatment*: lebrikizumab 250 mg Q4W or Q8W
- *Variables of interest*: IGA (0,1) and EASI-75
- *Population-level summary*: response proportion in each treatment group
- *Handling of Intercurrent Events (ICEs)*:
  a) Treatment discontinuation due to lack of efficacy: composite strategy. Subjects who discontinue treatment due to lack of efficacy will be considered as treatment failures (non-responders).
  b) Treatment discontinuation due to any other reasons: a hypothetical strategy will be used to estimate what the response would have been if subjects continued with treatment.
  c) Dose modification to lebrikizumab 250 mg Q2W: composite strategy. Subjects whose dose is modified to lebrikizumab 250 mg Q2W will be considered as treatment failures (non-responders).

Analysis Method:
The SAP specified using descriptive statistics to summarize the efficacy results. The SAP stated: "No statistical tests will be performed."

Missing data and data after ICE of treatment discontinuation due to any reason other than lack of efficacy was specified to be imputed using multiple imputation (MI). The SAP specified using the Markov chain Monte Carlo (MCMC) method to impute the data 25 times within each treatment group independently.

8.1.2. Trial Results

Compliance with Good Clinical Practices

The Applicant stated that this trial was conducted in accordance with the protocol, consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable ICH Good Clinical Practices (GCP) Guidelines, and applicable laws and regulations.

Subject Disposition

A total of 103 subjects were enrolled and randomized in KGAA Addendum 11. Table 3 presents the subject disposition for KGAA Addendum 11. A total of 3 subjects discontinued treatment early. A higher proportion of subjects moved to lebrikizumab 250 mg Q2W in the Q8W group than the Q4W group (12% vs. 6%). The Applicant stated that one additional subject (KGAB-(b) (6)) met the criteria to be adjusted from Q4W to Q2W at Visit 203 (i.e., Week 24 of Addendum 11); however, due to data entry error in the Interactive Web-Response System (IWRS), the subject's dose was not adjusted, and the subject remained on Q4W dosing.

Table 3: Subject Disposition – KGAA Addendum 11 (ITT[1])

	Lebrikizumab 250 mg Q8W (N=51) n (%)	Lebrikizumab 250 mg Q4W (N=52) n (%)	Total (N=103) n (%)
Discontinued Treatment	2 (3.9)	1 (1.9)	3 (2.9)
Lost to follow-up	1 (2.0)	0	1 (1.0)
Protocol deviation	0	1 (1.9)	1 (1.0)
Withdrawal by subject	1 (2.0)	0	1 (1.0)
Dose modification to Q2W	6 (12)	3 (5.8)	9 (8.7)
Move to Q2W at Week 8	2 (3.9)	1 (1.9)	3 (2.9)
Move to Q2W at Week 16	0	1 (1.9)	1 (1.0)
Move to Q2W at Week 24	4 (7.8)	1 (1.9)	5 (4.9)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] Intent-to-Treat (ITT) population: all randomized subjects in KGAA Addendum 11.

Demographic and Baseline Disease Characteristics

Table 4 presents the demographics and baseline disease characteristics for KGAA Addendum 11. The demographics and baseline disease characteristics were generally balanced across the treatment arms.

Table 4: Demographics and Baseline Disease Characteristics – KGAA Addendum 11 (ITT[1])

Characteristic	Lebrikizumab 250 mg Q8W (N=51)	Lebrikizumab 250 mg Q4W (N=52)	Total (N=103)
Age (years)			
Mean (SD)	28.8 (15.3)	26.4 (13.7)	27.6 (14.5)
Median	25.0	22.0	23.0
Min, Max	12.0, 66.0	12.0, 65.0	12.0, 66.0
Categories, n (%)			
12 to < 18	18 (35.3)	22 (42.3)	40 (38.8)
≥ 18	33 (64.7)	30 (57.7)	63 (61.2)
Sex, n (%)			
Female	24 (47.1)	25 (48.1)	49 (47.6)
Male	27 (52.9)	27 (51.9)	54 (52.4)
Race, n (%)			

Characteristic	Lebrikizumab 250 mg Q8W (N=51)	Lebrikizumab 250 mg Q4W (N=52)	Total (N=103)
White	20 (39.2)	18 (34.6)	38 (36.9)
Asian	26 (51.0)	26 (50.0)	52 (50.5)
Black or African American	3 (5.9)	3 (5.8)	6 (5.8)
Other	2 (3.9)	5 (9.6)	7 (6.8)
Ethnicity, n (%)			
Hispanic or Latino	9 (17.6)	4 (7.7)	13 (12.6)
Not Hispanic or Latino	41 (80.4)	48 (92.3)	89 (86.4)
Not Reported	1 (2.0)	0 (0.0)	1 (1.0)
Country, n (%)			
United States	24 (47.1)	25 (48.1)	49 (47.6)
Outside United States	27 (52.9)	27 (51.9)	54 (52.4)
Baseline (Addendum 11)			
IGA Score, n (%)			
0 - Clear	15 (29.4)	17 (32.7)	32 (31.1)
1 - Almost Clear	18 (35.3)	17 (32.7)	35 (34.0)
2 - Mild	15 (29.4)	13 (25.0)	28 (27.2)
3 - Moderate	3 (5.9)	5 (9.6)	8 (7.8)
Baseline (Addendum 11)			
EASI Score			
Mean (SD)	3.0 (4.3)	2.4 (3.6)	2.7 (3.9)
Median	1.0	0.6	0.8
Min, Max	0.0, 16.8	0.0, 14.0	0.0, 16.8
Categories, n (%)			
EASI-75	42 (82.4)	44 (84.6)	86 (83.5)
Not EASI-75	9 (17.6)	8 (15.4)	17 (16.5)

Source: Statistical Reviewer's Analysis and Applicant's Analysis; ADSL.xpt
[1] Intent-to-Treat (ITT) population: all randomized subjects in KGAA Addendum 11.

Rescue Medication Use

Table 5 summarizes rescue medication use during KGAA Addendum 11. A total of 33 (32%) subjects used recue medication, with 19 (37%) of the subjects in the Q8W group and 14 (27%) of the subjects in the Q4W group requiring rescue medication.

Table 5: Summary of Rescue Medication Use – KGAA Addendum 11 (ITT[1])

	Lebrikizumab 250 mg Q8W (N=51) n (%)	Lebrikizumab 250 mg Q4W (N=52) n (%)	Total (N=103) n (%)
Subjects with ≥1 rescue medication	19 (37.3)	14 (26.9)	33 (32.0)
Topical therapy	19 (37.3)	13 (25.0)	32 (31.1)
Topical corticosteroids	19 (37.3)	10 (19.2)	29 (28.2)
Low-Moderate potency	8 (15.7)	7 (13.5)	15 (14.6)
High potency	13 (25.5)	5 (9.6)	18 (17.5)
Topical calcineurin inhibitor	4 (7.8)	5 (9.6)	9 (8.7)
Systemic treatment	2 (3.9)	1 (1.9)	3 (2.9)
Systemic corticosteroids	0	1 (1.9)	1 (1.0)
Immunosuppressants	2 (3.9)	0	2 (1.9)

Source: Adapted from Table KGAA.4.7 in Clinical Study Report for KGAA Addendum 11.
[1] Intent-to-Treat (ITT) population: all randomized subjects in KGAA Addendum 11.

Efficacy Results – Primary Endpoints

Table 6 presents the results of the primary efficacy endpoints for KGAA Addendum 11. These results are based on all randomized subjects. For both endpoints, the response rates were higher in the Q4W group.

Table 6: Results of the Primary Efficacy Endpoints – KGAA Addendum 11 (ITT[1,2])

Endpoint	Lebrikizumab 250 mg Q8W (N=51)	Lebrikizumab 250 mg Q4W (N=52)
IGA score of 0 or 1 at Week 32		
Response Rate	62.0%	73.0%
95% CI	(48.3%, 75.8%)	(60.9%, 85.1%)
EASI-75 at Week 32		
Response Rate	79.1%	86.2%
95% CI	(67.6%, 90.5%)	(76.8%, 95.7%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADIGAMC.xpt, ADEASIMC.xpt
[1] Intent-to-Treat (ITT) population: all randomized subjects in KGAA Addendum 11.
[2] Subjects who discontinued rescue therapy due to lack of efficacy or whose dose was modified to lebrikizumab 250 mg Q2W were considered non-responders. Data after treatment discontinuation due to any other reason were considered missing. Missing data was imputed using MI-MCMC.

As noted in Section 8.1.1, the protocol addendum did not specify any inclusion criteria based on disease severity (e.g., IGA and EASI). Table 7 presents the results for IGA score of 0 or 1 at Week 32 based on the subjects who were IGA responders at Week 0 (baseline of addendum). The table also presents the results for EASI-75 at Week 32 based on the subjects who were EASI-75 responders at Week 0 (baseline of addendum). For both endpoints, the response rates were higher in the Q4W group.

