ORIGINAL ARTICLE

# Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis

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## ABSTRACT

### BACKGROUND

Lebrikizumab, a high-affinity IgG4 monoclonal antibody targeting interleukin-13, prevents the formation of the interleukin-4Rα–interleukin-13Rα1 heterodimer receptor signaling complex.

### METHODS

We conducted two identically designed, 52-week, randomized, double-blind, placebo-controlled, phase 3 trials; both trials included a 16-week induction period and a 36-week maintenance period. Eligible patients with moderate-to-severe atopic dermatitis (adults [≥18 years of age] and adolescents [12 to <18 years of age, weighing ≥40 kg]) were randomly assigned in a 2:1 ratio to receive either lebrikizumab at a dose of 250 mg (loading dose of 500 mg at baseline and week 2) or placebo, administered subcutaneously every 2 weeks. Outcomes for the induction period were assessed up to 16 weeks and are included in this report. The primary outcome was an Investigator's Global Assessment (IGA) score of 0 or 1 (indicating clear or almost clear skin; range, 0 to 4 [severe disease]) with a reduction (indicating improvement) of at least 2 points from baseline at week 16. Secondary outcomes included a 75% improvement in the Eczema Area and Severity Index score (EASI-75 response) and assessments of itch and of itch interference with sleep. Safety was also assessed.

### RESULTS

In trial 1, the primary outcome was met in 43.1% of 283 patients in the lebrikizumab group and in 12.7% of 141 patients in the placebo group (P<0.001); an EASI-75 response occurred in 58.8% and 16.2%, respectively (P<0.001). In trial 2, the primary outcome was met in 33.2% of 281 patients in the lebrikizumab group and in 10.8% of 146 patients in the placebo group (P<0.001); an EASI-75 response occurred in 52.1% and 18.1%, respectively (P<0.001). Measures of itch and itch interference with sleep indicated improvement with lebrikizumab therapy. The incidence of conjunctivitis was higher among patients who received lebrikizumab than among those who received placebo. Most adverse events during the induction period were mild or moderate in severity and did not lead to trial discontinuation.

### CONCLUSIONS

In the induction period of two phase 3 trials, 16 weeks of treatment with lebrikizumab was effective in adolescents and adults with moderate-to-severe atopic dermatitis. (Funded by Dermira; ADvocate1 and ADvocate2 ClinicalTrials.gov numbers, NCT04146363 and NCT04178967, respectively.)

Atopic dermatitis is the most prevalent chronic inflammatory skin disease,[1,2] with a worldwide prevalence of approximately 20% among children[3] and of 2 to 7% among adults.[4-7] Historical data suggest that onset of atopic dermatitis occurs by 5 years of age in approximately 90% of patients.[8,9] Although the condition abates with age in most patients, the lifetime prevalence of atopic dermatitis is 10 to 30%, and newer analyses suggest that adult-onset atopic dermatitis occurs in 26% of patients.[9-11] Owing to its manifestation, mainly chronic pruritus and inflamed skin, together with atopic and nonatopic coexisting conditions,[12] atopic dermatitis is associated with impaired quality of life and a substantial burden of disease.[13-15] Sleep disturbance, primarily due to itching, is common and has a major effect on quality of life.[16,17] Furthermore, atopic dermatitis has considerable psychosocial effects on patients.[10,18-20]

First-line treatment for mild-to-moderate disease and acute flares includes topical medicines such as emollients and topical glucocorticoids.[21] When the response to topical therapy is inadequate in patients with moderate-to-severe disease, the addition of systemic therapy or phototherapy (or both) is recommended.[22] Therapeutic monoclonal antibodies such as dupilumab and tralokinumab, as well as new Janus kinase inhibitors, have been approved in many countries to treat moderate-to-severe atopic dermatitis. Despite these advances, there remains an unmet medical need for long-term management of atopic dermatitis[23-25] owing to the heterogeneous nature of the disease.

The multifaceted pathogenesis of atopic dermatitis is associated with skin-barrier dysfunction and a complex interaction of genetic, immunologic, and environmental factors.[2,26,27] The dysregulation of type 2 helper T cells, which preferentially produce cytokines such as interleukins 4, 13, and 31, plays a central role in the pathogenesis of atopic dermatitis.[28] Interleukin-13 is implicated as the primary cytokine in atopic dermatitis,[29,30] and serum levels of interleukin-13 correlate with disease severity.[31] Lebrikizumab is a high-affinity IgG4 monoclonal antibody that selectively binds soluble interleukin-13 with a slow rate of dissociation and high potency.[32] Lebrikizumab prevents the formation of the interleukin-4R$\alpha$–interleukin-13R$\alpha$1 heterodimer signaling complex, thus blocking interleukin-13 signaling without interfering with interleukin-4 signaling.[33] Lebrikizumab does not prevent the binding of interleukin-13 to the interleukin-13R$\alpha$2 (decoy) receptor, which allows for the internalization of interleukin-13 into the cell.[34]

*A Quick Take is available at NEJM.org*

Findings from a phase 2b, multicenter, randomized, clinical trial[35] and earlier phase 2b studies (e.g., ClinicalTrials.gov number, NCT02465606)[36] validated the critical role of interleukin-13 signaling in the pathogenesis of atopic dermatitis and confirmed the need for further studies. Here, we report the efficacy and safety outcomes from the first 16 weeks of two 52-week, phase 3 trials of lebrikizumab monotherapy: ADvocate1 and ADvocate2.

