Summary Report of Benefit-Risk Assessment

EBGLYSS SOLUTION FOR INJECTION IN PRE-FILLED PEN 250MG/2ML

NEW DRUG APPLICATION

Active Ingredient(s)	Lebrikizumab
Product Registrant	DKSH SINGAPORE PTE. LTD.
Product Registration Number	SIN17229P
Application Route	Abridged evaluation
Date of Approval	02 May 2025

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A INTRODUCTION

Ebglyss is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy.

The active substance, lebrikizumab, is an immunoglobulin (IgG4) monoclonal antibody that binds selectively to interleukin (IL)-13 and inhibits the downstream effects. IL-13 is the central mediator driving multiple pathophysiological aspects of atopic dermatitis through promoting type 2 inflammation and mediating its effects on tissue. Lebrikizumab inhibits IL-13-induced response including the release of proinflammatory cytokines, chemokines and IgE.

Ebglyss is available as solution for injection containing 250 mg/2 ml of lebrikizumab in a prefilled pen (synonymous with “autoinjector”). Other ingredients are L-histidine, glacial acetic acid, sucrose, polysorbate 20 and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, lebrikizumab, is manufactured at Samsung Biologics Co., Ltd., Incheon, Republic of Korea. The drug product, Ebglyss, is manufactured at Eli Lilly and Company, Indiana, USA.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on [redacted] production-scale batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in the manufacturing process and specifications.

The drug substance specifications were established in accordance with ICH Q6B guideline and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance [redacted]. The packaging is [redacted] polycarbonate containers that are sealed with a [redacted], polypropylene copolymer screw cap closure.

Drug product:

The manufacturing process involves thawing, pooling and homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored between 2-8 ºC with a patient-use period of 7 days stored up to 30°C. The primary container closure system is a Type I glass syringe barrel with a 27G needle, closed with a rigid needle shield and a laminated bromobutyl elastomeric plunger. The filled primary container closure system is subsequently assembled into a prefilled pen.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of lebrikizumab in the treatment of moderate-to-severe atopic dermatitis (AD) was based primarily on three pivotal Phase III studies (KGAB, KGAC, and KGAD). These were randomised, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy and safety of lebrikizumab as monotherapy (studies KGAB and KBAC) or in combination with topical corticosteroids (TCS) (study KGAD) in adult and adolescent patients with moderate-to-severe AD who had inadequate response to treatment with topical medications.

Studies KGAB and KGAC (monotherapy)

Studies KGAB and KGAC were similar in study design and consisted of a 16-week induction period and a 36-week maintenance period. During the induction period, subjects were randomised in a 2:1 ratio to receive lebrikizumab 250 mg every two weeks (Q2W) with a loading dose of 500 mg given at Week 0 and 2 or placebo Q2W via subcutaneous (SC) injection.

After completion of the Week 16 visit, responders entered the maintenance blinded period and were re-randomised in a 2:2:1 ratio to receive lebrikizumab 250 mg Q2W, lebrikizumab 250 mg every four weeks (Q4W), or placebo (lebrikizumab withdrawal). A responder was defined as a subject who achieved an Investigator's Global Assessment (IGA) score of 0 or 1 or an Eczema Area and Severity Index (EASI) 75 response at Week 16 without receiving any rescue therapy.

Patients who were non-responders at Week 16, received rescue therapy during the induction period, or did not maintain an EASI 50 response at Week 24, 32, 40, or 48 following re-randomisation to the maintenance blinded period were assigned to an escape arm and received open-label lebrikizumab 250 mg Q2W through Week 52. Use of topical or systemic treatments for AD was prohibited during the induction period except as rescue therapy. Intermittent use of topical rescue medications was permitted during the maintenance period. The study design and use of placebo as the comparator are considered acceptable to assess the efficacy of lebrikizumab as monotherapy in the treatment of moderate-to-severe AD.

The co-primary efficacy endpoints were the percentage of subjects with IGA 0 or 1 and a ≥2-point reduction from baseline at Week 16, and the percentage of subjects achieving EASI 75 (≥75% reduction from baseline in EASI) at Week 16. Key secondary efficacy endpoints for the induction period included the percentage of subjects achieving EASI 90 at Week 4 and Week 16, percentage of subjects with ≥4-point improvement from baseline in Pruritus Numerical Rating Scale (Pruritus NRS) among subjects with baseline score of ≥4 points at Weeks 2, 4 and 16, percentage of subjects with ≥4-point improvement from baseline in Dermatology Life Quality Index (DLQI) among subjects with baseline score of ≥4 points, percentage of subjects with ≥2-point improvement from baseline in Sleep-Loss Scale among subjects with baseline score of ≥2 points, as well as percent changes in EASI and Pruritus NRS score from baseline at Week 16, and changes in DLQI total score and Sleep-Loss Scale score from baseline at Week 16. Key secondary efficacy endpoints for the maintenance blinded period included the percentage of re-randomised subjects who maintained EASI 75, IGA 0 or 1 and a ≥2-point reduction from baseline, percent change in EASI Score from baseline at Week 52 for those patients re-randomised at Week 16, and Pruritus NRS score of ≥4-point improvement from baseline at Week 52.

The primary and key secondary efficacy endpoints were analysed on the intent-to-treat (ITT) population in study KGAB, and on the modified ITT population in study KGAC. The modified ITT population excluded all subjects from a specific site due to critical audit finding of non-compliance with protocol entry criteria. In both studies, a pre-specified graphical multiple testing approach was implemented to control the overall type I error rate at 2-sided alpha of 0.05 for all primary and key secondary endpoints for the induction period. For co-primary endpoints, an intersection-union method was used, which required statistical significance to be demonstrated for both co-primary endpoints at the 2-sided 0.05 level. If both co-primary endpoints were significant, the key secondary endpoints would be tested following a pre-specified hierarchical testing procedure.

In study KGAB, a total of 424 subjects were randomised and included in the ITT population: 283 subjects in the lebrikizumab arm and 141 subjects in the placebo arm. At Week 16, 157 subjects who responded to lebrikizumab were re-randomised to lebrikizumab 250 mg Q2W (62 subjects), lebrikizumab 250 mg Q4W (63 subjects), or placebo (32 subjects) during the maintenance period.

In study KGAC, a total of 445 subjects were randomised. Due to critical findings from a site audit, data from all 18 subjects enrolled at this site were excluded and 427 subjects were included in the modified ITT population: 281 subjects in the lebrikizumab arm and 146 subjects in the placebo arm. At Week 16, 134 subjects who responded to lebrikizumab were re-randomised to lebrikizumab 250 mg Q2W (51 subjects), lebrikizumab 250 mg Q4W (55 subjects), or placebo (28 subjects) during the maintenance period.

Subject demographic and baseline characteristics were well balanced between the study arms in both studies. Across the two studies, the mean age was 35.8 years, and 12.0% of subjects were adolescents aged 12 to <18 years with body weight ≥40 kg. Male and female genders were equally represented. The majority of subjects were White (63.7%), and 22.6% of subjects were Asian. At baseline, 61.5% of subjects had IGA score of 3 (moderate AD) and 38.5% of subjects had IGA score of 4 (severe AD). The mean EASI was 29.6, the mean Pruritus NRS was 7.2, and the mean DLQI was 15.5 at baseline. Prior systemic treatment for AD was reported for 47.8% of subjects, of which majority (39.6%) received prior systemic corticosteroids.