Table 7: Efficacy Results in Baseline Responders[1,2] – KGAA Addendum 11

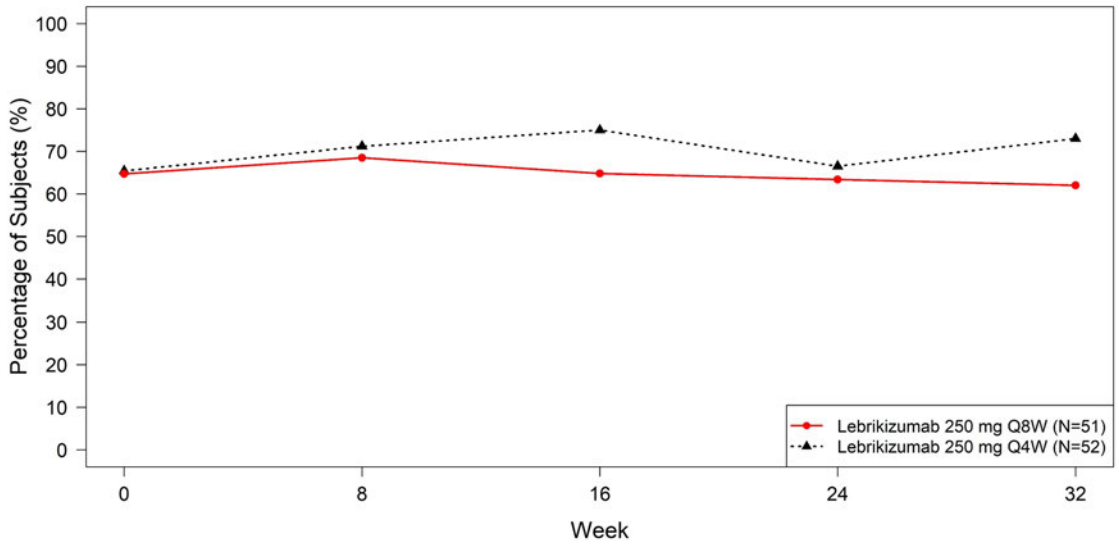
	Lebrikizumab 250 mg Q8W	Lebrikizumab 250 mg Q4W
Number of Subjects who were IGA Responders (IGA score of 0 or 1) at Week 0 [Baseline of Addendum]	**N=33**	**N=34**
IGA score of 0 or 1 at Week 32		
Response Rate	75.5%	94.0%
95% CI	(60.8%, 90.3%)	(85.9%, 100%)
Number of Subjects who were EASI-75 Responders at Week 0 [Baseline of Addendum]	**N=42**	**N=44**
EASI-75 at Week 32		
Response Rate	88.9%	95.1%
95% CI	(78.9%, 98.8%)	(88.5%, 100%)

Source: Statistical Reviewer's Analysis; ADSL.xpt, ADIGAMC.xpt, ADEASIMC.xpt
[1] All randomized subjects that had an IGA score of 0 or 1 OR EASI-75 at baseline of Addendum 11.
[2] Subjects who discontinued rescue therapy due to lack of efficacy or whose dose was modified to lebrikizumab 250 mg Q2W were considered non-responders. Data after treatment discontinuation due to any other reason were considered missing. Missing data was imputed using MI-MCMC.

Efficacy Over Time

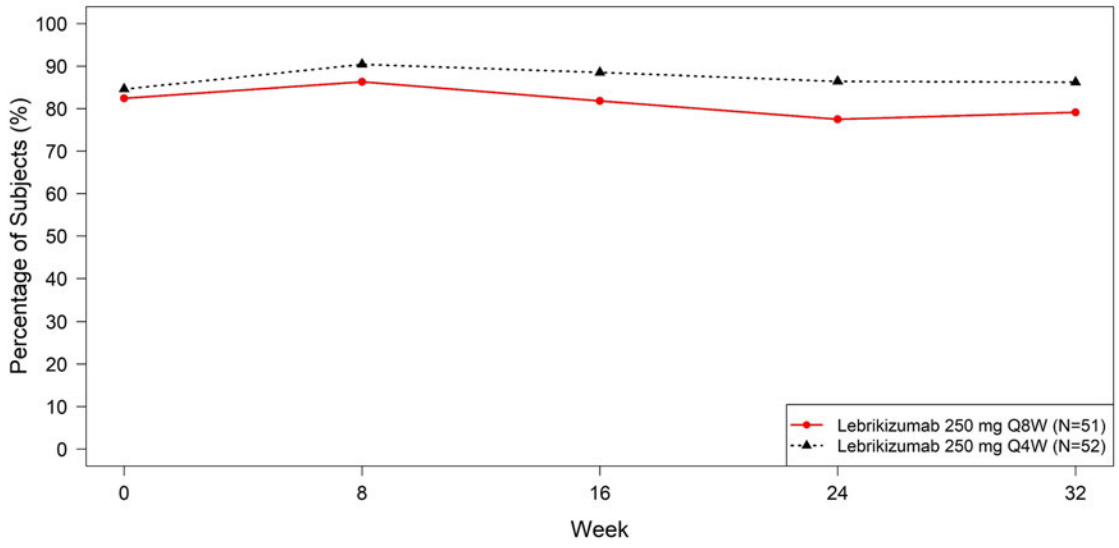
Figure 6 and Figure 7 presents the results for IGA response (i.e., IGA score of 0 or 1) over time and EASI-75 response over time, respectively. These results are based on all randomized subjects.

Figure 6: IGA Response Over Time – KGAA Addendum 11 (ITT[1,2])



Source: Statistical Reviewer's Analysis; ADSL.xpt, ADIGAMC.xpt
[1] Intent-to-Treat (ITT) population: all randomized subjects in KGAA Addendum 11.
[2] Subjects who discontinued rescue therapy due to lack of efficacy or whose dose was modified to lebrikizumab 250 mg Q2W were considered non-responders. Data after treatment discontinuation due to any other reason were considered missing. Missing data was imputed using MI-MCMC.

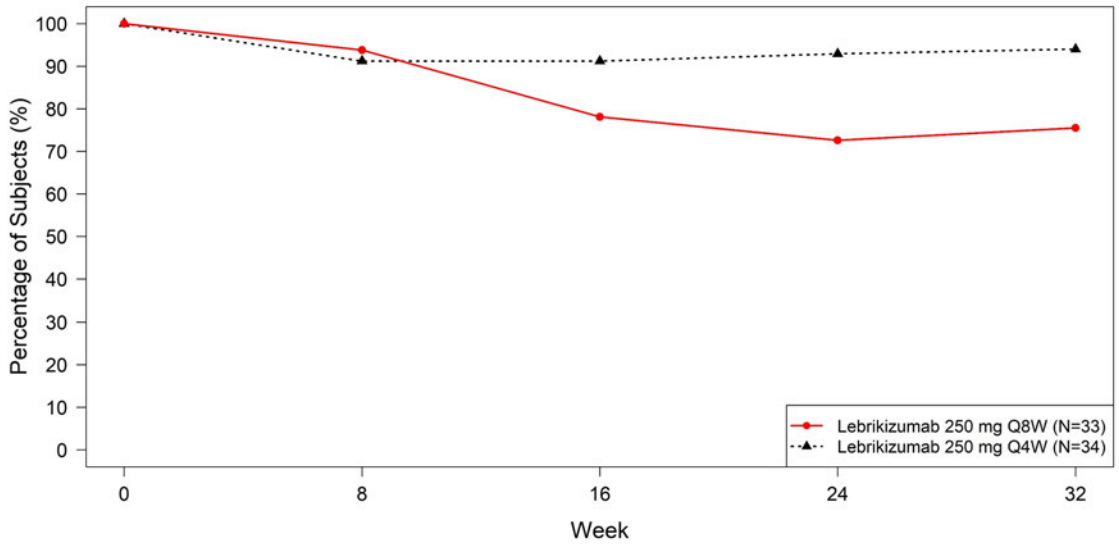
Figure 7: EASI-75 Response Over Time – KGAA Addendum 11 (ITT[1,2])



Source: Statistical Reviewer's Analysis; ADSL.xpt, ADEASIMC.xpt
[1] Intent-to-Treat (ITT) population: all randomized subjects in KGAA Addendum 11.
[2] Subjects who discontinued rescue therapy due to lack of efficacy or whose dose was modified to lebrikizumab 250 mg Q2W were considered non-responders. Data after treatment discontinuation due to any other reason were considered missing. Missing data was imputed using MI-MCMC.

