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Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials

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Abstract

Background Lebrikizumab is a novel, high-affinity monoclonal antibody that selectively binds to interleukin (IL)-13.

Objectives To evaluate the efficacy and safety of lebrikizumab monotherapy in adolescent and adult patients with moderate-to-severe atopic dermatitis (AD) over 52 weeks of treatment in ADvocate1 (NCT04146363) and ADvocate2 (NCT04178967).

Methods Patients who responded to lebrikizumab 250 mg every 2 weeks (Q2W) at the end of the 16-week induction period were re-randomized 2 : 2 : 1 to receive lebrikizumab Q2W, lebrikizumab 250 mg every 4 weeks (Q4W) or placebo Q2W (lebrikizumab withdrawal) for 36 additional weeks. Response at week 16 was defined as achieving a 75% reduction in Eczema Area Severity Index (EASI 75) or an Investigator's Global Assessment (IGA) of 0 or 1, with a $\geq$2-point improvement and no rescue medication use. Multiple imputation was used to handle missing data. Intermittent use of topical therapy was permitted during the maintenance period.

Results After 52 weeks, an IGA of 0 or 1 with a $\geq$2 point improvement was maintained by 71.2% of patients treated with lebrikizumab Q2W, 76.9% of patients treated with lebrikizumab Q4W and 47.9% of patients in the lebrikizumab withdrawal arm. EASI 75 was maintained by 78.4% of patients treated with lebrikizumab Q2W, 81.7% of patients treated with lebrikizumab Q4W and 66.4% of patients in the lebrikizumab withdrawal arm at week 52. Across treatment arms, proportions of patients using any rescue therapy were 14.0% (ADvocate1) and 16.4% (ADvocate2). During the combined induction and maintenance periods of ADvocate1 and ADvocate2, 63.0% of lebrikizumab-treated patients reported any treatment emergent adverse event, with most events (93.1%) being mild or moderate in severity.

Conclusions After a 16-week induction period with lebrikizumab Q2W, lebrikizumab Q2W and Q4W maintained similar improvement of the signs and symptoms of moderate-to-severe AD, with a safety profile consistent with previously published data.

What is already known about this topic?

- The efficacy and safety of lebrikizumab during the first 16 weeks of ADvocate1 and ADvocate2 were published separately.
- During the first 16 weeks of treatment, lebrikizumab achieved statistically significant and clinically meaningful improvements in the signs and symptoms of moderate-to-severe atopic dermatitis (AD) in adults and adolescents compared with placebo, with a safety profile consistent with past studies.

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What does this study add?

- We present the 52-week results of treatment with lebrikizumab in ADvocate1 and ADvocate2.
- The data show the durability of lebrikizumab Q2W and Q4W in improving the signs and symptoms of moderate-to-severe AD, with a safety profile consistent with previous studies.

Atopic dermatitis (AD) is a chronic, relapsing, heterogeneous skin disease that affects 2–7% of the adult population.[1–4] Approximately 30% of adults and adolescents with AD have moderate-to-severe disease and many have comorbid asthma and rhinitis.[1,5–8] Symptoms of AD negatively impact quality of life and include intense itching, skin pain and impaired sleep.[9,10] For moderate-to-severe AD, long-term treatment durability is an important goal for chronic therapy.

First-line pharmacological therapy for mild-to-moderate disease includes topical corticosteroids, topical calcineurin inhibitors, and, in the US, topical phosphodiesterase 4 inhibitors.[11,12] Phototherapy may also be used, but most patients with an insufficient response require progression to systemic therapies.[11] For chronic, long-term management of moderate-to-severe AD, physicians may turn to biologics or oral Janus kinase (JAK) inhibitors, with the goal of reducing inflammation through selective immune modulation.[13] Currently available biologics target cytokines or cytokine receptors that are involved in the underlying pathophysiology of AD. Although the available biologics have exhibited some level of long-term disease control with an acceptable safety profile, a significant number of patients fail to achieve sustained long-term clinical benefit.[14,15] While JAK inhibitors often quickly address the symptoms of AD, both short- and long-term safety concerns limit their use to specific populations.[16,17]

Lebrikizumab is a novel, high-affinity monoclonal antibody that selectively binds to interleukin (IL)-13, the dominant skin cytokine in AD pathogenesis.[18] Lebrikizumab prevents the formation of the IL-13Rα1/IL-4Rα heterodimer receptor signalling complex, thus blocking IL-13 bioactivity. Lebrikizumab exhibits high binding affinity, a slow disassociation rate and neutralizes IL-13 with high potency.[19] However, lebrikizumab does not interfere with the body's natural mechanism to remove excess IL-13. Herein, we describe the 52-week results of lebrikizumab treatment of patients with moderate-to-severe AD in two phase III studies – ADvocate1 and ADvocate2 – with a focus on long-term responses in patients who met the criteria for response at week 16 (Video S1; see Supporting Information).