Summary of efficacy results during induction period (KGAB and KGAC)

	Study KGAB		Study KGAC	
	Lebrikizumab	**Placebo**	**Lebrikizumab**	**Placebo**
Co-primary endpoints				
IGA 0 or 1 and ≥2-point reduction from baseline at Week 16, n/N (%)	122/283 (43.1)	18/141 (12.7)	93/281 (33.2)	16/146 (10.8)
Difference (95% CI)	29.7 (21.6, 37.8)		21.9 (14.2, 29.6)	
p-value	<0.001		<0.001	
EASI 75 at Week 16, n/N (%)	166/283 (58.8)	23/141 (16.2)	146/281 (52.1)	26/146 (18.1)
Difference (95% CI)	42.0 (33.3, 50.6)		33.3 (24.4, 42.2)	
p-value	<0.001		<0.001	
Key secondary endpoints (adjusted for multiplicity)				
EASI 90 at Week 16, n/N (%)	108/283 (38.3)	13/141 (9.0)	86/281 (30.7)	14/146 (9.5)
Difference (95% CI)	28.8 (21.3, 36.3)		20.7 (13.3, 28.1)	
p-value	<0.001		<0.001	
Percentage change in EASI from baseline to Week 16, LSM (SE)	-64.3 (3.2)	-26.0 (4.0)	-61.5 (3.3)	-28.0 (3.9)
Difference (95% CI)	-38.3 (-46.4, -30.2)		-33.6 (-41.2, -26.0)	
p-value	<0.001		<0.001	
EASI 90 at Week 4, n/N (%)	35/283 (12.4)	2/141 (1.6)	18/281 (6.3)	2/146 (1.5)
Difference (95% CI)	10.7 (6.2, 15.2)		4.9 (1.4, 8.4)	
p-value	<0.001		0.023	
Pruritus NRS score ≥4-point improvement at Week 16, n/N (%)	121/263 (45.9)	17/130 (13.0)	101/253 (39.8)	15/134 (11.5)
Difference (95% CI)	32.9 (24.6, 41.3)		28.3 (20.0, 36.5)	
p-value	<0.001		<0.001	
Percentage change in Pruritus NRS score from baseline to Week 16, LSM (SE)	-45.5 (3.1)	-15.1 (3.8)	-36.6 (3.3)	-9.02 (3.9)
Difference (95% CI)	-30.4 (-38.1, -22.7)		-27.5 (-34.9, -20.2)	
p-value	<0.001		<0.001	
Pruritus NRS score ≥4-point improvement at Week 4, n/N (%)	56/263 (21.5)	3/130 (2.3)	42/253 (16.8)	4/134 (3.0)
Difference (95% CI)	19.3 (13.7, 25.0)		13.2 (7.7, 18.7)	
p-value	<0.001		<0.001	
Pruritus NRS score ≥4-point improvement at Week 2, n/N (%)	16/263 (6.1)	1/130 (0.9)	9/253 (3.6)	1/134 (0.7)
Difference (95% CI)	5.3 (1.9, 8.6)		2.7 (-0.1, 5.4)	
p-value	0.017		0.113	
DLQI ≥4-point improvement at Week 16, n/N (%)	171/226 (75.6)	39/116 (33.8)	143/215 (66.3)	39/115 (33.6)
Difference (95% CI)	41.8 (31.2, 52.3)		33.0 (22.2, 43.8)	
p-value	<0.001		<0.001	
Change in DLQI total score from baseline to Week 16, LSM (SE)	-8.7 (1.1)	-2.9 (1.1)	-7.3 (1.2)	-2.4 (1.2)
Difference (95% CI)	-5.8 (-7.1, -4.5)		-4.9 (-6.3, -3.5)	
p-value	<0.001		<0.001	
Sleep-Loss Scale score ≥2-point improvement at Week 16, n/N (%)	76/195 (39.0)	4/91 (4.7)	45/161 (28.0)	8/97 (8.2)
Difference (95% CI)	34.6 (26.2, 43.0)		18.9 (9.6, 28.1)	
p-value	<0.001		<0.001	
Change in Sleep-Loss Scale score from baseline to Week 16, LSM (SE)	-1.1 (0.1)	-0.4 (0.1)	-1.1 (0.1)	-0.4 (0.1)
Difference (95% CI)	-0.8 (-0.9, -0.6)		-0.7 (-0.9, -0.5)	
p-value	<0.001		<0.001	

In both studies, lebrikizumab demonstrated statistically significant improvements over placebo for the co-primary endpoints. The percentage of subjects with IGA 0 or 1 and a ≥2-point reduction from baseline at Week 16 was significantly higher in the lebrikizumab arm compared to the placebo arm (KGAB: 43.1% vs 12.7%, difference 29.7% [95% CI: 21.6, 37.8], p<0.001;

KGAC: 33.2% vs 10.8%, difference 21.9% [95% CI: 14.2, 29.6], p<0.001). Statistically significantly higher percentage of subjects achieved EASI 75 at Week 16 in the lebrikizumab arm compared to the placebo arm (KGAB: 58.8% vs 16.2%, difference 42.0% [95% CI: 33.3, 50.6], p<0.001; KGAC: 52.1% vs 18.1%, difference 33.3% [95% CI: 24.4, 42.2], p<0.001). The primary analyses were consistent in various sensitivity analyses using alternative imputation methods, demonstrating robustness of the data.

Treatment efficacy of lebrikizumab was supported by the key secondary endpoints. In studies KGAB and KGAC, 38.3% and 30.7% of subjects in the lebrikizumab arm achieved EASI 90 at Week 16, compared to 9.0% and 9.5% of subjects in the placebo arm; the treatment difference was 28.8% (95% CI: 21.3, 36.3; p<0.001) in study KGAB and 20.7% (95% CI: 13.3, 28.1; p<0.001) in study KGAC. Similarly, significantly higher proportion of subjects in the lebrikizumab arm achieved Pruritus NRS score ≥4-point improvement at Week 16 (KGAB: 45.9% vs 13.0%, difference 32.9% [95% CI: 24.6, 41.3], p<0.001; KGAC: 39.8% vs 11.5%, difference 28.3% [95% CI: 20.0, 36.5], p<0.001), DLQI ≥4-point improvement at Week 16 (KGAB: 75.6% vs 33.8%, difference 41.8% [95% CI: 31.2, 52.3], p<0.001; KGAC: 66.3% vs 33.6%, difference 33.0% [95% CI: 22.2, 43.8], p<0.001), and Sleep-Loss Scale score ≥2-point improvement at Week 16 (KGAB: 39.0% vs 4.7%, difference 34.6% [95% CI: 26.2, 43.0], p<0.001; KGAC: 28.0% vs 8.2%, difference 18.9% [95% CI: 9.6, 28.1], p<0.001). For the key secondary endpoints which were included in multiplicity-adjusted testing schemes, statistically significant improvements with lebrikizumab versus placebo were demonstrated for all endpoints, except for percentage of subjects with Pruritus NRS score ≥4-point improvement at Week 2 in study KGAC; however, numerical improvements were observed in subjects treated with lebrikizumab versus placebo.

During the maintenance blinded period, subjects who responded to lebrikizumab treatment were re-randomised to receive lebrikizumab 250 mg Q4W, lebrikizumab 250 mg Q2W, or placebo (lebrikizumab withdrawal). At Week 52, for the pooled population of the two studies, the proportion of subjects who continued to exhibit IGA 0 or 1 and a ≥2-point reduction from baseline was 76.9%, 71.2% and 47.9% for lebrikizumab Q4W, lebrikizumab Q2W and placebo, respectively. The proportion of subjects who maintained EASI 75 at Week 52 was 81.7%, 78.4% and 66.4% for lebrikizumab Q4W, lebrikizumab Q2W and placebo, respectively. Compared to placebo (66.3%), higher proportions of subjects in the lebrikizumab Q4W (84.7%) and Q2W (84.6%) arms continued to exhibit ≥4-point reduction in the Pruritus NRS score from baseline at Week 52. The results showed that responses were maintained with both Q4W and Q2W lebrikizumab regimen, with Q4W showing slightly better efficacy, supporting the proposed maintenance dosing regimen of 250 mg Q4W.