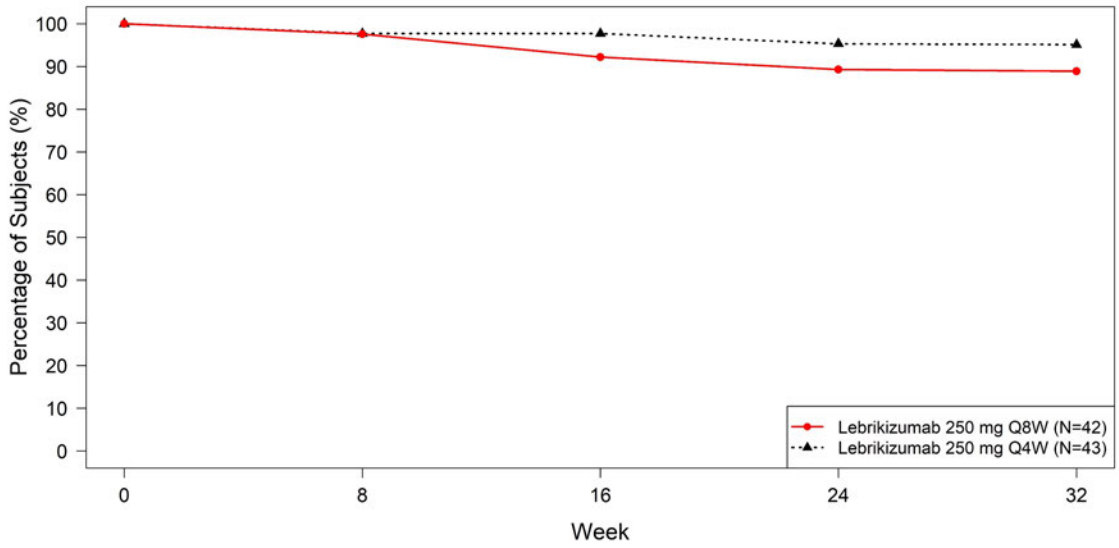
Figure 8 and Figure 9 present the results for IGA response and EASI-75 response over time in subjects who were responders at baseline.

Figure 8: IGA Response Over Time in Baseline IGA Responders[1,2] – KGAA Addendum 11



Source: Statistical Reviewer's Analysis; ADSL.xpt, ADIGAMC.xpt
[1] All randomized subjects that had an IGA score of 0 or 1 at baseline of Addendum 11.
[2] Subjects who discontinued rescue therapy due to lack of efficacy or whose dose was modified to lebrikizumab 250 mg Q2W were considered non-responders. Data after treatment discontinuation due to any other reason were considered missing. Missing data was imputed using MI-MCMC.

Figure 9: EASI-75 Response Over Time in Baseline EASI-75 Responders[1,2] – KGAA Addendum 11



Source: Statistical Reviewer's Analysis; ADSL.xpt, ADEASIMC.xpt
[1] All randomized subjects that had EASI-75 at baseline of Addendum 11.
[2] Subjects who discontinued rescue therapy due to lack of efficacy or whose dose was modified to lebrikizumab 250 mg Q2W were considered non-responders. Data after treatment discontinuation due to any other reason were considered missing. Missing data was imputed using MI-MCMC.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety focused on data from KGAA Addendum 11, which allowed assessment of the lebrikizumab 250 mg Q8W maintenance dosing regimen. KGAA Addendum 11 was conducted in adult and adolescent subjects ages 12 to <18 years who weighed ≥40kg, had moderate to severe AD, and who completed treatment with open-label lebrikizumab 250 mg Q2W or Q4W during Study KGAA then were rerandomized 1:1 to open-label lebrikizumab 250 mg Q4W or Q8W.

The study designs for KGAA Addendum 11 and Trial KGAA are summarized in Section 7.1 Table of Clinical Studies.

The large integrated safety database provided with the original submission for lebrikizumab Q2W and Q4W demonstrated lebrikizumab's safety profile. It was comprised of 1756 subjects enrolled in two replicate adequate and well-controlled monotherapy trials (Studies KGAB and KGAC) and one supportive trial that evaluated lebrikizumab with protocol-specified, concomitant use of topical corticosteroids (Study KGAD).

Because Q8W dosing results in lower drug concentrations, the safety profile of this proposed regimen is not expected to carry higher risk compared to the approved maintenance regimen of 250 mg Q4W.

8.2.2. Review of the Safety Database

Overall Exposure

Mean total patient days of exposure to lebrikizumab for the KGAA Addendum 11 safety population was 1181.6 (range = 923-1333) with total patient-years of 333.2 as shown in Table 9 below.

Table 8: Study Treatment Exposure Without the Gap between Week 100 of Study KGAA and the First Dose in Addendum 11

	Any Lebrikizumab (N=103)
Days of exposure, n (%)	
<900	0
>= 900 and <930	8 (7.8%)
>= 930 and < 960	4 (3.9%)
>= 960 and < 990	1 (1.0%)
>= 990 and < 1020	0
>= 1020 and < 1050	13 (12.6%)
>= 1050 and < 1080	3 (2.9%)
>= 1080 and < 1110	1 (1.0%)
>= 1110 and < 1140	0
>= 1140 and < 1170	2 (1.9%)
>= 1170 and < 1200	21 (20.4%)
>= 1200	50 (48.5%)
Patient days of exposure	
Number of patients	103
Mean	1181.6
SD	132.5
Minimum	923
Q1	1046

MEDIAN	1198
Q3	1292
Maximum	1333
Total patient-years[a]	333.2

Source: Modified Applicant Table KGAA.4.8. from KGAA Q8W CSR Body
[a] Total patient-year is calculated as sum of duration of exposure in days for all patients in dosing regimen/365.25.

Adequacy of the safety database:

The conclusions that can be made from the KGAA Addendum 11 data alone are limited as the population is not fully representative of a population who received 16 weeks of treatment Q2W (i.e., induction therapy) given the subjects have already received at least 100 weeks of lebrikizumab during Study KGAA. Instead, the KGAA Addendum 11 data are used to support a demonstration of model predictability.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no issues with data integrity or submission quality.

Categorization of Adverse Events

Adverse events (AEs) were reported based on the MedDRA Version 27.1. The coding of AEs for this supplemental BLA submission appeared adequate and allowed for accurate estimation of AE risks.

As with the original review, a treatment emergent adverse event (TEAE) was defined as an event that first occurred or worsened in severity after baseline. AEs that were ongoing at the exit visit of the parent trial were carried over and followed. New AEs occurring from the time of consent to the end of study KGAA (including addendum 11) were reported in the AE section of the eCRF. Information regarding the onset, duration, severity, seriousness, action taken, outcome, and relationship to study drug were recorded.

A serious adverse event (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

The definition of AE, TEAE, and SAE are acceptable. The classification system used by investigators to describe the severity of AEs, as well as the causal relationship between AE and study product are also acceptable. The Applicant's identification and presentation of AEs of special interest are appropriate.

Routine Clinical Tests

The Applicant performed routine clinical laboratory testing (hematology, chemistry, urinalysis), as well as physical examinations and vital signs, throughout the Study KGAA Addendum 11.

The safety assessments were adequate for the population, disease, and indication and allowed for reasonable characterization of the safety of lebrikizumab 250 mg Q4W and lebrikizumab 250 mg Q8W.

8.2.4. Safety Results

Deaths

There were no deaths reported for Study KGAA Addendum 11.

Serious Adverse Events

There were no subjects who reported serious adverse events (SAEs) during KGAA Addendum 11 (Week 152 through Week 184).

Dropouts and/or Discontinuations Due to Adverse Effects

No subjects were reported to have had AEs that led to treatment discontinuation during KGAA Addendum 11. One subject (J2T-DM-KGAC-(b) (6)), a 25-year-old Asian female who received lebrikizumab Q2W during KGAA then lebrikizumab Q4W during KGAA Addendum 11 had dosing interrupted due to an AE of mild Covid-19.

Significant Adverse Events

No subjects were reported to have had severe AEs.

Treatment Emergent Adverse Events and Adverse Reactions

The proportion of subjects who experienced any TEAE was higher in the Q4W treatment arm (17, 32.7%) relative to the Q8W arm (13, 25.5%). However, the small number of subjects in each arm and lack of a placebo-controlled group limits the ability to make a direct comparison of treatment groups. The system organ class (SOC) with the highest incidence was Infections and Infestations followed by Skin and subcutaneous tissue disorders. No new safety findings were reported for either maintenance dose.