Patients and methods

Study design and patient selection

The study design of the induction period for ADvocate1 (NCT04146363) and ADvocate2 (NCT04178967) are described elsewhere.[20] Briefly, ADvocate1 and ADvocate2 were identical, randomized, double-blinded, placebo-controlled, parallel-group, monotherapy phase III trials of lebrikizumab in patients with moderate-to-severe AD. During the 16-week induction period, patients were randomized in a 2 : 1 ratio to either lebrikizumab 250 mg or placebo every 2 weeks (Q2W) using an electronic data capture (EDC) system. After 16 weeks of treatment, responders [patients who achieved a 75% reduction in the Eczema and Severity Index (EASI) from baseline (EASI 75) or Investigator's Global Assessment (IGA) 0 or 1, with 2-point improvement and no rescue medication use] were re-randomized using the EDC system in a 2 : 2 : 1 ratio to receive lebrikizumab 250 mg Q2W, lebrikizumab 250 mg every 4 weeks (Q4W) or placebo Q2W (lebrikizumab withdrawal) for a period of 36 weeks. Per-protocol nonresponders at week 16, including patients who received either topical or systemic rescue therapy during the induction period, were assigned to receive lebrikizumab 250 mg Q2W as part of an escape arm. During the 36-week maintenance period, patients who did not maintain an acceptable response of at least a 50% reduction in EASI from baseline (EASI 50) were also assigned to the escape arm. Once in the escape arm, patients who did not achieve EASI 50 after at least 8 weeks of treatment were terminated from the study (Figure S1; see Supporting Information). In this article, all references to baseline refer to week 0 and all references to re-randomization refer to week 16.

The sponsor, investigators, study site personnel and patients were blinded to treatment assignments, and the integrity of the blinding was maintained for the duration of both studies. To maintain blinding, lebrikizumab and placebo were visibly indistinguishable from each other, and all patients received the same number of injections, regardless of their treatment allocation. These studies defined rescue therapy as the use of any topical or systemic treatment for AD. During the 36-week maintenance period, patients were permitted to use topical rescue medication intermittently without discontinuing from the studies. The use of short-term systemic rescue medication was evaluated on a case-by-case basis. Patients who completed the 52-week treatment period were offered to enter a long-term extension study (ADjoin; NCT04392154).

Eligible patients included adolescents aged at least 12 years and weighing ≥ 40 kg, and adults with moderate-to-severe chronic AD,[21] and a history of inadequate response to topical therapies or determination that the use of topical therapies was medically inadvisable. At baseline, patients were required to have an EASI ≥ 16, IGA score ≥ 3 and ≥ 10% body surface area involvement.

ADvocate1 and ADvocate2 were conducted from 24 September 2019 to 3 May 2022 and from 29 October 2019 to 28 April 2022, respectively.

Outcomes and assessments

The primary and major secondary endpoints for this study at 16 weeks are reported elsewhere.[20] The prespecified endpoints specific for the maintenance period reported herein included: (i) the percentage of patients who maintained

EASI 75 response at week 52; (ii) the percentage of patients who maintained IGA 0/1 response and ≥2-point improvement at week 52; (iii) the percentage of patients who maintained ≥4-point reduction on the pruritus numerical rating scale (NRS) at week 52; and (iv) the percentage change in EASI from baseline to week 52. We also report the percentage of patients who achieved a 90% reduction in EASI (EASI 90) by visit from those who achieved EASI 75 at week 16. During the trials, safety was assessed by monitoring vital signs, adverse events (AEs), concomitant medication use, serum chemistry, haematology and urinalysis laboratory testing and physical examination.

Statistical analysis

The sample sizes for these studies were based on statistical analyses of the 16-week primary endpoints reported elsewhere.[20] In ADvocate1, efficacy and patient-reported outcomes analyses used the maintenance primary population (MPP). The MPP included all patients who received lebrikizumab Q2W during the 16-week induction period, met the criteria for response to study drug and were subsequently re-randomized to lebrikizumab Q2W, lebrikizumab Q4W or placebo (lebrikizumab withdrawal) at week 16. To be included in the MPP, patients must have received at least one dose of study treatment in the 36-week maintenance period. Safety analyses in ADvocate1 were conducted on the 'all lebrikizumab safety population' (ALSP), including all randomized patients who received one dose or more of lebrikizumab treatment during the combined induction and maintenance periods. ADvocate1 safety analyses were also performed on the MPP.

Similar populations were used in ADvocate2 analyses; however, the eligibility criteria of having moderate-to-severe AD could not be confirmed for 18 patients from a single study site. Of these 18 patients, 17 entered the maintenance period and were excluded from maintenance efficacy and safety analyses. Thus, efficacy and safety analyses in ADvocate2 were performed on the modified MPP (mMPP) and modified ALSP (mALSP).

Owing to the small number of patients in each dose group from week 16 to week 52, analyses for ADvocate1 and ADvocate2 also used pooled populations that combined the data from both studies. The integrated efficacy and safety analyses were performed on the pooled mMPP and pooled mALSP, respectively (Table S1; see Supporting Information).