Subgroup analyses from studies KGAB and KGAC showed generally consistent treatment effects across pre-specified subgroups by age, sex, race, geographical region, weight, disease severity, and prior use of systemic treatments. Efficacy results in adolescent subjects aged 12 to 17 years were similar to those observed in the overall study population. For the pooled adolescent population of the two studies, 46.6% of adolescent subjects in the lebrikizumab arm achieved IGA 0 or 1 and a ≥2-point reduction from baseline at Week 16, compared to 14.3% in the placebo arm. The percentage of adolescent subjects who achieved EASI 75 at Week 16 was 62.0% in the lebrikizumab arm and 17.3% in the placebo arm.

Study KGAD (in combination with TCS)

Study KGAD was a 16-week study with a design similar to the induction period of studies KGAB and KGAC. Subjects were randomised in a 2:1 ratio to receive lebrikizumab 250 mg Q2W with a loading dose of 500 mg given at Week 0 and 2 or placebo Q2W, in combination with TCS.

Low or medium potency TCS treatment was initiated at Week 0 in all subjects and was allowed to be tapered or stopped as needed, based on treatment response. Low potency topical calcineurin inhibitor (TCI) was permitted for use on sensitive areas only. Subjects who responded to lebrikizumab in study KGAD at Week 16 were eligible to participate in the long-term extension (LTE) supportive study KGAA where subjects were re-randomised 2:1 to receive lebrikizumab 250 mg Q2W or Q4W in combination with TCS over 100 weeks. Subjects who did not meet responder criteria in study KGAD at Week 16 were eligible to participate in study KGAA and received lebrikizumab 250 mg Q2W (with subjects on placebo receiving a loading dose of 500 mg at Week 0 and 2 of study KGAA). A responder was defined as a subject who achieved an IGA score of 0 or 1 or an EASI 75 response at Week 16 without receiving rescue therapy.

Study KGAD had the same co-primary efficacy endpoints as studies KGAB and KGAC, i.e., the percentage of subjects with IGA 0 or 1 and a ≥2-point reduction from baseline at Week 16, and the percentage of subjects achieving EASI 75 at Week 16. Key secondary efficacy endpoints included the percentage of subjects achieving EASI 90, percentage of subjects with ≥4-point improvement from baseline in Pruritus NRS among subjects with baseline score of ≥4 points, percentage of subjects with ≥4-point improvement from baseline in DLQI among subjects with baseline score of ≥4 points, as well as changes in EASI, Pruritus NRS score, DLQI total score and Sleep-Loss Scale score from baseline at Week 16.

The primary and key secondary efficacy endpoints were analysed on the modified ITT population, which excluded subjects from a specific site due to critical audit finding of non-compliance with protocol entry criteria. To control the overall type I error rate at a 2-sided alpha of 0.05, multiplicity-adjusted testing schemes were implemented whereby the co-primary and key secondary endpoints were tested following a pre-specified hierarchical testing procedure.

A total of 228 subjects were randomised in the study, and 211 subjects were included in the modified ITT population (after exclusion of 17 subjects from a specific site due to findings of a site audit): 145 subjects in the lebrikizumab arm and 66 subjects in the placebo arm. Subject demographic and baseline characteristics were well balanced between the study arms. The mean age was 37.2 years, and 21.8% of subjects were adolescents aged 12 to <18 years with body weight ≥40 kg. Male and female genders were evenly represented. The majority of subjects were White (61.6%), and 14.7% of subjects were Asian. At baseline, 69.2% of subjects had IGA score of 3 (moderate AD) and 30.8% of subjects had IGA score of 4 (severe AD). The mean EASI was 27.3, the mean Pruritus NRS was 7.1, and the mean DLQI was 14.4 at baseline. Prior systemic treatment for AD was reported for 47.4% of subjects, of which majority (29.9%) received prior systemic corticosteroids. A total of 96.7% of subjects received concomitant TCS as per protocol; the most commonly used TCS were triamcinolone (90.5%) and hydrocortisone (68.7%).

Summary of efficacy results (KGAD)

	Lebrikizumab+TCS	**Placebo+TCS**
Co-primary endpoints		
IGA 0 or 1 and ≥2-point reduction from baseline at Week 16, n/N (%)	60/145 (41.2)	15/66 (22.1)
Difference (95% CI)	18.3 (5.1, 31.5)	
p-value	0.011	
EASI 75 at Week 16, n/N (%)	101/145 (69.5)	28/66 (42.2)
Difference (95% CI)	26.4 (12.1, 40.8)	
p-value	<0.001	
Key secondary endpoints (adjusted for multiplicity)		
EASI 90 at Week 16, n/N (%)	60/145 (41.2)	14/66 (21.7)

Difference (95% CI)	18.9 (6.1, 31.7)	
p-value	0.008	
Percentage change in EASI from baseline to Week 16, LSM (SE)	-76.8 (4.1)	-53.1 (5.1)
Difference (95% CI)	-23.6 (-33.6, -13.7)	
p-value	<0.001	
Pruritus NRS score ≥4-point improvement at Week 16, n/N (%)	66/130 (50.6)	18/57 (31.9)
Difference (95% CI)	19.2 (4.3, 34.1)	
p-value	0.017	
Percentage change in Pruritus NRS score from baseline to Week 16, LSM (SE)	-50.7 (4.5)	-35.5 (6.4)
Difference (95% CI)	-15.2 (-27.7, -2.7)	
p-value	0.017	
EASI 75 & Pruritus NRS score ≥4-point improvement at Week 16, n/N (%)	50/130 (38.3)	10/57 (16.8)
Difference (95% CI)	21.6 (8.3, 35.0)	
p-value	0.005	
DLQI ≥4-point improvement at Week 16, n/N (%)	81/105 (77.4)	28/48 (58.7)
Difference (95% CI)	17.2 (0.1, 34.3)	
p-value	0.036	
Change in DLQI total score from baseline to Week 16, LSM (SE)	-9.8 (1.8)	-6.5 (1.9)
Difference (95% CI)	-3.3 (-5.3, -1.3)	
p-value	0.001	
Sleep-Loss Scale score ≥2-point improvement at Week 16, n/N (%)	30/88 (34.5)	6/34 (18.4)
Difference (95% CI)	20.8 (2.1, 39.5)	
p-value	0.048	
Change in Sleep-Loss Scale score from baseline to Week 16, LSM (SE)	-1.1 (0.1)	-0.8 (0.1)
Difference (95% CI)	-0.3 (-0.6, -0.0)	
p-value	0.025	

In the study, lebrikizumab+TCS demonstrated statistically significant improvements over placebo+TCS for the co-primary endpoints. The percentage of subjects with IGA 0 or 1 and a ≥2-point reduction from baseline at Week 16 was significantly higher in the lebrikizumab+TCS arm compared to the placebo+TCS arm (41.2% vs 22.1%, difference 18.3% [95% CI: 5.1, 31.5], p=0.011). Statistically significantly higher percentage of subjects achieved EASI 75 at Week 16 in the lebrikizumab+TCS arm compared to the placebo+TCS arm (69.5% vs 42.2%, difference 26.4% [95% CI: 12.1, 40.8], p<0.001). The results from primary analyses were consistent in various sensitivity analyses using alternative imputation methods, demonstrating robustness of the results. In addition, treatment effect with lebrikizumab+TCS compared to placebo+TCS was generally consistent across pre-specified subgroups, including adolescent subjects (IGA 0 or 1: 57.3% vs 28.6%; EASI 75: 88.0% vs 57.1%).