Table 9: TEAEs Reported in ≥1% of Subjects by SOC and PT – KGAA Addendum 11

System Organ Class Preferred Term	LEB Q4W N = 52 n (%)	LEB Q8W N = 51 n (%)	All Leb N = 103 n (%)
Any AE	17 (32.7)	13 (25.5)	30 (29.1)
Infections and infestations	**8 (15.4)**	**5 (9.8)**	**13 (12.6)**
Upper respiratory tract infection*	3 (5.8)	0 (0.0)	3 (2.9)
Folliculitis	1 (1.9)	1 (2.0)	2 (1.9)
Cellulitis	0 (0.0)	1 (2.0)	1 (1.0)
Conjunctivitis	1 (1.9)	0 (0.0)	1 (1.0)
Covid-19	1 (1.9)	0 (0.0)	1 (1.0)
Lower respiratory tract infection	1 (1.9)	0 (0.0)	1 (1.0)
Staphylococcal infection	0 (0.0)	1 (2.0)	1 (1.0)

System Organ Class Preferred Term	LEB Q4W N = 52 n (%)	LEB Q8W N = 51 n (%)	All Leb N = 103 n (%)
Tinea versicolour	0 (0.0)	1 (2.0)	1 (1.0)
Tooth abscess	1 (1.9)	0 (0.0)	1 (1.0)
Urinary tract infection	0 (0.0)	1 (2.0)	1 (1.0)
Skin and subcutaneous tissue disorders	**3 (5.8)**	**2 (3.9)**	**5 (4.9)**
Acne	1 (1.9)	0 (0.0)	1 (1.0)
Dermatitis atopic	0 (0.0)	1 (2.0)	1 (1.0)
Dermatitis contact	0 (0.0)	1 (2.0)	1 (1.0)
Ingrown hair	1 (1.9)	0 (0.0)	1 (1.0)
Rash vesicular	1 (1.9)	0 (0.0)	1 (1.0)
Nervous system disorders	**2 (3.8)**	**1 (2.0)**	**3 (2.9)**
Headache*	2 (3.8)	1 (2.0)	3 (2.9)
Respiratory, thoracic and mediastinal disorders	**2 (3.8)**	**1 (2.0)**	**3 (2.9)**
Nasal obstruction	1 (1.9)	0 (0.0)	1 (1.0)
Respiratory tract congestion	0 (0.0)	1 (2.0)	1 (1.0)
Rhinitis allergic	1 (1.9)	0 (0.0)	1 (1.0)
Injury, poisoning and procedural complications	**2 (3.8)**	**0 (0.0)**	**2 (1.9)**
Concussion	1 (1.9)	0 (0.0)	1 (1.0)
Radius fracture	1 (1.9)	0 (0.0)	1 (1.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**2 (3.9)**	**2 (1.9)**
Arthralgia	0 (0.0)	1 (2.0)	1 (1.0)
Myalgia	0 (0.0)	1 (2.0)	1 (1.0)
Congenital, familial and genetic disorders	**0 (0.0)**	**1 (2.0)**	**1 (1.0)**
Accessory navicular syndrome	0 (0.0)	1 (2.0)	1 (1.0)
Endocrine disorders	**0 (0.0)**	**1 (2.0)**	**1 (1.0)**
Polycystic ovarian syndrome	0 (0.0)	1 (2.0)	1 (1.0)
Eye disorders	**1 (1.9)**	**0 (0.0)**	**1 (1.0)**
Cataract	1 (1.9)	0 (0.0)	1 (1.0)
Gastrointestinal disorders	**2 (3.8)**	**0 (0.0)**	**2 (1.9)**
Gastritis	1 (1.9)	0 (0.0)	1 (1.0)
Hepatobiliary Event*	0 (0.0)	1 (2.0)	1 (1.0)
General disorders and administration site conditions	**1 (1.9)**	**0 (0.0)**	**1 (1.0)**
Chest pain	1 (1.9)	0 (0.0)	1 (1.0)
Metabolism and nutrition disorders	**1 (1.9)**	**0 (0.0)**	**1 (1.0)**
Diabetes mellitus	1 (1.9)	0 (0.0)	1 (1.0)
Psychiatric disorders	**1 (1.9)**	**0 (0.0)**	**1 (1.0)**
Attention deficit hyperactivity disorder	1 (1.9)	0 (0.0)	1 (1.0)

Source: Reviewer's Table. OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "LQ4WE" and SAFFL = Y (LEB Q4W); TRT02A = "LQ8WE" and SAFFL = Y (LEB Q8W); TRT02A = "LQ4WE", "LQ8WE" and SAFFL = Y (All Leb); TEMADDFL = "Y" (Adverse Events).
Percent threshold: All Leb ≥ 1%.
*Headache = headache, migraine
*Hepatobiliary Event = Alanine aminotransferase increased
*Upper respiratory tract infection = Nasopharyngitis, Upper respiratory tract infection

Laboratory Findings

There were no clinically meaningful trends in laboratory results for either treatment arm. Given the relatively small number of subjects in each treatment arm and lack of placebo group, comparison of findings is limited. Nonetheless, two subjects, both described below, had abnormal laboratory findings worth noting.

Subject J2T-DM-KGAB-(b) (6) (Study KGAA SUBJID (b) (6)) – elevation of ALT ≥3× ULN; **Q4W**
A 16-year-old Asian female with a medical history of fatty liver disease and fluctuating transaminase levels, had ALT elevation at screening, Weeks 8, 16, 32 and 52 in parent Study KGAB ranging from 27 to 66 U/L (normal range 5 to 20 U/L). Her ALT peaked at 119 Ul/L at KGAA Addendum 11 baseline. Despite use of lebrikizumab Q4W during Study KGAA Addendum 11 she did not have a hepatic-associated adverse event or symptoms, and her ALT serum levels decreased to 41 U/L by Addendum 11 Week 32 which was near her KGAB baseline reading of 45 U/L.

Reviewer comment: Given the subject's history of known fatty liver disease and decline in ALT levels despite continued lebrikizumab exposure, it is unlikely that the event was related to lebrikizumab 250 mg Q4W use.

Subject J2T-DM-KGAB-(b) (6) (Study KGAA SUBJID (b) (6)) - increase of eosinophils (≥5000 per µL); Q4W-**Q2W** (b) (6)
A 16-year-old Asian male who was reported to have had increased eosinophils starting at Week 28 during parent study KGAB, had fluctuating mild to moderate elevated eosinophils throughout the KGAA 100-week treatment period with an initial level of 3.2 x 10^9/L at Week 0 that decreased to 0.1 x 10^9/L (reference range 0 to 0.7 x 10^9/L) at Week 16. At KGAA Addendum 11 baseline, his eosinophils were mildly elevated at 0.8 x 10^9/L; however, at Week 32, they peaked at 5.8 x 10^9/L approximately 50 days after he transitioned to lebrikizumab 250 mg Q2W (recall, per protocol, because the subject did not maintain an EASI-50 response [from the parent study baseline] at Week 8 of Addendum 11, he transitioned to lebrikizumab 250 mg Q2W for the remainder of Addendum 11).
No associated AE was reported.

Reviewer comment: This reviewer notes that the subject had a single AE, moderate right eye cataract, reported during Study KGAA, 56 days after he entered Addendum 11. Although the event was reported as recovered/resolved following a procedure, details regarding the suspected etiology of the AE were not provided. Although a link between high eosinophil counts and cataract development in patients with atopic dermatitis has been described in published literature[1,2], a relationship between the elevated serum eosinophils and the event of cataract in Subject J2T-DM-KGAB-(b) (6) cannot be determined based on the limited information.

Vital Signs

There were no clinically meaningful changes in vital sign parameters (blood pressure, respiratory rate, pulse rate, or temperature.

Electrocardiograms (ECGs)

ECGs were not performed during KGAA Addendum 11.

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[1] Komatsu, K., Masuda, Y., Kubota, H. et al. Association of eosinophil major basic protein with intraocular lens dislocation in atopic dermatitis. *Sci Rep.* 2025; 15, 16861. https://doi.org/10.1038/s41598-025-02083-y
[2] Yamamoto, N., Hiramatsu, N., Isogai, S. et al. Mechanism of atopic cataract caused by eosinophil granule major basic protein. *Med Mol Morphol*. 2020; 53, 94–103. https://doi.org/10.1007/s00795-019-00234-5

Immunogenicity

Of the 103 subjects who entered Study KGAA Addendum 11, 81 were TE ADA-evaluable during the Study KGAA Addendum 11 treatment period (i.e., these subjects provided a sample during the 100-week KGAA Main study and had at least 1 sample drawn in Addendum 11).

At Week 100 of Study KGAA, one subject was TE ADA-positive. This subject was from the Q2W group and was re-randomized to the Q4W group in Addendum 11 and became TE ADA-negative.

Four subjects who were TE ADA-negative at Week 100 of Study KGAA became TE ADA-positive during the Study KGAA Addendum 11 treatment period: 3 subjects had a treatment sequence of Q2W-**Q4W** (TE ADA-positive incidence of 7.9%) and 1 subject had a treatment sequence of Q2W-**Q8W** (TE ADA-positive incidence of 2.9%). Of these 4 subjects, one experienced a potential hypersensitivity event.