For the 36-week maintenance period of these studies, patients who received systemic rescue medication (e.g. oral corticosteroids, immunosuppressants, biologics and phototherapy), discontinued treatment due to lack of efficacy or transferred to the escape arm had values set to their baseline value subsequent to this time through to week 52; patients who received topical rescue medication or discontinued treatment for any other reasons had values set to missing subsequent to this time through to week 52. Multiple imputation was used to handle the missing data. The binary endpoints were analysed by a Cochran–Mantel–Haenszel test adjusted by region and study (for pooled analysis only). The continuous endpoints were analysed with the use of ANCOVA, with treatment group, baseline value, region and study as a fixed factor (for pooled analysis only). All statistical tests were two-sided and performed at the 0.05 level of significance. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient disposition, baseline demographics and disease characteristics

In ADvocate1, 157 patients (55.5%) who received lebrikizumab Q2W during the induction period achieved protocol-defined response and were re-randomized at week 16 to receive maintenance blinded treatment. Of these patients, 62 continued to receive lebrikizumab Q2W, 63 were assigned to lebrikizumab Q4W and 32 were withdrawn from lebrikizumab and given placebo (Figure S2; see Supporting Information). In ADvocate2, a total of 134 patients (47.7%) who received lebrikizumab Q2W during the induction period achieved protocol-defined response and were re-randomized at week 16 to maintenance blinded treatment. Of these patients, 51 continued to receive lebrikizumab Q2W, 55 were assigned to lebrikizumab Q4W and 28 were withdrawn from lebrikizumab and given placebo (Figure S3; see Supporting Information).

In the lebrikizumab Q2W, Q4W and withdrawal treatment arms, the proportion of patients who discontinued treatment were 12.9% (ADvocate1) and 7.8% (ADvocate2), 7.9% (ADvocate1) and 5.5% (ADvocate2), and 9.4% (ADvocate1) and 10.7% (ADvocate2), respectively. In the lebrikizumab Q2W, Q4W and withdrawal treatment arms, the proportion of patients who enrolled into the escape arm during the 36-week maintenance period was 9.7% (ADvocate1) and 11.8% (ADvocate2), 6.3% (ADvocate1) and 1.8% (ADvocate2), and 21.9% (ADvocate1) and 10.7% (ADvocate2), respectively.

In the pooled results, patient demographics and baseline disease characteristics were well balanced among treatment groups (Table 1). The mean (SD) patient age was 35.5 (17.0) years and the mean (SD) duration since the onset of AD was 21.8 (14.6) years. Baseline IGA score was well balanced among groups in ADvocate1. In ADvocate2, patients randomized to lebrikizumab Q4W appeared to have less severe disease at induction baseline (IGA 3, 69.1%; IGA 4, 30.9%) than patients assigned to the lebrikizumab Q2W (IGA 3, 62.7%; IGA 4, 37.3%) or lebrikizumab withdrawal (IGA 3, 60.7%; IGA 4, 39.3%) treatment arms (Table S2; see Supporting Information).

The week 0 baseline mean (SD) EASI in ADvocate1 and ADvocate2 was 29.1 (11.9) and 29.2 (11.3), respectively. In ADvocate1, the proportion of patients who scored ≥4 on the pruritus NRS at week 0 were 96.7% (lebrikizumab Q2W), 93.5% (lebrikizumab Q4W) and 93.8% (lebrikizumab withdrawal). In ADvocate2, the proportion of patients in each treatment arm who scored ≥4 on the pruritus NRS at week 0 were 98.0%, 90.7% and 100%, respectively. In both studies, disease characteristics at week 16 re-randomization were similar across all treatment arms (Table S3; see Supporting Information). At week 16, 100% of patients in both studies had achieved EASI 75. After week 16 re-randomization and with data pooled from both studies, the mean EASI percentage improvement from week 0 baseline was

Table 1 Baseline demographics and disease characteristics at week 0 among treatment groups in two phase III trials of lebrikizumab (LEB) in moderate-to-severe atopic dermatitis (AD)

	ADvocate1 and ADvocate2 (pooled mMPP)		
	PBO (LEB withdrawal; *n*=60)	**LEB Q4W (*n*=118)**	**LEB Q2W (*n*=113)**
Baseline demographics			
Mean (SD) age (years)	33.8 (16.6)	35.8 (17.3)	36.1 (17.0)
≥18 (adults)	52 (86.7)	101 (85.6)	100 (88.5)
12 to <18 (adolescents)	8 (13.3)	17 (14.4)	13 (11.5)
Female sex	36 (60.0)	69 (58.5)	53 (46.9)
Race[a]			
Asian	15 (25.0)	17 (14.4)	19 (16.8)
Black/African American	8 (13.3)	12 (10.2)	9 (8.0)
White	33 (55.0)	86 (72.9)	80 (70.8)
Mean (SD) weight (kg)	72.7 (17.2)	74.6 (18.7)	76.2 (22.3)
Mean (SD) BMI (kg m^{-2})	25.3 (4.8)	26.2 (5.9)	26.3 (6.9)
Geographical region			
US	22 (36.7)	51 (43.2)	44 (38.9)
Europe	18 (30.0)	38 (32.2)	40 (35.4)
Rest of the world	20 (33.3)	29 (24.6)	29 (25.7)
Baseline disease characteristics			
Mean (SD) duration since AD onset (years)	20.4 (14.9)	22.6 (14.8)	21.7 (14.2)
IGA score			
3 (moderate)	37 (61.7)	78 (66.1)	70 (61.9)
4 (severe)	23 (38.3)	40 (33.9)	43 (38.1)
Mean (SD) EASI	28.9 (11.2)	28.8 (12.6)	29.5 (10.8)
Mean (SD) pruritus NRS	7.5 (1.8)	7.0 (2.1)	7.2 (1.7)
≥4[b]	57 (96.6)	107 (92.2)	108 (97.3)
Mean (SD) sleep-loss scale	2.3 (1.1)	2.1 (1.0)	2.3 (0.9)
Mean (SD) BSA affected	42.9 (22.4)	43.9 (23.2)	45.3 (20.6)
Mean (SD) POEM	21.1 (5.3)	19.9 (5.8)	21.0 (5.0)
Mean (SD) DLQI[c]	15.2 (7.5)	14.6 (7.5)	14.9 (6.9)