Treatment efficacy of lebrikizumab in combination with TCS was supported by the key secondary endpoints. At week 16, 41.2% of subjects in the lebrikizumab+TCS arm achieved EASI 90, compared to 21.7% of subjects in the placebo+TCS arm (difference 18.9% [95% CI: 6.1, 31.7], p=0.008). Significantly higher proportion of subjects in the lebrikizumab+TCS arm achieved Pruritus NRS score ≥4-point improvement (50.6% vs 31.9%, difference 19.2% [95% CI: 4.3, 34.1], p=0.017), DLQI ≥4-point improvement (77.4% vs 58.7%, difference 17.2% [95% CI: 0.1, 34.3], p=0.036), and Sleep-Loss Scale score ≥2-point improvement (34.5% vs 18.4%, difference 20.8% [95% CI: 2.1, 39.5], p=0.048). Overall, statistically significant improvements with lebrikizumab+TCS versus placebo+TCS were demonstrated for all the key secondary endpoints that were included in multiplicity-adjusted testing schemes.

Supporting data were obtained from the LTE study KGAA, in which a total of 86 lebrikizumab-treated responders from study KGAD were re-randomised to receive either lebrikizumab 250 mg Q4W or lebrikizumab 250 mg Q2W in combination with TCS. The proportion of subjects maintaining IGA 0 or 1 after 56 weeks of lebrikizumab treatment was 86.8% in the lebrikizumab Q4W+TCS arm and 75.4% in the lebrikizumab Q2W+TCS arm. Treatment effects were also maintained after 56 weeks of lebrikizumab treatment for EASI 75 (81.2% in the lebrikizumab Q4W+TCS arm and 85.6% in the lebrikizumab Q2W+TCS arm), EASI 90 (62.2% in the lebrikizumab Q4W+TCS arm and 74.9% in the lebrikizumab Q2W+TCS arm), and Pruritus NRS ≥4-point improvement (81.3% in the lebrikizumab Q4W+TCS arm and 87.7% in the lebrikizumab Q2W+TCS arm).

In conclusion, lebrikizumab demonstrated statistically significant and clinically relevant improvements over placebo when used as monotherapy or in combination with TCS for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of lebrikizumab was based primarily on safety data derived from the placebo-controlled (PC) studies, comprising a total of 1,187 patients who received at least one dose of study treatment during the induction period (AD Induction Period PC Integrated Analysis Set): 783 subjects in the lebrikizumab arm (638 received lebrikizumab and 145 received lebrikizumab+TCS) and 404 subjects in the placebo arm (338 received placebo and 66 received placebo+TCS). Supportive data were provided in 291 subjects who received study treatment during the maintenance period in the placebo-controlled studies (AD Maintenance Period PC Analysis Set), 1,343 subjects who received study treatment during the induction and maintenance period (AD Combined Induction and Maintenance Periods Analysis Set), and 1,720 subjects who were exposed to lebrikizumab at any dose (AD All Lebrikizumab Exposure Analysis Set).

Of the 1,720 subjects with moderate-to-severe AD (including 372 adolescents) who received lebrikizumab at any dose, the overall exposure to lebrikizumab was 1,637.02 patient-years as of the data cutoff date of 06 June 2022. A total of 891 subjects (including 270 adolescents) were exposed to lebrikizumab for at least 1 year.

Overview of safety profile in placebo-controlled studies

AE	Induction period (Weeks 0-16)		Maintenance period (Weeks 16-52)		
	Lebrikizumab (N=783)	Placebo (N=404)	Lebrikizumab Q4W (N=118)	Lebrikizumab Q2W (N=113)	Placebo (Leb withdrawal) (N=60)
Any AE	384 (49.2%)	215 (53.1%)	61 (51.7%)	56 (49.7%)	30 (50.0%)
Treatment-related AE	131 (16.8%)	42 (10.4%)	22 (18.6%)	12 (10.7%)	7 (11.6%)
SAE	10 (1.3%)	8 (1.9%)	2 (1.7%)	2 (1.8%)	1 (1.6%)
Discontinuations due to AE	18 (2.3%)	6 (1.4%)	2 (1.7%)	1 (0.9%)	0
Deaths	0	1 (0.2%)	0	0	0

During the induction period, 49.2% of lebrikizumab-treated subjects and 53.1% of placebo-treated subjects experienced at least one treatment-emergent adverse event (TEAE). The majority of the TEAEs were mild or moderate in severity. Severe TEAEs were less frequently

reported in the lebrikizumab arm compared to placebo (2.3% vs 4.4%). The TEAEs which were more frequently reported in the lebrikizumab arm compared to placebo included conjunctivitis (6.5% vs 1.8%), nasopharyngitis (4.4% vs 3.2%), headache (4.4% vs 2.9%), conjunctivitis allergic (1.8% vs 0.7%), dry eye (1.4% vs 0.9%), and rhinitis allergic (1.0% vs 0.2%). The safety profile of lebrikizumab was comparable when used with or without TCS.

During the maintenance period, the incidences of TEAEs were comparable across lebrikizumab Q4W (51.7%), lebrikizumab Q2W (49.7%), and placebo (50.0%). The majority of the TEAEs were mild or moderate in severity. The TEAEs which were more frequently reported in the lebrikizumab Q4W arm compared to placebo included COVID-19 (9.4% vs 3.3%), nasopharyngitis (7.6% vs 5.0%), conjunctivitis allergic (5.9% vs 3.3%), headache (4.2% vs 1.6%), oral herpes (3.4% vs 1.6%), and folliculitis (2.5% vs 0).

The incidences of serious adverse events (SAEs) were comparable across lebrikizumab and placebo arms, for both induction (1.3% vs 1.9%) and maintenance (1.7% [Q4W] vs 1.6%) periods. All SAEs were single cases with no trend identified. The incidences of AEs leading to study drug discontinuation were low (induction period: 2.3% vs 1.4%; maintenance period: 1.7% [Q4W] vs 0). No lebrikizumab-related deaths were reported across all lebrikizumab AD studies.

The AEs of special interest (AESIs) with lebrikizumab included conjunctivitis, infections, eosinophilia and eosinophil-related disorders, hypersensitivity reactions, injection site reactions (ISR), AD exacerbation, hepatic safety, suicide/self-injury, and malignancies. During the induction period, more subjects in the lebrikizumab arm experienced TEAEs of conjunctivitis cluster (conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial) compared to placebo (8.5% vs 2.5%). Treatment-emergent infections were reported for 21.2% of subjects in the lebrikizumab arm and 18.9% of subjects in the placebo arm. Excluding ocular-related disorders, nasopharyngitis (4.4% vs 3.2%) and herpes zoster (0.6% vs 0) were reported slightly more frequently for lebrikizumab compared to placebo. Eosinophilia AEs were infrequently reported and comparable between lebrikizumab and placebo (0.6% vs 0.8%); however, more subjects in the lebrikizumab arm experienced increased postbaseline blood eosinophils compared to placebo (20.3% vs 11.7%) and severe elevation of blood eosinophils (greater than 5000 cells/mm^3) was only detected in lebrikizumab-treatment subjects (0.4%).

Compared to placebo, lebrikizumab-treated subjects reported fewer immediate hypersensitivity reactions (2.8% vs 6.2%), AD exacerbation events (6.4% vs 18.9%) and more ISRs (2.6% vs 1.5%) during the induction period. Most of the AESIs were mild or moderate in severity and did not lead to treatment discontinuation. Data did not suggest an increased risk of hepatic events, suicide/self-injury, or malignancies with lebrikizumab treatment.