Subject ID	Treatment	Adverse event
J2T-DM-KGAB-(b) (6)	Q2W-**Q4W**	moderate vesicular rash that resolved following use of concomitant medications. Dosing was not changed, interrupted, or discontinued
J2T-DM-KGAE-	Q2W-**Q4W**	no hypersensitivity AE
J2T-DM-KGAE-	Q2W-**Q4W**	no reported AEs
J2T-DM-KGAC-	Q2W-**Q8W**	no hypersensitivity AE

Due to the very small number of subjects who developed TE ADA during Study KGAA Addendum 11, the impact of TE ADA on safety (and efficacy) cannot be determined.

8.2.5. Analysis of Submission-Specific Safety Issues

The adverse events of special interest (AESIs) were selected based on the potential association with the mechanism of action of lebrikizumab, AEs observed for other drugs in the same class as lebrikizumab, and the increased likelihood for the event to occur in the AD population. The protocol-defined AESIs for Study KGAA Addendum 11 included conjunctivitis, Herpes infection or Zoster, and parasitic infection or an infection related to an intracellular pathogen. Table 11 shows that conjunctivitis was the only AESI reported in KGAA Addendum 11.

Table 10: Incidence Rates of AESIs – KGAA Addendum 11

	LEB 250 mg Q8W (N = 51) n (%)	LEB 250 mg Q4W (N = 52) n (%)	Any LEB (N = 103) n (%)
All TEAEs	10 (19.6)	16 (30.8)	26 (25.2)
AESIs by PT			
Conjunctivitis cluster[a]	0	1 (1.9)	1 (1.0)
Keratitis cluster[b]	0	0	0
Potential opportunistic infections (broad)	0	0	0
Herpes infections	0	0	0
Parasitic infections	0	0	0

Source: Modified Applicant Tables KGAA.5.3 and 5.5 from KGAA Q8W CSR Body

[a] Conjunctivitis cluster includes the following PTs: *Conjunctivitis*, *Conjunctivitis allergic*, *Conjunctivitis bacterial*, *Conjunctivitis viral*, and *Giant papillary conjunctivitis*.

[b] Keratitis cluster includes the following PTs: *Keratitis*, *Atopic keratoconjunctivitis*, *Allergic keratitis*, *Ulcerative keratitis*, and *Vernal keratoconjunctivitis*.

Subject J2T-MC-KGAK-(b) (6) – Conjunctivitis – Q4W
A 30-year-old White male with no medical history of previous conjunctivitis received LQ2W-LQ4W during Study KGAA. He reported 2 mild conjunctivitis events both of which occurred during KGAA Addendum 11. The first event occurred on KGAA Addendum 11 Study Day 79 (lebrikizumab total exposure for 1120 days) and resolved on Study Day 81 following an unspecified treatment. The second event of conjunctivitis was reported on KGAA Addendum 11 Study Day 213 (lebrikizumab total exposure for 1254 days) and resolved on Study Day 241, during the Safety Follow-Up period after he received an unspecified treatment. The events did not lead to dosing interruption or discontinuation.

Reviewer comment: Conjunctivitis may occur after months or years into treatment due to cumulative drug toxicity, age-related changes, or a change in the body's immune response to long-term stimuli. It is possible the two events of mild conjunctivitis were related to the use of lebrikizumab Q4W.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No COA analyses were conducted to inform safety/tolerability in Study KGAA including Addendum 11.

8.2.7. Safety Analyses by Demographic Subgroups

Due to the small size of KGAA Addendum 11, differences based on demographics are difficult to detect. Most of the subjects enrolled in KGAA Addendum 11 were Asian (50.5%) and White (36.9%) and 18 years old and older (61.2%). The proportion of females (47.6%) and males (52.4%) were comparable. KGAA Addendum 11 does not provide additional information on drug-demographic interactions.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

KGAA Addendum 11 was not designed to evaluate the potential risk of malignancy.

Human Reproduction and Pregnancy

There were no pregnancies in KGAA Addendum 11.

Pediatrics and Assessment of Effects on Growth

KGAA Addendum 11 was not designed to evaluate differences in growth parameters of weight, height, and body mass index (BMI) between the adolescent lebrikizumab 250 mg Q4W and lebrikizumab 250 mg Q8W treatment groups.

When Ebglyss received initial FDA approval for the treatment of adult and pediatric patients 12 years of age and older who weigh at least 40 kg with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, two Pediatric Research Equity Act (PREA) post-marketing requirements (PMRs) were issued. One PMR (4514-1) is to conduct a randomized,

double-blind, placebo-controlled trial to assess the PK and safety of lebrikizumab in pediatric patients 6 months to <6 years, 6 years to <12 years, and ≥12 years to <18 years weighing <40 kg with moderate to severe atopic dermatitis, and the second requirement (4514-1) is to conduct an open-label, long-term extension study to evaluate the long term safety of lebrikizumab in the same pediatric population. See to Section 13 for details regarding pediatric study requirements for lebrikizumab under PREA.

The pediatric study requirement from birth to < 6 months of age was waived because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group since it may be challenging to establish failure of adequate disease control by topical therapies in children < 6 months of age.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

These topics were not assessed as part of this supplement.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No new safety concerns for lebrikizumab have been identified through postmarket experience to date.

Expectations on Safety in the Postmarket Setting

The safety profile of lebrikizumab 250 mg Q8W appears consistent with the known safety profile of lebrikizumab 250 mg Q2W and Q4W. No new or unexpected safety findings were observed during Study KGAA Addendum 11. Based on the available safety data, the expectation is that the postmarketing safety experience for adults and adolescents who weigh at least 40 kg with moderate to severe AD receiving a maintenance dose of lebrikizumab 250 mg Q8W will likely be similar or no worse than the lebrikizumab safety experience known to date.

8.2.11. Integrated Assessment of Safety

The data provided in this supplement from adult and adolescent subjects who weigh at least 40 kg with moderate to severe AD demonstrated a safety profile that is similar to what has been established for lebrikizumab 250 mg Q2W and Q4W in the treatment of AD. The results of Study KGAA Addendum 11 included no deaths, SAEs, or TEAEs leading to treatment discontinuation. All TEAEs were mild or moderate in severity. No new safety findings were reported for either maintenance dose.
As stated above, postmarketing safety experience for the target population receiving the maintenance dose of lebrikizumab 250 mg Q8W is expected to be similar to the safety experience that has already been established for lebrikizumab 250 mg Q2W and Q4W.

8.3. Statistical Issues

There were no major statistical issues that affected the overall study conclusions. According to the SAP, “No statistical tests will be performed.” Descriptive statistics were used to summarize the efficacy results.

8.4. Conclusions and Recommendations

The conclusions that can be made from the KGAA Addendum 11 data alone are limited as the size of the trial was small, the open-label design may have introduced detection/assessment bias, and the population was not fully representative of a population who received 16 weeks of treatment Q2W (i.e., induction therapy)

given the subjects had already received at least 100 weeks of lebrikizumab during the Main KGAA study. Instead, the KGAA Addendum 11 data were used to support a demonstration of model predictability.

Through exposure-efficacy response modeling and the supportive clinical data from 103 subjects (63 adults and 40 adolescents) with moderate to severe AD, the Applicant provided evidence that a maintenance dose of lebrikizumab (EBGYLSS) 250 mg Q8W will have similar effects as a maintenance dose of lebrikizumab 250 mg Q4W in adult and adolescent subjects who weigh at least 40 kg with moderate to severe atopic dermatitis (AD) and whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

The Applicant demonstrated that the lebrikizumab maintenance dosing option of lebrikizumab 250 mg every 8 weeks is effective for its intended use in the target population and that the new, less frequent dosing option appears to have a safety profile that is consistent with the known safety profile of lebrikizumab 250 mg Q2W and Q4W that was based on a large integrated safety database from two replicate adequate and well-controlled monotherapy trials and one TCS-combination trial under the original BLA 761306.

A maintenance dose of lebrikizumab (EBGYLSS) 250 mg Q8W does not appear to change the benefit-risk profile. Therefore, approval is recommended for BLA 761306/S-006 to add an additional maintenance dose option of 250 mg Q8W for the treatment of moderate to severe atopic dermatitis in adults and pediatric patients 12 years of age and older who weigh at least 40 kg and whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee was not convened for this supplement.

10 Pediatrics

See sections 8.2.9 Additional Safety Explorations, Pediatrics and Assessment of Effects on Growth and 13 Postmarketing Requirements and Commitment for discussion of PREA PMRs.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
The review team considered the Applicant's proposed updates to the DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics sections of the United States Prescribing Information (USPI) to be reasonable. However, the team did not agree with including information or statements regarding (b) (6) Additionally, the Applicant was informed that exposure response information is required in subsection 12.2 per 21CFR201.57(c)(13)(i)(B). The final recommendations for the PI will be reflected in the final PI.

Patient Labeling
The changes to the USPI to include an additional maintenance dosing option of lebrikizumab 250 mg every 8 weeks did not impact the Medication Guide or Instructions for Use and did not have a promotional impact; therefore, no changes to patient labeling were made.