Data are *n* (%) unless otherwise indicated. mMPP, modified MPP; PBO, placebo; BMI, body mass index; Q4W, every 4 weeks; Q2W, every 2 weeks; EASI, Eczema Area and Severity Index; NRS, numerical rating scale; BSA, body surface area; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index. [a]American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Multiple, and Other also reported. [b]Number of patients with nonmissing data, used as denominator (*n*=59 for withdrawal, *n*=116 for LEB Q4W, *n*=111 for LEB Q2W). [c]Only in those who completed DLQI at baseline (*n*=50 for withdrawal, *n*=94 for LEB Q4W, *n*=91 for LEB Q2W).

90.5% (lebrikizumab Q2W), 89.0% (lebrikizumab Q4W) and 87.3% (lebrikizumab withdrawal).

Maintenance primary population efficacy outcomes

In combining the results of ADvocate1 and ADvocate2 (Figure 1 and Table 2), the proportion of patients who maintained an IGA of 0 or 1 with a ≥2-point improvement at week 52 was 71.2%, 76.9% and 47.9% in those assigned to the lebrikizumab Q2W, lebrikizumab Q4W and lebrikizumab withdrawal treatment arms, respectively. At week 52, patients assigned to the lebrikizumab Q2W, lebrikizumab Q4W and lebrikizumab withdrawal treatment arms exhibited durable EASI 75 response rates of 78.4%, 81.7% and 66.4%, respectively, and EASI 90 response rates of 64.0%, 66.4% and 41.9%, respectively (Table 2). The percentage of patients who maintained a ≥4-point improvement on the pruritus NRS from week 16 to week 52 was 84.6%, 84.7% and 66.3% in those assigned to the lebrikizumab Q2W, lebrikizumab Q4W and lebrikizumab withdrawal treatment arms, respectively. Relative to their week 0 baseline, the mean percentage change in EASI at week 52 in patients assigned to the lebrikizumab Q2W, lebrikizumab Q4W and lebrikizumab withdrawal arm was –78.6%, –84.4% and –67.6%, respectively. Supporting analyses for pooled study results are available in Table S4 (see Supporting Information).

The individual study efficacy outcomes for ADvocate1 and ADvocate2 are provided in Tables S5 and S6 and Figures S4 and S5 (see Supporting Information).

Across treatment arms, the proportion of patients using any rescue therapy was relatively low (ADvocate1, 14.0%; ADvocate2, 16.4%). In the pooled results, the percentage of patients who used any rescue medication during the maintenance period was comparable among patients re-randomized to lebrikizumab Q2W (12.4%), lebrikizumab Q4W (16.1%) and the lebrikizumab withdrawal arm (18.3%) (Table S7; see Supporting Information). The majority of rescue medication use was topical, with low rates of systemic rescue medication use in patients assigned to lebrikizumab Q2W (1.8%), lebrikizumab Q4W (2.5%) and the lebrikizumab withdrawal arm (0%).

Safety

In the pooled mALSP for the combined induction and maintenance periods, 63.0% of patients reported any treatment emergent AE (TEAE; Table 3). In the patients who reported a TEAE, most events (93.1%) were mild or moderate in severity. Serious AEs were reported in 3.0% of patients. In ADvocate2, one lebrikizumab-treated patient in the escape arm died during the maintenance period due to pancreatic carcinoma, which was assessed as being unrelated to the study drug. Across both studies, 3.1% of patients reported