Among the 147 adolescents from the placebo-controlled studies, TEAEs were reported at a lower frequency in the lebrikizumab arm compared to the placebo arm (35.6% vs 55.3%) during the induction period. All events were mild or moderate in severity, and no deaths occurred. There were no clinically meaningful differences observed for growth parameters (weight, height, and BMI) in adolescents between lebrikizumab and placebo. Among the 372 adolescents who were exposed to lebrikizumab at any dose across the AD program, the incidences of TEAEs (61.0% vs 65.2%), SAEs (2.2% vs 3.6%), and AEs leading to treatment discontinuation (3.0% vs 4.6%) were comparable to those in adults. The safety profile in adolescents were consistent with that observed in adults.

Overall, the safety profile of lebrikizumab was manageable and considered acceptable for patients with moderate-to-severe AD.

E ASSESSMENT OF BENEFIT-RISK PROFILE

AD is the most prevalent chronic and relapsing inflammatory skin disease which can have significant burden on patient's quality of life. The current treatment options for moderate-to-severe AD include topical treatments such as topical corticosteroids and topical calcineurin inhibitors, as well as systemic treatments in patients not adequately controlled with topical medications, such as JAK inhibitors (e.g., abrocitinib) and biologics (e.g., dupilumab). Despite the currently available treatment options, patients may not achieve optimal disease control.

The efficacy of lebrikizumab in the treatment of moderate-to-severe AD was supported by two Phase III studies (KGAB and KGAC) evaluating lebrikizumab as monotherapy and one Phase III study (KGAD) evaluating lebrikizumab in combination with TCS. All the three pivotal studies met the co-primary endpoints, demonstrating statistically significant and clinically meaningful improvements in IGA score and EASI 75 at Week 16 for lebrikizumab compared to placebo. The treatment difference was 21.9%-29.7% (monotherapy) and 18.3% (in combination with TCS) for percentage of subjects with IGA 0 or 1 and a ≥2-point reduction from baseline, and 33.3%-42.0% (monotherapy) and 26.4% (in combination with TCS) for percentage of subjects achieving EASI 75, at Week 16. Lebrikizumab, with or without TCS, also demonstrated statistically significant improvements over placebo in key secondary endpoints including EASI 90, Pruritus NRS ≥4-point improvement, DLQI ≥4-point improvement, and Sleep-Loss Scale ≥2-point improvement at Week 16.

As shown in studies KGAB and KGAC, treatment efficacy was maintained till Week 52 with lebrikizumab 250 mg Q4W maintenance dose. Among subjects who achieved IGA 0 or 1 at Week 16, 76.9% of subjects in the lebrikizumab Q4W arm maintained the response at Week 52, compared to 47.9% of subjects in the placebo (lebrikizumab withdrawal) arm. Similarly, 81.7% of responders based on EASI 75 and 84.7% of responders based on Pruritus NRS maintained the response at Week 52, compared to 66.4% and 66.3% in the placebo (lebrikizumab withdrawal) arm. In addition, consistent treatment efficacy was observed in adolescent subjects, as well as in other pre-specified subgroups.

The safety profile of lebrikizumab was manageable. The incidence of TEAEs were comparable between lebrikizumab and placebo; majority were mild or moderate in severity. SAEs and AEs leading to discontinuations were low and comparable between treatment arms. No deaths were assessed by the investigator as related to lebrikizumab. Conjunctivitis was more frequently reported with lebrikizumab than placebo; most were mild or moderate in severity and occurred during the induction period. Herpes zoster and severe elevation of blood eosinophils (greater than 5000 cells/mm^3) were reported only in lebrikizumab-treated subjects with low incidences (<1.0%). The incidence of injection site reactions was numerically higher for lebrikizumab compared to placebo. The safety risks have been adequately described in the package insert.

Overall, the benefit-risk profile of lebrikizumab in the treatment of moderate-to-severe AD in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy was considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Ebglyss for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy was deemed favourable and approval of the product registration was granted on 02 May 2025.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

Ebglyss 250 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ebglyss 250 mg solution for injection in pre-filled pen

Each single-use pre-filled pen contains 250 mg of lebrikizumab in 2 mL solution (125 mg/mL).

Lebrikizumab is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to opalescent, colourless to slightly yellow to slightly brown solution, free of visible particles.

The lebrikizumab solution has a pH of 5.4-6.0 and is 230-333 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ebglyss is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of atopic dermatitis.

Posology

The recommended dose of lebrikizumab is 500 mg (two 250 mg injections) at both week 0 and week 2, followed by 250 mg administered subcutaneously every other week up to week 16.

Consideration should be given to discontinuing treatment in patients who have shown no clinical response after 16 weeks of treatment. Some patients with initial partial response may further improve with continued treatment every other week up to week 24.

Once clinical response is achieved, the recommended maintenance dose of lebrikizumab is 250 mg every fourth week.

Lebrikizumab can be used with or without topical corticosteroids (TCS). Topical calcineurin inhibitors (TCI) may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Elderly (≥ 65 years)
No dose adjustment is recommended for elderly patients (see section 5.2).

Renal and hepatic impairment
No dose adjustment is recommended for patients with renal or hepatic impairment (see section 5.2).

Body weight
No dose adjustment for body weight is recommended (see section 5.2).

Paediatric population

The safety and efficacy of lebrikizumab in children aged 6 months to <12 years or adolescents 12 to 17 years of age and weighing less than 40 kg have not yet been established. No data are available.

Method of administration

Subcutaneous use.

Lebrikizumab is administered by subcutaneous injection into the thigh or abdomen, except for 5 cm around the navel. If somebody else administers the injection, the upper arm can also be used.

For the initial 500 mg dose, two 250 mg injections should be administered consecutively in different injection sites.

It is recommended to rotate the injection site with each injection. Lebrikizumab should not be injected into skin that is tender, damaged or has bruises or scars.

A patient may self-inject lebrikizumab or the patient's caregiver may administer lebrikizumab if their healthcare professional determines that this is appropriate. Proper training should be provided to patients and/or caregivers on the administration of lebrikizumab prior to use. Detailed instructions for use are included at the end of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of lebrikizumab should be discontinued and appropriate therapy initiated.

Conjunctivitis

Patients treated with lebrikizumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination (see section 4.8).

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if lebrikizumab will influence the immune response against helminth infections by inhibiting IL-13 signalling.

Patients with pre-existing helminth infections should be treated before initiating treatment with lebrikizumab. If patients become infected while receiving lebrikizumab and do not respond to antihelminth treatment, treatment with lebrikizumab should be discontinued until infection resolves.

Vaccinations

Prior to initiating therapy with lebrikizumab, it is recommended that patients are brought up to date with all age-appropriate immunisations according to current immunisation guidelines. Live and live attenuated vaccines should not be given concurrently with lebrikizumab as clinical safety and efficacy has not been established. Immune responses to non-live vaccines were assessed in a combined tetanus, diphtheria and acellular pertussis vaccine (TdaP) and a meningococcal polysaccharide vaccine (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Live vaccines

The safety and efficacy of concurrent use of lebrikizumab with live and live attenuated vaccines has not been studied. Live and live attenuated vaccines should not be given concurrently with lebrikizumab.

Non-live vaccines

Immune responses to non-live vaccines were assessed in a study in which adult patients with atopic dermatitis were treated with lebrikizumab 500 mg at weeks 0 and 2 followed by lebrikizumab 250 mg every other week. After 12 weeks of lebrikizumab administration, patients were vaccinated with a combined tetanus, diphtheria, and acellular pertussis vaccine TdaP vaccine (T cell-dependent) and a meningococcal polysaccharide vaccine (T cell-independent) and immune responses were assessed 4 weeks later. Antibody responses to both non-live vaccines were not negatively impacted by the concomitant lebrikizumab treatment. No adverse interactions between the non-live vaccines and lebrikizumab were noted in the study. Therefore, patients receiving lebrikizumab may receive concurrent inactivated or non-live vaccinations. For information on live vaccines see section 4.4.