## METHODS

### STUDY DESIGN AND OVERSIGHT

We conducted two identically designed, 52-week, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trials — ADvocate1 (trial 1) and ADvocate2 (trial 2) — to evaluate the efficacy and safety of lebrikizumab monotherapy in adult and adolescent patients with moderate-to-severe atopic dermatitis. Each trial comprised two treatment periods: a 16-week induction period and a 36-week maintenance period (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Adults (≥18 years of age) and adolescents (12 to <18 years of age, weighing ≥40 kg) were eligible if they had moderate-to-severe atopic dermatitis with a baseline Eczema Area and Severity Index (EASI) score of at least 16 (range, 0 to 72, with higher values indicating a greater severity and extent of disease), an Investigator's Global Assessment (IGA) score of at least 3 (range, 0 [clear skin] to 4 [severe disease], with the score describing the overall appearance of atopic dermatitis lesions at a given time point), an affected body-surface area of at least 10%, and chronic atopic dermatitis for at least 1 year for which topical treatment was inadequate or inadvisable. The EASI assesses four signs of disease (erythema, papulation or edema, excoriation, and lichenification) across four body regions. Patients were excluded from the trials if they had previously been treated with lebrikizumab, dupilumab, or tralokinumab. Additional methods and detailed

eligibility criteria are provided in the trial protocols, which are available at NEJM.org. Trial registration information is provided in Table S8.

The trials were undertaken in accordance with the ethical principles of the Declaration of Helsinki.[37] The trials were sponsored by Dermira, a wholly owned subsidiary of Eli Lilly. Dermira and Eli Lilly were responsible for the trial design. Trial data were gathered by investigators, Dermira, and Eli Lilly. Data were analyzed by Dermira and Eli Lilly. All the authors participated in the interpretation of the data and provided input into the drafting of the manuscript, critical feedback, and final approval for submission of the manuscript for publication. The first draft of this article was written by an employee of Eli Lilly, with additional writing and editing assistance provided by a second employee of Eli Lilly; neither of these employees is an author. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trials to the protocols.

### INDUCTION PERIOD

At the baseline visit (day 1), eligible patients were randomly assigned in a 2:1 ratio to receive either lebrikizumab at a dose of 250 mg (with a 500-mg loading dose given at baseline and at week 2) or placebo, administered subcutaneously every 2 weeks. Randomization was performed with the use of an electronic data-capture system, with stratification according to geographic region (United States vs. European Union vs. the rest of the world), age group (adolescent vs. adult), and disease severity (IGA score of 3 vs. 4). The sponsor, investigators, trial-site personnel, and patients were unaware of the trial-group assignments, and blinding integrity was maintained for the duration of both trials.

The use of topical treatments (high-, moderate-, or low-potency topical glucocorticoids, topical calcineurin inhibitor, or crisaborole) or systemic treatments (oral glucocorticoids, cyclosporine, dupilumab, tralokinumab, or phototherapy) for atopic dermatitis was prohibited through week 16 except when such use was deemed to be appropriate as rescue therapy. Topical treatment (such as moderate-potency topical glucocorticoids) was the preferred first-line rescue therapy. If systemic rescue therapy was deemed to be necessary, lebrikizumab was discontinued. Patients who received rescue therapy were eligible to enter an "escape" group to receive open-label lebrikizumab administered every 2 weeks after completing the week 16 visit and a washout period for systemic rescue medication.

After the completion of the week 16 visit, patients who met the protocol-specified criteria for having a response to lebrikizumab (defined as an IGA score of 0 or 1 with a reduction of ≥2 points from baseline or a 75% improvement in the EASI score [EASI-75 response] without rescue medication use) underwent randomization again to receive lebrikizumab administered every 2 weeks, lebrikizumab administered every 4 weeks, or placebo (i.e., lebrikizumab withdrawal) during the maintenance period. Patients who did not have a response by week 16 were assigned to the escape group to receive open-label lebrikizumab administered every 2 weeks.