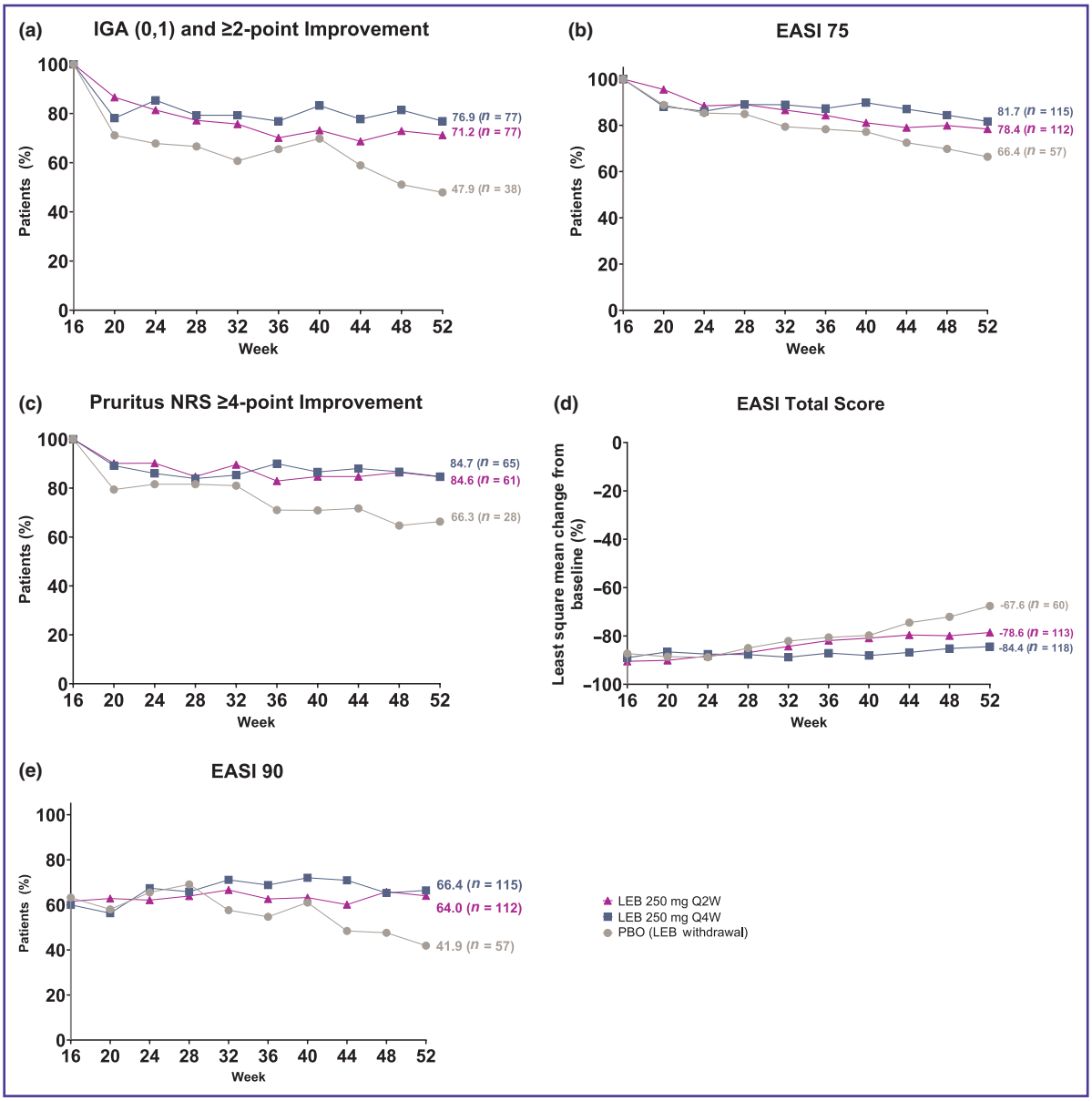

Figure 1 Maintenance of response over time in lebrikizumab (LEB) responders re-randomized at week 16. Q2W, every 2 weeks; Q4W, every 4 weeks; PBO, placebo.

an AE that led to treatment discontinuation. For data specific to the 36-week maintenance period, the safety profile of lebrikizumab was generally consistent between Q2W and Q4W dosing (Table S8; see Supporting Information).

The most common TEAEs across both studies throughout the entire 52-week treatment period were AD (8.9%), conjunctivitis (8.2%), nasopharyngitis (8.2%) and allergic conjunctivitis (6.0%). The frequency of injection site reactions was low (2.4%), and no cases of anaphylaxis were reported. A small proportion of patients reported a TEAE of eosinophilia (1.5%); no eosinophil-related disorders were reported. The frequency of herpesvirus infection was 5.0%. A blinded medical review of potential opportunistic infections was completed prior to database lock and none were assessed to be opportunistic, based on the Winthrop criteria.[22] No parasitic infections were reported. No clinically significant trends were observed in laboratory tests or vital signs.

Discussion

Most patients who showed a robust response to lebrikizumab Q2W during the first 16 weeks of treatment maintained a response up to week 52 when continuing to receive lebrikizumab Q2W. A similar durable response was also seen in the patients who were re-randomized to lebrikizumab Q4W vs. those who continued to receive lebrikizumab Q2W. These results suggest that an induction period of lebrikizumab Q2W followed by less frequent Q4W dosing of lebrikizumab can be sufficient to sustain a response for most patients with moderate-to-severe AD. Of note,

Table 2 Efficacy outcomes at week 52 in lebrikizumab (LEB) responders re-randomized at week 16 among treatment groups in two phase III trials of LEB in moderate-to-severe atopic dermatitis

	ADvocate1 and ADvocate2 (pooled mMPP)					
	PBO (LEB withdrawal)		LEB Q4W		LEB Q2W	
	Response	*n*	Response	*n*	Response	*n*
IGA (0,1) and ≥2-point improvement[a]	18 (47.9)	38	59 (76.9)	77	55 (71.2)	77
EASI 75[b]	38 (66.4)	57	94 (81.7)	115	88 (78.4)	112
Pruritus NRS ≥4-point improvement from baseline[c]	19 (66.3)	28	55 (84.7)	65	52 (84.6)	61
LSM (SE) percentage EASI change from baseline[d]	–67.6 (4.6)	60	–84.4 (3.1)	118	–78.6 (3.1)	113
EASI 90[e]	24 (41.9)	57	76 (66.4)	115	72 (64.0)	112