Concomitant therapies

Given that lebrikizumab is a monoclonal antibody, no pharmacokinetic interactions are expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of lebrikizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of lebrikizumab during pregnancy.

Breast-feeding

It is unknown whether lebrikizumab is excreted in human milk or absorbed systemically after ingestion. Maternal IgG is known to be present in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue from lebrikizumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies showed no impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Lebrikizumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are conjunctivitis (6.9%), injection site reactions (2.6%), conjunctivitis allergic (1.8%) and dry eye (1.4%).

Tabulated list of adverse reactions

Across all clinical studies in atopic dermatitis, a total of 1720 patients were administered lebrikizumab, of which, 891 patients were exposed to lebrikizumab for at least one year. Unless otherwise stated, the frequencies are based on a pool of 4 randomised, double-blind studies in patients with moderate-to-severe atopic dermatitis where 783 patients were treated with subcutaneous lebrikizumab during the placebo-controlled period (first 16 weeks of treatment).

Listed in Table 1 are adverse reactions observed from clinical trials presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

Table 1. List of adverse reactions

MedDRA System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Common Uncommon	Conjunctivitis Herpes zoster
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Eye disorders	Common Uncommon	Conjunctivitis allergic Dry eye Keratitis Blepharitis
General disorders and administration site conditions	Common	Injection site reaction

Description of selected adverse reactions

Conjunctivitis and related events

During the first 16 weeks of treatment conjunctivitis, conjunctivitis allergic, blepharitis and keratitis were reported more frequently in patients treated with lebrikizumab (6.9%, 1.8%, 0.8% and 0.6% respectively) compared to placebo (1.8%, 0.7%, 0.2% and 0.3%).
During maintenance treatment period (16-52 weeks) the incidence of conjunctivitis and conjunctivitis allergic with lebrikizumab was 5.0% and 5.9% respectively.
Across all clinical studies, among lebrikizumab-treated patients treatment discontinuation due to conjunctivitis and conjunctivitis allergic occurred in 0.7% and 0.3% of cases, respectively. Severe cases of conjunctivitis and conjunctivitis allergic occurred in 0.1% and 0.2% of cases, respectively. 72% of patients recovered, of those 57% recovered within 90 days.

Eosinophilia

Lebrikizumab-treated patients had a greater mean increase from baseline in eosinophil count compared to patients treated with placebo. In lebrikizumab treated patients 20.3% had any increase in eosinophil count compared to 11.7% with placebo. In general, the increase in the lebrikizumab-treated patients was mild or moderate and transient. Eosinophilia $\geq$5000 cells/mcL was observed in 0.4% lebrikizumab-treated patients and none of the placebo-treated patients. Adverse reactions of eosinophilia were reported in 0.6% of patients treated with lebrikizumab and with a similar rate in patients treated with placebo during the initial treatment period. Eosinophilia did not result in treatment discontinuation and no eosinophil-related disorders were reported.

Injection site reactions

Injection site reactions (including pain and erythema) were reported more frequently in patients who received lebrikizumab (2.6%) compared to placebo (1.5%). The majority (95 %) of injection site reactions were mild or moderate in severity, and few patients (< 0.5%) discontinued lebrikizumab treatment.

Herpes zoster

Herpes zoster was reported in 0.6% of the patients-treated with lebrikizumab and none of the patients in the placebo group. All herpes zoster events reported were mild or moderate in severity and none led to permanent discontinuation of treatment.

Long term safety

The long-term safety of lebrikizumab was assessed in 5 clinical studies. In the two monotherapy studies (ADvocate- 1, ADvocate-2) up to 52 weeks and in patients enrolled in the TCS combination therapy study (ADhere) and followed in a long-term extension study (ADjoin) for a total of 56 weeks and the monotherapy ADore study in adolescents for also up to 52 weeks. The safety profile of lebrikizumab as monotherapy through week 52 or in combination with TCS through week 56 is consistent with the safety profile observed up to week 16.

Paediatric population

Adolescents 12 to 17 years of age

The safety of lebrikizumab was assessed in 372 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis, including 270 patients exposed for at least one year. The safety profile of lebrikizumab in these patients was similar to the safety profile in adults with atopic dermatitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Single intravenous doses up to 10 mg/kg and multiple subcutaneous doses up to 500 mg have been administered to humans in clinical trials without dose-limiting toxicity. There is no specific treatment for lebrikizumab overdose. In the event of overdose, the patient should be monitored for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other dermatological preparations, agents for dermatitis, excluding corticosteroids, ATC code: D11AH10

Mechanism of action

Lebrikizumab is an immunoglobulin (IgG4) monoclonal antibody that binds with high affinity to interleukin (IL)-13 and selectively inhibits IL-13 signalling through the IL-4 receptor alpha (IL-4Rα)/ IL-13 receptor alpha 1 (IL-13Rα1) heterodimer, thereby inhibiting the downstream effects of IL-13. Inhibition of IL-13 signalling is expected to be of benefit in diseases in which IL-13 is a key contributor to the disease pathogenesis. Lebrikizumab does not prevent the binding of IL-13 to the IL-13 receptor alpha 2 (IL-13Rα2 or decoy receptor), which allows the internalisation of IL-13 into the cell.

Pharmacodynamic effects

In lebrikizumab clinical studies, lebrikizumab reduced the levels of serum periostin, total immunoglobulin E (IgE), CC chemokine ligand (CCL)17 [thymus and activation-regulated chemokine (TARC)], CCL18 [pulmonary and activation-regulated chemokine (PARC)], and CCL13 [monocyte chemotactic protein-4 (MCP-4)]. The decreases in the type 2 inflammation mediators provide indirect evidence of inhibition of the IL-13 pathway by lebrikizumab.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

Clinical efficacy and safety

Adults and adolescents with atopic dermatitis

The efficacy and safety of lebrikizumab as monotherapy (ADvocate-1, ADvocate-2) and with concomitant TCS (ADhere) were evaluated in three randomised, double-blind, placebo-controlled pivotal studies in 1062 adults and adolescents (aged 12 to 17 years and weighing ≥40 kg) with moderate-to-severe atopic dermatitis, defined by an Eczema Area and Severity Index (EASI) ≥ 16, Investigator's Global Assessment (IGA) ≥ 3, and a body surface area (BSA) involvement of ≥ 10%. Patients enrolled into the three studies previously had an inadequate response to topical medication or determination that topical treatments are otherwise medically inadvisable.

In all three studies, patients received an initial dose of 500 mg of lebrikizumab (two 250 mg injections) at weeks 0 and 2, followed by 250 mg every other week (Q2W) until week 16, or matching placebo in a 2:1 ratio. In ADhere, study patients also received concomitant low-to-mid potency TCS or TCI on active lesions. Patients were permitted to receive rescue treatment at the discretion of the investigator to control intolerable symptoms of atopic dermatitis. Patients requiring systemic rescue treatment were discontinued from study treatment.

Patients achieving IGA 0 or 1 or at least a 75% reduction in EASI (EASI 75) without having received any rescue therapy were re-randomised in a blinded manner to (i) lebrikizumab 250 mg Q2W; (ii) lebrikizumab 250 mg every 4 weeks (Q4W); or (iii) matching placebo up to 52 weeks.

In ADvocate-1 and 2, patients not achieving IGA 0 or 1 or EASI 75 at week 16, or who received rescue medication prior to week 16, were entered into an Escape Arm and treated with open-label lebrikizumab 250 mg Q2W through Week 52.

In ADvocate-1 and ADvocate-2, after completing the 52-week study, and in ADhere, after completing the 16-week study, patients were offered the option to continue treatment in a separate long-term extension study (ADjoin).