### EFFICACY AND SAFETY ASSESSMENTS

The primary efficacy outcome was an IGA score of 0 or 1 with a reduction (indicating improvement) of at least 2 points from baseline at week 16. Key secondary efficacy outcomes in the multiplicity control strategy of the Food and Drug Administration (FDA) included the following: EASI-75 response at week 16; a 90% improvement in the EASI score from baseline (EASI-90 response) at week 16; a reduction of at least 4 points on the Pruritus Numeric Rating Scale (NRS; range, 0 [no itch] to 10 [worst itch imaginable] in the assessment of the patient-reported worst severity of itch over the previous 24 hours) from baseline at week 16; an IGA score of 0 or 1 with reduction of at least 2 points from baseline at week 16 in adult patients; a reduction of at least 2 points on the Sleep-Loss Scale (which measures the extent of sleep loss due to itch interference during the previous night, from 0 ["not at all"] to 4 ["unable to sleep at all"]) from baseline at week 16; an IGA score of 0 or 1 with a reduction of at least 2 points from baseline at week 4; and reductions of at least 4 points on the Pruritus NRS from baseline at week 4 and at week 2. A full list of outcomes is provided in Table S4.

IGA and EASI scores were assessed every 2 weeks in the trial clinic. Pruritus NRS and Sleep-Loss Scale assessments were recorded daily by the patient in an electronic diary and are reported as prorated weekly mean scores. A de-

tailed description of the efficacy outcomes in provided in Table S5.

Safety was assessed by the monitoring of adverse events, serum chemical tests, hematologic and urinalysis laboratory evaluations, physical examinations, and vital signs. An external data and safety monitoring board monitored patient safety by conducting formal unblinded reviews of accumulated safety data approximately every 6 months.

### STATISTICAL ANALYSIS

Trial power was calculated on the basis of the primary outcome (IGA score of 0 or 1 with a reduction of ≥2 points from baseline at week 16) with the use of a two-group continuity-corrected chi-square test. We estimated that a sample of 96 patients in the lebrikizumab group and 48 patients in the placebo group would provide the trial with more than 95% power to detect a significant difference at a two-sided significance level of 0.05 for the primary outcome, assuming that 34.7% of the patients in the lebrikizumab group and 7.7% of those in the placebo group would have a primary outcome response, as estimated on the basis of data from the phase 2b trial.[35] However, to ensure that sufficient safety information would be collected and that a sufficient percentage of patients would meet the response criteria for undergoing randomization again at week 16 into the maintenance period, the sample size was increased to approximately 400 in each trial.

The efficacy analyses in trial 1 were based on the intention-to-treat population (which included all the patients who had undergone randomization). In trial 2, a total of 18 patients from a single trial site were excluded from the intention-to-treat population because some or all of the trial participants did not meet the eligibility criterion of moderate-to-severe atopic dermatitis. Thus, all the data from that trial site were removed, and the efficacy analyses in trial 2 were based on a modified intention-to-treat population. Similarly, safety analyses were conducted in the safety population in trial 1 (which included all the patients who had undergone randomization and received at least one dose of lebrikizumab or placebo) and in the modified safety population in trial 2 (which excluded the patients from the trial site mentioned above).

Data subsequent to the use of rescue medication or the discontinuation of treatment due to lack of efficacy were imputed as nonresponse. Remaining data were imputed with the use of multiple imputation. Binary outcomes were analyzed by means of a Cochran–Mantel–Haenszel test with adjustment for the stratification factors (geographic region, age group, and disease severity). Continuous outcomes were analyzed by means of analysis of covariance, with trial group, baseline value, and the stratification factors included in the model.

The overall type I error in the induction period for the hypothesis testing in the analyses of the primary and key secondary outcomes was controlled with a graphical multiple testing strategy at a two-sided alpha level of 0.05 (Figs. S2 and S3). Other secondary outcomes that are reported in this article were not controlled for type I error or multiplicity. All the statistical tests were two-sided and were performed at a significance level of 0.05. Details of the statistical analyses are provided with the protocol, and results from prespecified supportive analyses are provided in Table S2.

## RESULTS

### CHARACTERISTICS OF THE PATIENTS

Patients were enrolled from September 24, 2019, to February 26, 2021, in trial 1 and from October 29, 2019, to March 19, 2021 in trial 2. In trial 1, a total of 424 patients were randomly assigned to the lebrikizumab group (283 patients) or the placebo group (141) (Fig. S4); the mean (±SD) age of these patients was 35.5±17.3 years, and 55 (13.0%) were adolescents; 214 patients (50.5%) were female. In trial 2, a total of 427 patients were randomly assigned to the lebrikizumab group (281 patients) or the placebo group (146) (Fig. S5); the mean age of these patients was 36.2±16.9 years, and 47 (11.0%) were adolescents; 211 patients (49.4%) were female. The demographic and disease characteristics of the patients were similar across both trials and across the trial groups (Table 1). Overall, 63.7% of the patient population was White, 22.6% was Asian, and 9.9% was Black; the representativeness of the trial populations is shown in Table S1.