Data are *n* (%) unless otherwise indicated. Following multiple imputation, the number of responders was obtained by multiplying the estimated percentage by the number of individuals in the analysis population and rounding to the nearest integer. mMPP, modified maintenance primary population; PBO, placebo; Q4W, every 4 weeks; Q2W, every 2 weeks; IGA, Investigator's Global Assessment; EASI, Eczema Area and Severity Index; EASI 75, 75% reduction in EASI from baseline; NRS, numerical rating scale; LSM, least square mean; SE, standard error; EASI 90, 90% reduction in EASI from baseline. [a]Percentage of patients who achieved IGA 0 or 1 and a ≥2-point improvement at week 16 who continued to exhibit an IGA 0 or 1 and a ≥2-point improvement from baseline at week 52. [b]Percentage of patients who achieved EASI 75 at week 16 who continued to exhibit EASI 75 at week 52 (EASI 75 calculated relative to baseline EASI). [c]Percentage of patients who reported ≥4-point improvement on the pruritus NRS at week 16 and continued to report a ≥4-point reduction at week 52. [d]Baseline refers to week 0. Includes seven patients who did not meet responder criteria at week 16 and were incorrectly re-randomized to the maintenance blinded treatment. [e]Percentage of patients who achieved EASI 75 at week 16 and achieved EASI 90 at week 52 (EASI 90 calculated relative to baseline EASI).

a relatively high proportion of patients who responded to lebrikizumab Q2W during the induction period who were withdrawn from lebrikizumab (i.e. re-randomized to placebo) sustained clinical responses 36 weeks after drug withdrawal. The maintenance of response in these patients suggests that lebrikizumab may positively impact the signs and symptoms of AD long after stopping treatment. These findings are novel for the treatment of AD and may be due to the unique mechanism of action of lebrikizumab, which exhibits a half-life of 25 days,[23] a high binding affinity for IL-13, a lower rate of disassociation and higher potency than other biologics used to treat AD, such as tralokinumab.[19,24]

In addition to physician-assessed responses, patients treated with both Q2W and Q4W lebrikizumab reported a sustained reduction in the symptoms of itching up to week 52. These findings highlight the qualitative improvements of the patients who experience intense itching with AD. Since physicians may not use EASI or IGA as tools to define patient response in daily clinical practice, monitoring improvement in itching may help in the evaluation of an individual patient's response to lebrikizumab.

Overall, the safety results of these studies were consistent with the established safety profile of lebrikizumab.[25–27] The proportion of patients reporting conjunctivitis during the combined induction and maintenance periods was 8.3% (ADvocate1) and 8.1% (ADvocate2), respectively. This is comparable with the proportion reported during the induction period.[20] Of the patients who reported conjunctivitis, 32.8% (ADvocate1) and 36.7% (ADvocate2) reported a prior history of conjunctivitis. Importantly, a longer duration of drug exposure over 52 weeks did not result in a higher incidence of conjunctivitis or any clinically meaningful differences in AEs when compared with the safety profile reported over 16 weeks of therapy. Similarly, no clinically meaningful differences were seen between patients who were given lebrikizumab more frequently (Q2W) and those treated with lebrikizumab Q4W. Although partly mitigated by pooling the studies, the small number of patients and low frequency of AEs in each dose group at week 52 limit the interpretation of the results. Additional long-term data are needed to continue to characterize the safety profile of lebrikizumab.

Intermittent use of rescue therapy was allowed in these trials from week 16 to week 52, to reflect the real-world treatment of AD; however, the reported rates of topical and systemic rescue treatment for AD were low. The low rates of rescue medication use between the three maintenance treatment arms establish the observed efficacy as largely being attributable to lebrikizumab, as opposed to clinical effects related to rescue therapy. These studies were not formally designed to evaluate the superiority of lebrikizumab over placebo with respect to long-term efficacy. Statistical significance could not be drawn for the key endpoints at week 52, owing to a lack of multiplicity control.

Treatment with lebrikizumab results in a durable improvement in the signs and symptoms of disease up to week 52 in patients with moderate-to-severe AD, with a safety profile consistent with previously published data. Lebrikizumab's comparable efficacy when given Q2W or Q4W suggests that maintenance treatment for AD can be achieved with a less frequent dosing regimen.

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Table 3 Overview of treatment-emergent adverse events (TEAEs) from week 0 through to week 52 in patients receiving one dose or more of lebrikizumab (LEB) in two phase III trials of LEB in moderate-to-severe atopic dermatitis (AD)