12 Risk Evaluation and Mitigation Strategies (REMS)

REMS are not required for this efficacy supplement.

13 Postmarketing Requirements and Commitment

At the time of BLA 761306 approval, two Pediatric Research Equity Act (PREA) post-marketing requirements (PMRs) were issued:

4514-1 Conduct a randomized, double-blind, placebo-controlled trial to assess the PK and safety of lebrikizumab in pediatric patients 6 months to <6 years, 6 years to <12 years, and ≥12 years to <18 years weighing <40 kg with moderate to severe atopic dermatitis.

Final Protocol Submission: 04/2022 (Completed)
Study Completion: 01/2026
Final Report Submission: 04/2026

4514-2 Conduct an open-label, long-term extension study to evaluate the long-term safety of lebrikizumab in pediatric patients 6 months to <12 years, and >12 years <18 years weighing less than 40 kg with moderate to severe atopic dermatitis.

Final Protocol Submission: 01/2023 (Completed)
Study Completion: 01/2028
Final Report Submission: 04/2028

Two phase 3 trials were agreed upon to address the PMRs: Trial DRM06-AD13 (J2TMC-KGBI) and Trial DRM06-AD16 (J2T-MC-KGBJ), respectively, hereafter referred to as Trials KGBI and KGBJ.

- **Trial KGBI** is a randomized, double-blind, placebo-controlled trial in pediatric subjects aged 6 months to <12 years of age and 12 to <18 years of age who weigh <40 kg. As agreed to in the pediatric study plan (PSP), this trial includes 2 cohorts:

  1. Cohort 1 would be comprised of approximately 150 subjects 6 years to <12 years of age & 12 years to <18 years of age who weigh <40kg.

  2. Cohort 2 would consist of approximately 90 subjects 6 months to <6 years of age (60 subjects aged 2 to <6 years old and 30 subjects aged 6 months to <2 years old).

  The Agency recommended that enrollment of Cohort 2 begin after evaluation of pharmacokinetics (PK) in subjects 6-18 years of age was completed and after obtaining safety data from 30 to 50 subjects 6-12 years of age in Cohort 1.

- **Trial KGBJ** is an open-label, long-term extension safety trial in subjects aged 6 months to <12 years old and 12 to <18 years old with a body weight <40 kg.

Since original approval of BLA 761306, the Agency and Applicant have had a number of interactions to discuss changes to the pediatric AD program as the Applicant had revised their approach based on updated statistical assumptions that are reliant on the treatment effect from the lebrikizumab-TCS combination trial instead of response rates from dupilumab's phase 3 pediatric trial. Based on their modified approach, the Applicant

proposed the trial population for Trial KGBI would include updated subject numbers at the time of sBLA submission:

- 6 mos to <2 years = **15** instead of 30
- 2 years to <6 years = **70** instead of ~60
- 6 years to <12 years of age and 12 years to <18 years of age who weigh <40kg = **270** instead of 150

The Agency considered the Applicant's proposal as reasonable and emphasized that at least 15 subjects (completers) aged 6 months to less than 2 years be exposed to lebrikizumab to support descriptive analysis for the active regimen as well as comparative evaluations between regimens.

The Agency also granted a Deferral Extension to address PMR 4514-1.

During the review of this supplement, the Pediatric Review Committee (PeRC) and the Division agreed that it is reasonable not to issue a new PREA PMR during this review cycle and instead, in the S-006 approval letter, refer to the PMRs 4514-1 and 4514-2 already established under the original BLA.

14 Division Director (OCP) Comments

15 Division Director (Clinical) Comments/Associate Director for Therapeutic Review

I agree with the discipline reviews' conclusion, labeling recommendations and regulatory action.

16 Appendices

16.1. References

References are included in this review as footnotes.

16.2. 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 4 clinical investigators for Study KGAA including KGAA Addendum 11. There do not appear to be any concerns regarding any conflicts of interest related to financial payments to the investigators.

Covered Clinical Study (Name and/or Number): KGAA

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 240		
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): 4		
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: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S 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) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16.3. OCP Appendices (Technical documents supporting OCP recommendations)

Pharmacometrics Review

16.3.1. Executive Summary

The Applicant is seeking regulatory approval for an additional maintenance dosing regimen for lebrikizumab (EBGLYSS) in moderate-to-severe atopic dermatitis. The proposed regimen includes induction with 500 mg at Weeks 0 and 2, followed by 250 mg every 2 weeks until Week 16 or later when adequate response is achieved. For maintenance, the applicant proposes adding 250 mg every 8 weeks as an alternative to the currently approved every-4-week regimen.

This review addresses whether Q8W maintenance dosing is appropriate for patients achieving adequate response following Q2W induction therapy. Lebrikizumab PK was characterized by a 2-compartment model with body weight as a significant covariate. Two complementary exposure-efficacy modeling approaches - independent PK-EASI/PK-IGA models and a combined PK-EASI-IGA model which predicted small differences between Q4W and Q8W dosing (approximately 4-7% for EASI 75 and IGA 0,1 response rates).

Model predictions were prospectively validated using clinical data from Study KGAA Addendum 11, with observed response rates closely aligning with predictions. No subpopulation was identified that would preferentially benefit from every-8-week dosing. These findings support both maintenance dosing options to allow individualized treatment decisions.

16.3.2. FDA Assessment of Model Risk

The pharmacometrics analyses focused on the assessment of population PK and exposure-response (ER) for efficacy endpoints, as shown in **Table 11**. The overall model risk was assessed as low.

Table 11: FDA Assessment of Model Risk

Elements	Details
Question of Interest	Is the proposed Q8W maintenance dosing regimen of lebrikizumab 250 mg appropriate for participants with moderate-to-severe atopic dermatitis who achieved adequate clinical response following Q2W induction therapy?
Context of Use	The PopPK model generated individual exposure metrics for E-R analysis. E-R analyses were conducted to evaluate exposure-dependent changes in efficacy endpoints (EASI 75 and IGA 0,1 response rates).
Decision Consequence	Low. Small predicted differences between Q4W and Q8W dosing regimens (4-7%) with overlapping prediction intervals. Clinical data from Study KGAA Addendum 11 support model predictions.
Model Influence	Low. Dosage regimen is supported by MIDD evidence with clinical validation data used as confirmatory evidence.
Model Risk	Low

16.3.3. Population PK Analysis

16.3.3.1. Executive Summary

The Applicant is seeking approval for lebrikizumab Q8W maintenance dosing for treatment of moderate-to-severe atopic dermatitis (AD). The key population PK (PopPK) findings are summarized below:

- Lebrikizumab PK was characterized by a 2-compartment model with first-order absorption and linear elimination
- Body weight was identified as a statistically significant covariate and included via allometric scaling
- Mean half-life: approximately 24 (±6) days
- Subcutaneous bioavailability: 91%
- Model predictions aligned well with observed concentrations from Study KGAA Addendum 11 (Q8W dosing)

16.3.3.2. PopPK Assessment Summary

A PopPK model was developed to characterize the PK of lebrikizumab and identify the impact of covariates across 12 studies (4 in healthy participants, 8 in AD patients), as shown in **Table 12**. A total of 1,970 subjects contributed 8,909 measurable PK observations. Covariate summary statistics from the PK analysis are presented in **Table 13**.

Table 12: Clinical Studies Included in the Population PK Analysis

Study Number	Phase	Participant Population	Dosing Regimen	PK Sampling
J2T-DM-KGAG (TREBLE)	2	Adults with AD (with TCS)	125-250 mg Q4W or single dose	Intensive sampling during induction
J2T-DM-KGAF (DRM06-AD01)	2	Adults with AD (monotherapy)	125-250 mg Q2W or Q4W	Intensive sampling during induction
J2T-DM-KGAB (ADvocate 1)	3	Adults and adolescents with AD	250 mg Q2W induction, then Q2W/Q4W/placebo maintenance	Weeks 0-52: intensive and trough sampling
J2T-DM-KGAC (ADvocate 2)	3	Adults and adolescents with AD	250 mg Q2W induction, then Q2W/Q4W/placebo maintenance	Weeks 0-52: intensive and trough sampling
J2T-DM-KGAD (ADhere)	3	Adults and adolescents with AD (with TCS)	250 mg Q2W induction	Weeks 0-16: intensive and trough sampling
J2T-DM-KGAE	3	Adolescents with AD	250 mg Q2W	Weeks 0-52: trough sampling
J2T-MC-KGAK	3	Adults and adolescents with AD	250 mg Q2W	Week 0-16: trough sampling

J2T-DM-KGAA (ADjoin)	3	Long-term extension	250 mg Q2W or Q4W	Weeks 0-100: trough sampling
4 Phase 1 studies	1	Healthy volunteers	Various IV and SC doses	Intensive sampling