Endpoints

In all three studies, the co-primary endpoints were the percentage of patients with IGA 0 or 1 ("clear" or "almost clear"), with a ≥2-point reduction from baseline, and the percentage of patients achieving EASI 75 from baseline to week 16. Key secondary endpoints (adjusted for multiplicity) included the percentage of patients who achieved at least a 90% reduction in EASI (EASI 90), percentage of patients with at least 4-point improvement from baseline in Pruritus Numerical Rating Scale (Pruritus NRS), percentage of patients with at least 4-point improvement from baseline in Dermatology Life Quality Index (DLQI) and interference of itch on sleep (Sleep-Loss Scale), which is a patient-reported, single-item, daily scale measuring the extent of interference of itch on sleep over the last night on a 5-point Likert scale. An additional secondary endpoint (not adjusted for multiplicity) included the change from baseline in Patient Oriented Eczema Measure (POEM).

Subjects

Baseline characteristics
The monotherapy studies ADvocate-1 and ADvocate-2 enrolled 424 and 427 patients, respectively, and across studies the mean age was 35.8, the mean weight was 77.1 kg, 49.9% were female, 63.7% were white, 22.6% were Asian, and 9.9% were black, 12.0% were adolescents (12 to 17 years). Overall, 61.5% of patients had a baseline IGA of 3 (moderate atopic dermatitis), 38.5% of patients had a baseline IGA of 4 (severe atopic dermatitis), and 54.8% of patients had received prior systemic treatment. The mean baseline EASI was 29.6, the mean baseline Pruritus NRS was 7.2 and the mean baseline DLQI was 15.5.

The concomitant TCS study ADhere enrolled 211 patients and the mean age was 37.2, the mean weight was 76.2 kg, 48.8% were female, 61.6% were white, 14.7% were Asian, and 13.3% were black, 21.8% were adolescents. In this study, 69.2% of patients had a baseline IGA of 3 (moderate atopic dermatitis), 30.8% of patients had a baseline IGA of 4 (severe atopic dermatitis), and 47.4% of patients had received prior systemic treatment. The mean baseline EASI was 27.3, the mean baseline Pruritus NRS was 7.1 and the mean baseline DLQI was 14.4.

Clinical response

Monotherapy studies (ADvocate-1 and ADvocate-2) – induction period, weeks 0-16
In ADvocate-1 and ADvocate-2, a significantly greater proportion of patients randomised to lebrikizumab 250 mg Q2W achieved IGA 0 or 1 with a ≥2-point improvement from baseline, EASI 75, EASI 90, and an improvement of ≥4 points in Pruritus NRS and DLQI compared to placebo at week 16 (see Table 2).

In both monotherapy studies, lebrikizumab reduced daily worst itch severity compared to placebo, as measured by the percent change from baseline in Pruritus NRS, already at week 1 of treatment. The improvement in Pruritus NRS occurred in conjunction with improvements in skin inflammation related to atopic dermatitis and quality of life.

Table 2. Efficacy results of lebrikizumab monotherapy at week 16 in ADvocate-1 and Advocate-2

	ADvocate-1		ADvocate-2	
	Week 16			
	Placebo N=141	LEB 250 mg Q2W N=283	Placebo N=146	LEB 250 mg Q2W N=281
IGA 0 or 1, %[a]	12.7	43.1***	10.8	33.2***
EASI 75, %[b]	16.2	58.8***	18.1	52.1***
EASI 90, %[b]	9.0	38.3***	9.5	30.7***
Pruritus NRS (≥ 4-point improvement), %[c]	13.0	45.9***	11.5	39.8***
DLQI (Adults) (≥ 4-point improvement), %[d]	33.8	75.6***	33.6	66.3***

LEB = lebrikizumab; N = number of patients.
[a] Subjects with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points from baseline on a 0-4 IGA scale.
[b] Subjects with a 75% or 90% reduction in EASI from Baseline to Week 16, respectively.
[c] The percentage is calculated relative to the number of subjects with a baseline Pruritus NRS ≥4.
[d] The percentage is calculated relative to the number of subjects with a baseline DLQI ≥4.
*** p<0.001 versus placebo.

In the two studies, fewer patients randomised to lebrikizumab needed rescue treatment (topical corticosteroids, systemic corticosteroids, immunosuppressants) as compared to patients randomised to placebo (14.7% versus 36.6%, respectively, across both studies).

Monotherapy Studies (ADvocate-1 and ADvocate-2) – maintenance period, weeks 16-52
To evaluate maintenance of response, 157 subjects from ADvocate-1 and 134 subjects from ADvocate-2 treated with lebrikizumab 250 mg Q2W, who achieved IGA 0 or 1 or EASI 75 at week 16 without topical or systemic rescue treatment, were re-randomised in a blinded manner 2:2:1 to an additional 36-week treatment of (i) lebrikizumab 250 mg Q2W, or (ii) lebrikizumab 250 mg Q4W, or (iii) matching placebo for a cumulative 52-week study treatment (see Table 3).

Table 3. Efficacy results of lebrikizumab monotherapy at week 52 in subjects responding to treatment at week 16 in ADvocate-1 and ADvocate-2 (pooled analysis)

	ADvocate-1 and ADvocate-2 (pooled)	
	Week 52	
	Placebo[d] (LEB Withdrawal) N=60	LEB 250 mg Q4W N=118
IGA 0 or 1, %[a]	47.9	76.9**
EASI 75, %[b]	66.4	81.7*
EASI 90, %[b]	41.9	66.4**
Pruritus NRS (≥ 4-point improvement), %[c]	66.3	84.7

[a] Subjects with IGA 0/1 with a ≥2-point improvement from baseline at week 16 who continued to exhibit IGA 0/1 with a ≥2-point improvement at week 52.
[b] Subjects who achieved EASI 75 at week 16 and continued to exhibit EASI 75 at week 52, or subjects who achieved EASI 75 at Week 16 and exhibited EASI 90 at week 52, respectively.
[c] The percentage is calculated relative to the number of subjects with a baseline Pruritus NRS ≥4.
[d] Subjects responding to lebrikizumab 250 mg Q2W at week 16 (IGA 0 or 1 or EASI 75) and re-randomised to placebo.
*p<0.05; ** p<0.01 versus placebo.

Among subjects who received lebrikizumab during the induction period and continued lebrikizumab 250 mg Q2W open-label treatment up to week 52 in the Escape Arm, 58% achieved EASI 75 and 28%

achieved IGA 0 or 1 with a ≥2-point improvement from baseline at week 52 in ADvocate-1 and ADvocate-2 (pooled).

Concomitant TCS Study (ADhere)
In ADhere, from baseline to week 16, a significantly greater proportion of patients randomised to and dosed with lebrikizumab 250 mg Q2W + TCS achieved IGA 0 or 1, EASI 75, and improvements of ≥ 4 points in the Pruritus NRS and DLQI compared to placebo + TCS (see Table 4).

Table 4. Efficacy results of lebrikizumab combination therapy with TCS at week 16 in ADhere

	ADhere	
	Week 16	
	Placebo + TCS **N=66**	**LEB** **250 mg Q2W + TCS** **N=145**
IGA 0 or 1, %[a]	22.1	41.2*
EASI 75, %[b]	42.2	69.5***
EASI 90, %[b]	21.7	41.2**
Pruritus NRS (≥ 4-point improvement), %[c]	31.9	50.6*
DLQI (Adults) (≥ 4-point improvement), %[d]	58.7	77.4*

[a] Subjects with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points from baseline on a 0-4 IGA scale.
[b] Subjects with a 75% or 90% reduction in EASI from Baseline to week 16, respectively.
[c] The percentage is calculated relative to the number of subjects with a baseline Pruritus NRS ≥ 4.
[d] The percentage is calculated relative to the number of subjects with a baseline DLQI ≥4.
* p<0.05; **p<0.01; *** p<0.001 versus placebo.