	Total LEB exposure (*n* = 806)[a]	**ADvocate1 (*n* = 399)[b]**	**ADvocate2 (*n* = 407)[c]**
Any TEAE	508 (63.0)	232 (58.1)	276 (67.8)
Mild	236 (29.3)	124 (31.1)	112 (27.5)
Moderate	237 (29.4)	91 (22.8)	146 (35.9)
Severe	35 (4.3)	17 (4.3)	18 (4.4)
SAEs[d]	24 (3.0)	13 (3.3)	11 (2.7)
Death	1 (0.1)	0	1 (0.2)
AEs leading to treatment discontinuation[d]	25 (3.1)	9 (2.3)	16 (3.9)
TEAEs reported in ≥2% of LEB groups[e]			
AD	72 (8.9)	31 (7.8)	41 (10.1)
Conjunctivitis	66 (8.2)	33 (8.3)	33 (8.1)
Nasopharyngitis	66 (8.2)	27 (6.8)	39 (9.6)
Conjunctivitis allergic	48 (6.0)	22 (5.5)	26 (6.4)
COVID-19	38 (4.7)	24 (6.0)	14 (3.4)
Headache	36 (4.5)	13 (3.3)	23 (5.7)
Oral herpes	27 (3.3)	15 (3.8)	12 (2.9)
Vaccine complication	20 (2.5)	6 (1.5)	14 (3.4)
Folliculitis	17 (2.1)	4 (1.0)	13 (3.2)
Dry eye	16 (2.0)	3 (0.8)	13 (3.2)
UTI	13 (1.6)	5 (1.3)	8 (2.0)
URTI	12 (1.5)	4 (1.0)	8 (2.0)
Acne	12 (1.5)	2 (0.5)	10 (2.5)
Arthralgia	11 (1.4)	3 (0.8)	8 (2.0)
Dysmenorrhoea	4 (1.0)[f]	4 (2.0)[g]	0
Other TEAEs of clinical interest			
Herpesvirus infection[h]	40 (5.0)	20 (5.0)	20 (4.9)
Skin infections[i]	32 (4.0)	12 (3.0)	20 (4.9)
Injection site reactions[j]	19 (2.4)	7 (1.8)	12 (2.9)
Eosinophilia[k]	12 (1.5)	5 (1.3)	7 (1.7)
Potential opportunistic infections[l]	9 (1.1)	3 (0.8)	6 (1.5)
Malignancies[m]	6 (0.7)	2 (0.5)	4 (1.0)
NMSC	3 (0.4)	1 (0.3)	2 (0.5)
Malignancies excluding NMSC	3 (0.4)	1 (0.3)[n]	2 (0.5)[o,p]
Anaphylactic reactions	0	0	0
Eosinophil-related disorders[q]	0	0	0
Parasitic infections[r]	0	0	0

Data are *n* (%) unless otherwise indicated. TEAE, treatment emergent adverse event; SAE, serious adverse event; AE, adverse event; UTI, urinary tract infection; URTI, upper respiratory tract infection; NMSC, non-melanoma skin cancer. [a]Pooled 'all lebrikizumab modified safety population'. [b]'All lebrikizumab safety population'. [c]'All lebrikizumab modified safety population'. [d]Deaths are also included as SAEs and AEs leading to treatment discontinuation. [e]TEAEs are represented as single preferred terms unless otherwise noted. [f]Denominator adjusted because it is a sex-specific event for females (*n* = 397). [g]Denominator adjusted because it is a sex-specific event for females (*n* = 196). [h]Herpesvirus infection was defined using MedDRA high-level term of herpes-viral infection. [i]Skin infections were defined using MedDRA high-level term of skin structures and soft tissue infections, and additional single preferred terms of cellulitis, eczema impetiginous, folliculitis, staphylococcal skin infection, cellulitis staphylococcal, furuncle, erysipelas and fungal skin infection. [j]Injection site reactions were defined using MedDRA high-level term of injection site reactions excluding joint-related preferred terms. [k]Eosinophilia was defined using the MedDRA preferred terms of eosinophilia and allergic eosinophilia, as well as eosinophil count abnormal, eosinophil count increased and eosinophil percentage increased, which fall under the high-level term of white blood cell analysis. [l]A blinded medical review was completed prior to database lock; all potential opportunistic infections were assessed as not opportunistic based on the Winthrop criteria.[22] [m]Malignancies were defined using MedDRA malignant tumours standardized MedDRA query. Malignancies are summarized separately as NMSC and malignancies excluding NMSC. NMSC includes MedDRA preferred terms of squamous cell carcinoma of skin, Bowen's disease, basal cell carcinoma, basosquamous carcinoma, basosquamous carcinoma of skin, squamous cell carcinoma, skin cancer, carcinoma in situ of skin, keratoacanthoma, skin squamous cell carcinoma recurrent, lip squamous cell carcinoma, skin squamous cell carcinoma metastatic and penile squamous cell carcinoma. [n]Preferred term diagnosis of cutaneous T-cell lymphoma during treatment in the Escape Arm. [o]Preferred term diagnosis of pancreatic carcinoma with metastases to the bone and liver during treatment in the Escape Arm. [p] Preferred term diagnosis of ovarian germ cell teratoma during treatment in the Escape Arm. The teratoma was reclassified as benign following receipt of the pathology report after database lock occurred. [q]Eosinophil-related disorders was defined as all MedDRA preferred terms under the high-level term of eosinophilic disorders except eosinophilia and allergic eosinophilia. [r]Parasitic infections were defined using MedDRA high-level terms, including cestode infections, helminthic infections, nematode infections and trematode infections.

Conflicts of interest

A.B. has served as a speaker (received honoraria) for AbbVie, Arcutis, Bristol Myers Squibb, Eli Lilly and Company, Pfizer, Regeneron, Sanofi and UCB; served as a scientific adviser (received honoraria) for AbbVie, Abcentra, Affibody, Aligos, Almirall, Alumis, Amgen, AnaptysBio, Arcutis, Arena, ASLAN Pharmaceuticals, Athenex, Bluefin Biomedicine, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Dermavant, EcoR1, Eli Lilly and Company, Escient, Evelo, Evommune, Forte, Galderma, HighlightII Pharma, Incyte, InnoventBio, Janssen, Landos, LEO Pharma, Merck, Novartis, Pfizer, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, TLL Pharmaceutical, TrialSpark, UCB Pharma, Vibliome and Xencor; and has acted as a clinical study investigator (institution has received clinical study funds) for AbbVie, ACELYRIN, Almirall, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Concert, Dermavant, Eli Lilly and Company, Evelo, Evommune, Galderma, Incyte,

Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, Sun Pharma and UCB Pharma. J.P.T. is an advisor for AbbVie, Almirall, Arena Pharmaceuticals, Coloplast, OM Pharma, ASLAN Pharmaceuticals, Union Therapeutics, Eli Lilly and Company, LEO Pharma, Pfizer, Regeneron and Sanofi Genzyme; a speaker for AbbVie, Almirall, Eli Lilly and Company, LEO Pharma, Pfizer, Regeneron and Sanofi Genzyme; and has received research grants from Pfizer, Regeneron and Sanofi Genzyme. E.G.-Y. is a consultant for AbbVie, Almirall, Amgen, Asana Biosciences, Boehringer Ingelheim, Cara Therapeutics, Celgene, Concert, DBV, Dermira, DS Biopharma, Eli Lilly and Company, EMD Serono, Escalier, Galderma, Glenmark, Kyowa Kirin, LEO Pharma, Mitsubishi Tanabe, Pfizer, RAPT Therapeutics, Regeneron, Sanofi, Sienna Biopharma and Union Therapeutics; and reports institute grants for research from AbbVie, Almirall, Amgen, AnaptysBio, Asana Biosciences, Boehringer Ingelheim, Celgene, Dermavant, DS Biopharma, Eli Lilly and Company, Glenmark, Galderma, Innovaderm, Janssen, Kiniska, Kyowa Kirin, Leo Pharma, Novan, Pfizer, Ralexar, Regeneron, Sienna Biopharma, UCB and Union Therapeutics. T.B. has been a speaker and/or consultant and/or investigator for AbbVie, Affibody, Almirall, AnaptysBio, Arena, Asana Biosciences, ASLAN Pharmaceuticals, Bayer Health, BioVerSys, Boehringer-Ingelheim, Bristol Myers Squibb, Connect Pharma, Dermavant, Domain Therapeutics, EQRx, Galderma, Glenmark, GSK, Incyte, Innovaderm, IQVIA, Janssen, Kirin, Kymab, LEO Pharma, LG Chem, Lilly, L'Oréal, MSD, Novartis, Numab, OM Pharma, Pfizer, Pierre Fabre, Q32bio, RAPT, Sanofi/Regeneron and UCB; he is the founder and chairman of the board of the non-profit biotechnology company Davos Biosciences. E.S.-B. has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AbbVie, Novartis, Almirall, LEO Pharma, Sanofi, Pfizer and Eli Lilly and Company. E.S. reports personal fees from AbbVie, Amgen, Arena Pharmaceuticals, ASLAN Pharmaceuticals, Boston Consulting Group, Collective Acumen (CA, USA), Dermira, Eli Lilly and Company, Evidera, Excerpta Medica, Forte Bio RX, Galderma, GlaxoSmithKline, Incyte, Janssen, Kyowa Kirin Pharmaceutical Development, LEO Pharma, Medscape, Merck, Pfizer, Physicians World, Regeneron, Roivant, Sanofi Genzyme, Trevi Therapeutics, Valeant and WebMD. These potential conflicts of interest have been reviewed and managed by Oregon Health & Science University (OHSU). E.S. reports grants from (or served as principal investigator for) AbbVie, Amgen, Arcutis Biotherapeutics, ASLAN Pharmaceuticals, CorEvitas, Dermavant, Dermira, Eli Lilly, Incyte, Kymab, Kyowa Hakko Kirin, LEO Pharma, Pfizer, Regeneron, Sanofi and TARGET-DERM. These potential conflicts of interest have been reviewed and managed by OHSU. D.R. has received honoraria as a consultant for AbbVie, Abcuro, AltruBio, Arena, Boehringer-Ingelheim, Bristol Meyers Squibb, Celgene, Concert, CSL Behring, Dermavant, Dermira, Incyte, Janssen, Kyowa Kirin, Eli Lilly and Company, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharmaceuticals, UCB and VielaBio; has received research support from AbbVie, Amgen, Bristol Meyers Squibb, Celgene, Dermira, Galderma, Incyte, Janssen, Eli Lilly and Company, Merck, Novartis, Pfizer, and Regeneron Pharmaceuticals; and has served as a paid speaker for AbbVie, Amgen, Bristol Meyers Squibb, Celgene, Incyte, Janssen, Eli Lilly and Company, Novartis, Pfizer, Regeneron Pharmaceuticals and Sanofi. H.E., E.M., C.R.N., Z.L., C.X., E.P. and M.M.-C. are employees of Eli Lilly and Company. E.G.G. is an employee of Almirall S.A. J.I.S. has received grants and/or personal fees from AbbVie, AFYX Therapeutics, Arena Pharmaceuticals, Asana BioSciences, Bluefin, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly and Company, Galderma, GlaxoSmithKline, Incyte, Kiniksa, LEO Pharma, Luna Pharma, Menlo Therapeutics, Novartis, Pfizer, RAPT Therapeutics, Regeneron and Sanofi.

Data availability

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and European Union, and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Ethics statement

The studies were undertaken in accordance with the ethical principles of the Declaration of Helsinki, Council for International Organizations of Medical Sciences and Good Clinical Practice guidelines; they were approved by the relevant institutional review board or ethics committee at each of the 171 study sites in North America, Europe and the Asia-Pacific region. Informed consent was obtained from all patients before study procedures were initiated. All investigator sites were compensated.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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