Source: Adopted from Table 7.1. Lebrikizumab Population PK Report (AD)

Table 13: Covariates Evaluated in the Population PK Model

Covariate	Mean ± SD (Range)	Evaluated	Statistically Significant
Body weight (kg)	76.3 ± 20.6 (39.9-193)	Yes	Yes (allometric scaling)
Age (years)	34.2 ± 16.5 (12-93)	Yes	No
Sex (Female)	F: 1001 (51%); M: 969 (49%)	Yes	No
Race (White)	W: 1241 (63%); B: 288 (15%); As: 335 (17%); Others: 105 (5%)	Yes	No
ALT (IU/L)	22.5 ± 14.9 (5-178)	Yes	No
AST (IU/L)	23.0 ± 9.63 (6-129)	Yes	No
Hepatic function	Normal in >95%	Yes	No
Renal function	Normal in >95%	Yes	No

Source: Adopted from Table 7.4. Lebrikizumab Population PK Report (AD)

16.3.3.3. Data Handling

Missed Data and BLQ Observations:
- Concentration samples without corresponding dosing data were excluded from analysis
- Samples with missing time or date information were excluded
- BLQ concentrations (1.2% of total) were retained in the dataset but excluded from parameter estimation
- Participants with no observations above LLOQ were excluded

Missing Covariates:
- Continuous covariates: median value imputed
- Categorical covariates: grouped with most common category
- Covariates with >20% missing data excluded from analysis

16.3.3.4. Final PopPK Model

The final PopPK model is a 2-compartment model with first-order absorption and linear elimination for subcutaneous dosing, as shown in Figure 1. Parameter estimates for the final model are provided in **Table 14**.

Table 14: Parameter Estimates of the Final Population PK Model for Lebrikizumab

Model Parameter (Unit)	Population Estimate (%SEE)	Interindividual Variability %CV[a] (%SEE)	95% Confidence Interval from Bootstrap Analysis
ka (1/day)	0.285 (9.5)	44.1 (21.0)	(0.189-0.356)
F	0.91 (3)	187 (25.9)	(0.823-0.951)
CL (L/day)	0.168 (3.3)	25.1 (9.0)	(0.151-0.177)
V2 (L)	3.89 (7.3)	25.9 (25.8)	(2.48-4.39)
Q (L/day)	0.599 (16.4)	-	(0.388-0.793)
V3 (L)	1.51 (20.6)	-	(0.840-2.68)
Covariates effects			
Covariate for body weight on CL[b]	0.8 FIX	-	-
Covariate for body weight on V2[c]	1 FIX	-	-
Covariate for body weight on Q[d]	0.8 FIX	-	-
Covariate for body weight on V2[e]	1 FIX	-	-
Variance			
Covariance for CL-ka[f]	-	-0.0483 (22.6)	-
Covariance for ka-V2[f]	-	-0.028 (80)	-
Residual error[g]			
Proportional	0.0399 (4.9)		(0.0361-0.0440)
Additive (µg/mL)	0.0021 (45)		(0.000560-0.00528)

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; WTE = body weight at study entry.

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: Table 9.1. Lebrikizumab Population PK Report (AD)

Covariate Effects:
-Body weight on CL and volumes: Allometric scaling (exponent 0.75 for CL, 1.0 for volumes). No other covariates met inclusion criteria for clinical significance

Derived Parameters:
- Mean half-life: 24 ± 6 days
- Time to steady-state: approximately 12-16 weeks

The final population PK model demonstrated adequate predictive performance. Goodness-of-fit plots showed good agreement between predicted and observed concentrations, with data points distributed symmetrically around the line of identity. Prediction-corrected visual predictive checks stratified by dosing regimen confirmed that observed concentrations fell within the simulated 90% prediction intervals.

External validation against Study KGAA Addendum 11 confirmed model adequacy, with accurate predictions of steady-state trough concentrations for both Q8W dosing (predicted: 10.8 µg/mL; observed: 10.5 µg/mL) and Q4W dosing (predicted: 36.0 µg/mL; observed: 41.6 µg/mL). This close agreement for Q8W dosing, which

was not included in model development (**Table 15**), demonstrates the model's reliability for generating exposure estimates for exposure-response analyses.

Table 15: Comparison of Predicted and Observed Steady-State Trough Concentrations

Dosing Regimen	Predicted Median Ctrough,ss (µg/mL) (5th, 95th Percentile)	Observed Median Ctrough,ss (µg/mL) (5^{th}, 95th Percentile)
250 mg Q4W	36.0 (17.8-64.9)	41.6 (0.45-69)
250 mg Q8W	10.8 (3.88-23.7)	10.5 (0.045-28.3)

Source: Table 10.1. Lebrikizumab Population PK Report (AD)

FDA Reviewer's Comment: *The PopPK model adequately predicts lebrikizumab concentrations for Q8W dosing despite this regimen not being included in the model development dataset. The close agreement between predicted and observed concentrations supports the use of this model for generating individual exposure estimates for exposure-response analyses.*

16.3.4. Exposure-Efficacy Analysis

16.3.4.1. Approach 1: Independent PK-EASI and PK-IGA 0,1 Models

Independent exposure-response models were developed for EASI score and IGA 0,1 response, both of which adequately characterized placebo and drug effects across the clinical development program. The estimated half-maximal effective concentration was 57.0 µg/mL for the PK-EASI model and 52.9 µg/mL for the PK-IGA 0,1 model, demonstrating consistency in the exposure-response relationship across both efficacy endpoints. At Week 52, the predicted mean difference in response rates between every-4-week and every-8-week maintenance dosing was 4.9% for EASI 75 and 7.0% for IGA 0,1, indicating clinically comparable efficacy between the two maintenance regimens. These model predictions were subsequently validated using prospective clinical data from Study KGAA Addendum 11, with observed response rates closely aligning with model-predicted values and 95% prediction intervals overlapping the 95% confidence intervals of the clinical data.

Dataset: 1,363 participants; 13,225 EASI and 15,508 IGA observations from Studies KGAG, KGAF, KGAB, KGAC, KGAD (development) and KGAA/Addendum 11 (evaluation).

Table 16: Summary of Response Rates by Study at Key Timepoints

Study/Period	Regimen	N	EASI 75 (%)	IGA 0,1 (%)
Week 16	Placebo	188	26.6	17.6
	Q2W	492	64.2	43.6
Week 52 (Week 16 Responders)	Q2W→Q4W	115	91.3	83.3
KGAA Addendum 11 Week 32	Q4W	51	86.3	72.5
	Q8W	49	85.7	68.8

Source: Adopted from Table 2.7.2.4, 2.7.2.6, 2.7.2.7, 2.7.2.9, Lebrikizumab 2.7.2 summary-clin-pharm

Independent PK-EASI Model

Model Structure: Logit-transformed EASI score with mixture model for placebo response (EST1: 61.5%, faster/smaller; EST2: 38.5%, slower/larger) and indirect Emax model for drug effect.

Table 17: Key Parameter Estimates - PK-EASI Model

Parameter	unit	Estimate	RSE, %	95% CI	Shrinkage
Kout, first order rate constant for reduction in EASI Score	1/d	0.0506	4.05	0.0467 - 0.0548	--
Epbo0 in high placebo responders		0.0783	7.53	0.0676 - 0.0907	--
Epbo0 in low placebo responders		0.444	3.40	0.416 - 0.475	--
T50, Time of ½ maximal Epbo (high-resp)	days	0.00287	--	0.00243 - 0.00339	--
Fractional decrease in Epbo (low resp), >16 wks		0.139	--	0.101 - 0.189	--
Emax		0.952	--	0.947 - 0.956	--
EC50	µg/mL	57.0	17.9	40.3 - 80.6	--
sigmaE, residual variability		0.506	2.82	0.478 - 0.534	--
Baseline, KGAF/G		21.4	2.46	20.3 - 22.4	--
Baseline effect KGAB/C/D (ratio)		1.2235	3.02	1.15 - 1.3	--
HP-TCS on EPBO (ratio)		1.45086	28.4	0.643 - 2.26	--
Pr(1), high placebo responder	%	38.5	--	31.8 - 45.8	--
Random Effects					
ω^2 Kout	var	0.566	10.2	0.453 - 0.678	47.6
ω^2 Epbo0 (high placebo responders)	var	0.00250 (fixed)	--	--	--
ω^2 E0 (baseline)	var	1.27	7.4	1.08 - 1.45	18.4
ω^2 Epbo0 (low placebo responders)	var	0.00250 (fixed)	--	--	--
ω^2 EC50	var	5.95	17.8	3.87 - 8.03	47.3
ω^2 Epbo (induction period)	var	0.346	12.6	0.26 - 0.431	42.6
ω^2 Epbo (maintenance period)	var	0.277	21.5	0.16 - 0.394	62.4

Source: Table 4, POPULATION PK-PD REPORT

Model Evaluation: VPCs showed good agreement during induction and maintenance periods. External validation demonstrated adequate predictions for Q8W dosing.