In ADhere, subjects who received lebrikizumab 250 mg Q2W+TCS from week 0 to 16 used high potency TCS as rescue medication less often as compared to subjects who received placebo + TCS (1.4% and 4.5%, respectively).

Subjects who responded at week 16 in ADhere and entered ADjoin were treated with lebrikizumab 250 mg Q4W maintained their responses up to 56 weeks (86.8% for IGA 0 or 1 and 81.2% for EASI 75).

Other patient-reported outcomes

In both monotherapy studies (ADvocate-1 and ADvocate-2) and in the concomitant TCS study (ADhere) lebrikizumab 250 mg Q2W significantly improved POEM and interference of itch on sleep (Sleep-Loss Scale) at week 16 compared to placebo.

Adolescents (12 to 17 years of age)

In the monotherapy studies ADvocate 1 and ADvocate 2, the mean age of adolescent patients was 14.6 years, the mean weight was 68.2 kg, and 56.9% were female. In these studies, 63.7% had a baseline IGA of 3 (moderate atopic dermatitis), 36.3% had a baseline IGA of 4 (severe atopic dermatitis), and 47.1% had received prior systemic treatment. In the concomitant study with TCS ADhere, the mean age of adolescent patients was 14.6 years, mean weight was 62.2 kg, and 50.0% were female. In this study, 76.1% had a baseline IGA of 3 (moderate atopic dermatitis), 23.9% had a baseline IGA of 4 (severe atopic dermatitis), and 23.9% had received prior systemic treatment.

The efficacy results at week 16 in adolescent patients are presented in Table 5.

Table 5. Efficacy results of lebrikizumab monotherapy in ADvocate-1, ADvocate-2 and lebrikizumab combination therapy with TCS in ADhere at week 16 in adolescent patients

	ADvocate-1		ADvocate-2		ADhere	
	Week 16					
	Placebo N=18	LEB 250 mg Q2W N=37	Placebo N=17	LEB 250 mg Q2W N=30	Placebo + TCS N=14	LEB 250 mg Q2W + TCS N=32
IGA 0 or 1, %[a]	22.2	48.6	5.9	44.1**	28.6	57.3
EASI 75, %[a]	22.2	62.2**	12.0	61.7**	57.1	88.0*
EASI 90, %[a]	16.7	45.9*	6.1	34.3*	28.6	55.1
Pruritus NRS (≥ 4-point improvement), %[b]	22.8	54.3*	0.3	42.1	13.8	45.8

[a] At Week 16, subjects with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points from baseline on a 0-4 IGA scale, or a 75% or 90% reduction in EASI from baseline to week 16, respectively.
[b] The percentage is calculated relative to the number of subjects with a baseline Pruritus NRS ≥4.
* $p<0.05$; ** $p<0.01$ versus placebo.

Adolescent patients treated with lebrikizumab and lebrikizumab + TCS achieved clinically meaningful improvements in disease severity and maintained response up to week 52. Additional data from the single-arm ADore study with lebrikizumab in 206 adolescents support the efficacy of lebrikizumab in adolescent patients up to 52 weeks of treatment.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with lebrikizumab in one or more subsets of the paediatric population in atopic dermatitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After a subcutaneous dose of 250 mg lebrikizumab, peak serum concentrations were achieved approximately 7 to 8 days post dose.

Following the 500 mg loading doses at week 0 and week 2, steady-state serum concentrations were achieved with the first 250 mg Q2W dose at week 4.

Based on a population pharmacokinetic (PK) analysis, the predicted steady-state trough concentrations ($C_{trough,ss}$) following lebrikizumab 250 mg Q2W and Q4W subcutaneous dosing in patients with atopic dermatitis (median and 5^{th} - 95^{th} percentile) were 87 (46-159) µg/mL and 36 (18-68) µg/mL, respectively.

The absolute bioavailability was estimated at 86% based on a population PK analysis. Injection site location did not significantly influence the absorption of lebrikizumab.

Distribution

Based on a population PK analysis, the total volume of distribution at steady-state was 5.14 L.

Biotransformation

Specific metabolism studies were not conducted because lebrikizumab is a protein. Lebrikizumab is expected to degrade to small peptides and individual amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

In the population PK analysis, clearance was 0.154 L/day and was independent of dose. The mean elimination half-life was approximately 24.5 days.

Linearity/non-linearity

Lebrikizumab exhibited linear pharmacokinetics with dose-proportional increase in exposure over a dose range of 37.5 to 500 mg given as a subcutaneous injection in patients with AD or in healthy volunteers.

Special populations

Gender, age, and race

Gender, age (range 12 to 93 years), and race did not have a significant effect on the pharmacokinetics of lebrikizumab.

Renal and hepatic impairment

Specific clinical pharmacology studies to evaluate the effects of renal or hepatic impairment on the pharmacokinetics of lebrikizumab have not been conducted. Lebrikizumab, as a monoclonal antibody, is not expected to undergo significant renal or hepatic elimination. Population PK analyses show that markers of renal function (eGFR ranged from 27.4 to 335 mL/min/1.73 m^2) or hepatic function (AST ranged from 6 to 105 IU/L, and ALT ranged from 5 to 178 IU/L) had no clinically meaningful effect on the pharmacokinetics of lebrikizumab.

Body weight

Exposure to lebrikizumab was lower in subjects with higher body weight but this had no meaningful impact on clinical efficacy.

Paediatric population

Based on population PK analysis adolescents 12 to 17 years of age with atopic dermatitis had slightly higher lebrikizumab serum trough concentrations compared to adults, which was related to their lower body weight distribution.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity (including safety pharmacology endpoints) and toxicity to reproduction and development.

The mutagenic potential of lebrikizumab has not been evaluated; however monoclonal antibodies are not expected to alter DNA or chromosomes.

Carcinogenicity studies have not been conducted with lebrikizumab. Evaluation of the available evidence related to IL-13 inhibition and animal toxicology data with lebrikizumab does not suggest carcinogenic potential for lebrikizumab.

No effects on fertility parameters were observed in sexually mature monkeys after a long-term intravenous (females) or subcutaneous (males) treatment with lebrikizumab. Lebrikizumab had no effects on embryo-fetal or postnatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Glacial acetic acid (E260)
Sucrose
Polysorbate 20 (E432)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Ebglyss 250 mg solution for injection in pre-filled pen

2 years

After removal from the refrigerator, Ebglyss must be used within 7 days (up to 30°C) or discarded. Once stored out of refrigeration, do not place back in the refrigerator.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Ebglyss 250 mg solution for injection in pre-filled pen

2 mL solution in a 2.25 mL Type-1 clear glass syringe in a pre-filled pen with extra-small round flange, with a 27 gauge special thin wall x 8 mm stacked stainless steel needle, and closed with a laminated bromobutyl elastomeric plunger and a rigid needle shield.

Pack sizes:
1 pre-filled pen

6.6 Special precautions for disposal and other handling

Detailed instructions for administration of Ebglyss in a pre-filled pen are given at the end of the package leaflet.

The solution should be clear to opalescent, colourless to slightly yellow to slightly brown solution and free from visible particulates. If the solution is cloudy, discoloured or contains visible particulate matter, the solution should not be used.

After removing the 250 mg pre-filled pen from the refrigerator, it should be allowed to reach room temperature by waiting for 45 min before injecting Ebglyss.

The pre-filled pen should not be exposed to heat or direct sunlight and should not be shaken.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

Eli Lilly and Company, Indianapolis, Indiana 46285, USA

8. DATE OF REVISION OF THE TEXT

9 April 2025