Table 18: External Validation - KGAA Addendum 11 Week 32

Study Period	Regimen	Mean Simulated %EASI 75 (95% PI)	Observed KGAB/C in Modeling Dataset (95% CI)
KGAA Week 100	q2w.q2w.q2w	90.6 (84, 96)	89 (80.7, 94.6) n=81, N=91
	q2w.q4w.q4w	85.1 (76.5, 92)	92.7 (85.6, 97) n=89, N=96
	q2w.q8w.q8w	78.4 (69.5, 86)	NA
End of KGAA Addendum 11	q2w.q2w.q2w.q4w	92.2 (85.5, 98)	NA
	q2w.q2w.q2w.q8w	85.6 (78, 92.5)	
	q2w.q4w.q4w.q4w	94.7 (89, 99)	
	q2w.q4w.q4w.q8w	88.8 (81, 95)	
	q2w.q8w.q8w.q8w	92.4 (86.5, 97)	

Source: Table 11, POPULATION PK-PD REPORT

FDA Reviewer's Comment: *Model adequately predicts EASI 75 response rates across all regimens, including Q8W. Overlapping prediction and confidence intervals support model adequacy.*

Independent PK-IGA 0,1 Model

Model Structure: Logit of IGA 0,1 probability with direct saturable placebo effect and indirect Emax drug effect. TCS effects on placebo parameters were statistically significant but <15% magnitude.

Table 19: Key Parameter Estimates - PK-IGA 0,1 Model

Parameter	unit	Estimate	RSE, %	95% CI	Shrinkage
B1, Baseline value		-4.83 (fixed)	--	--	--
PLB, maximal placebo response		2.17	8.57	1.81 - 2.54	--
PL50, Time to ½ maximal placebo response	day	51.7	7.35	44.2 - 59.1	--
Kout, first order rate constant for loss of response, drug latent variable	day	0.00996	4.40	0.00914 - 0.0109	--
Emax		6.43	9.58	5.33 - 7.76	--
EC50	ug/mL	52.9	25.5	32.4 - 86.6	--
ANYHP on PLB, multiplicative		-0.447	16.9	-0.595 - -0.299	--
ANYTCS on PL50, multiplicative		-0.517	9.64	-0.615 - -0.419	--
Random Effects					
ω2 PLB	var	19.1	8.44	16 - 22.3	25.8

Source: Table 7, POPULATION PK-PD REPORT

Model Evaluation: VPCs showed good fit during induction. Some overprediction of Q2W response during maintenance was noted but did not impact Q4W vs. Q8W comparisons.

Table 20: External Validation - KGAA Addendum 11 Week 32

Study Period	Regimen	Mean Simulated %IGA 0 or 1	Observed KGAB/C in Modeling Dataset
KGAA Week 100	q2w.q2w.q2w.	90.8 (83.1, 97)	74.6 (62.1, 84.7) n=47, N=63
	q2w.q4w.q4w.	84.3 (74.6, 92.9)	80.9 (69.5, 89.4) n=55, N=68
	q2w.q8w.q8w	75.9 (64, 85.7)	NA
End of KGAA Addendum 11	q2w.q2w.q2w.q4w	85.7 (76.7, 93.7)	NA
	q2w.q2w.q2w.q8w	78.4 (67.8, 87.9)	
	q2w.q4w.q4w.q4w	84.6 (75, 92.4)	
	q2w.q4w.q4w.q8w	76.9 (66.4, 86.3)	
	q2w.q8w.q8w.q8w	76.3 (65.6, 86.6)	

Source: Table 12, . POPULATION PK-PD REPORT

FDA Reviewer's Comment: *Despite some overprediction, 95% prediction intervals overlap observed data for Q4W and Q8W. Model is adequate for comparing maintenance regimens. N*o covariates with clinically meaningful impact were identified. Age, sex, baseline EASI, and body weight (via PK) showed no significant effects. TCS effects were statistically significant but <15% magnitude without reducing inter-individual variability.

16.3.4.2. Approach 2: Combined PK-EASI-IGA Model

A combined ordered categorical model jointly characterized EASI (4 categories: <EASI 50, EASI 50, EASI 75, EASI 100) and IGA (5 categories: scores 0-4) responses, enabling simulation of protocol-specified escape rules. The joint EC50 estimate of 47.5 µg/mL was consistent with independent models. Predicted differences between Q4W and Q8W at Week 52 were 4.1% (EASI 75) and 5.5% (IGA 0,1), providing cross-validation of independent model results.

Statistically significant covariates (baseline EASI, race, TCS use) had <15% magnitude effects with minimal impact on IIV, indicating no clinical significance for dose selection.).
VPCs stratified by subpopulation showed good fit during induction and maintenance periods. VPCs with dynamically adjusted dosing demonstrated observed data within 95% CI. External validation against KGAA (Week 100) and KGAA Addendum 11 (Week 32) showed adequate predictions with overlapping prediction and confidence intervals (**Table 21**).

Table 21: Combined Model: Predicted vs. Observed Response Rates at Week 32

Endpoint	Regimen	Predicted Mean % (95% PI)	Observed % (95% CI)
EASI 75	Q4W	95.0 (88.3, 99)	86.3 (73.7, 94.3)
EASI 75	Q8W	91.4 (81.6, 98.1)	85.7 (72.8, 94.1)
IGA 0,1	Q4W	77.3 (66, 87.4)	72.5 (58.3, 84.1)
IGA 0,1	Q8W	70.3 (59.2, 81.6)	68.8 (53.7, 81.3)

FDA Reviewer's Comment: *The combined model adequately predicts both EASI and IGA response rates. The 95% prediction intervals overlap with observed clinical data, supporting model adequacy. The combined model provides additional confidence through its ability to simulate study designs with escape rules.*

16.3.4.3. Comparison of Q4W vs. Q8W Dosing

Table 22: Predicted Difference Between Q4W and Q8W Maintenance Dosing

Timepoint/Study Design	Model Approach	EASI 75 Difference Mean % (95% PI)	IGA 0,1 Difference Mean % (95% PI)
Week 52 (KGAB/KGAC Design)	Combined Model	4.06 (0.95, 7.58)	5.53 (1.94, 9.35)
	Independent Models	4.86 (1.00, 10.0)	6.96 (1.52, 14.5)
Week 32 (KGAA Addendum 11)	Combined Model	3.64 (0, 9.71)	7.05 (0.97, 14.6)
	Independent Models	6.89 (1.0, 14.0)	7.21 (0.97, 15.5)

FDA Comment: *Both modeling approaches yield consistent results with overlapping prediction intervals. Mean predicted differences are small (4-7%) and within clinical variability. Clinical data from Study KGAA Addendum 11 shows numerically similar response rates (EASI 75: 86.3% vs. 85.7%; IGA 0,1: 72.5% vs. 68.8%). Consistency between approaches strengthens confidence in predictions.*

16.3.5. Overall Assessment

The population pharmacokinetic analysis demonstrated that lebrikizumab PK is well-characterized by a 2-compartment model with first-order absorption and linear elimination, with body weight effects appropriately accounted for through allometric scaling. The model adequately predicts Q8W exposures, which are approximately 50% lower in average steady-state concentration compared to Q4W dosing, as validated against observed data from Study KGAA Addendum 11.

Two complementary exposure-efficacy modeling approaches were developed and rigorously validated. Both the independent PK-EASI and PK-IGA 0,1 models and the combined PK-EASI-IGA ordered categorical model yielded consistent EC_{50} estimates ranging from 47.5 to 57.0 µg/mL. These models predicted small differences of 4-7% in EASI 75 and IGA 0,1 response rates between Q4W and Q8W maintenance dosing regimens. Model predictions were validated using prospective clinical data from Study KGAA Addendum 11, with 95% prediction intervals overlapping observed 95% confidence intervals. Comprehensive covariate analyses identified no factors with clinically meaningful impact on the exposure-efficacy relationship. Topical corticosteroids (TCS) and high-potency topical corticosteroids (HP-TCS) were evaluated as potential covariates in the exposure-efficacy models for lebrikizumab. While statistically significant effects were identified in some models, these effects were of limited clinical magnitude and did not meaningfully impact dosing decisions.

16.3.6. Conclusions and Recommendations

The pharmacometric analyses support Q8W as an alternative maintenance dosing option for Week 16 responders following Q2W induction. This conclusion is based on adequate PopPK prediction of Q8W exposures, minor predicted differences between Q4W and Q8W (4-7%) from two independent exposure-efficacy models, prospective validation with Study KGAA Addendum 11 data, and cross-validation between modeling approaches. Both Q4W and Q8W are appropriate maintenance options, with selection individualized based on patient preference, convenience, and adherence considerations.

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