Discontinuation of participation in the trial occurred in higher percentages of patients in the

**Table 1. Demographic and Disease Characteristics of the Patients at Baseline in Trial 1 (Intention-to-Treat Population) and Trial 2 (Modified Intention-to-Treat Population).***

| Characteristic | Trial 1 | | Trial 2 | |
|---|---|---|---|---|
| | Placebo (N=141) | Lebrikizumab (N=283) | Placebo (N=146) | Lebrikizumab (N=281) |
| Age | | | | |
| Mean — yr | 34.2±16.4 | 36.1±17.8 | 35.3±17.2 | 36.6±16.8 |
| Distribution — no. (%) | | | | |
| 12 to <18 yr | 18 (12.8) | 37 (13.1) | 17 (11.6) | 30 (10.7) |
| ≥18 yr | 123 (87.2) | 246 (86.9) | 129 (88.4) | 251 (89.3) |
| Female sex — no. (%) | 73 (51.8) | 141 (49.8) | 75 (51.4) | 136 (48.4) |
| Race — no. (%)† | | | | |
| White | 93 (66.0) | 196 (69.3) | 85 (58.2) | 168 (59.8) |
| Asian | 31 (22.0) | 39 (13.8) | 44 (30.1) | 78 (27.8) |
| Black | 16 (11.3) | 33 (11.7) | 10 (6.8) | 25 (8.9) |
| Other | 1 (0.7) | 15 (5.3) | 7 (4.8) | 10 (3.6) |
| Weight — kg | 79.0±22.7 | 77.0±19.7 | 76.0±21.1 | 76.7±20.5 |
| Body-mass index‡ | 27.8±7.2 | 26.6±5.8 | 26.3±6.3 | 26.7±6.6 |
| Geographic region — no. (%) | | | | |
| United States | 62 (44.0) | 128 (45.2) | 60 (41.1) | 107 (38.1) |
| European Union | 46 (32.6) | 92 (32.5) | 38 (26.0) | 76 (27.0) |
| Rest of the world | 33 (23.4) | 63 (22.3) | 48 (32.9) | 98 (34.9) |
| Previous use of systemic treatment — no. (%) | 85 (60.3) | 144 (50.9) | 81 (55.5) | 156 (55.5) |
| Duration since onset of atopic dermatitis — yr | 23.8±15.4 | 22.0±14.9 | 20.1±14.1 | 20.8±15.2 |
| IGA score — no. (%)§ | | | | |
| 3 | 83 (58.9) | 170 (60.1) | 95 (65.1) | 175 (62.3) |
| 4 | 58 (41.1) | 113 (39.9) | 51 (34.9) | 106 (37.7) |
| EASI score¶ | 31.0±12.9 | 28.8±11.3 | 29.6±10.8 | 29.7±12.0 |
| Pruritus NRS score‖ | 7.3±1.7 | 7.2±1.9 | 7.2±1.9 | 7.1±1.9 |
| Sleep-Loss Scale score** | 2.3±1.0 | 2.3±1.0 | 2.2±0.9 | 2.2±0.9 |
| Percent of body-surface area affected | 47.8±23.9 | 45.3±22.5 | 46.0±21.1 | 46.1±22.6 |
| Dermatology Life Quality Index score†† | 15.7±7.2 | 15.3±7.4 | 15.9±7.6 | 15.4±7.0 |

* Plus–minus values are means ±SD. Analyses in trial 1 (ADvocate1) were based on the intention-to-treat population (which included all the patients who had undergone randomization). Analyses in trial 2 (ADvocate2) were based on a modified intention-to-treat population that excluded data for 18 patients from a single trial site because some or all of the trial participants did not meet the eligibility criterion of having moderate-to-severe atopic dermatitis.

† Race was reported by the patient. The category of "other" included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, and not reported. The race categories that were used in this trial were consistent with the race categories of the U.S. Census.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Investigator's Global Assessment (IGA) scores range from 0 (clear skin) to 4 (severe disease). Eligible patients had to have a score of at least 3 (moderate).

¶ The Eczema Area and Severity Index (EASI) assesses four signs of disease (erythema, papulation or edema, excoriation, and lichenification) across four body regions. The composite score ranges from 0 to 72, with higher values indicating a greater severity and extent of disease.

‖ The Pruritus Numeric Rating Scale (NRS) is a single-item questionnaire for assessing the worst severity of itch on an 11-point scale, with scores ranging from 0 (no itch) to 10 (worst itch imaginable).

** The Sleep-Loss Scale is a single-item questionnaire for assessing the extent of sleep loss due to itch interference during the previous night on the basis of a 5-point Likert scale ranging from 0 ("not at all") to 4 ("unable to sleep at all").

†† The Dermatology Life Quality Index is a participant-reported, 10-item questionnaire on which each of the 10 items is used to rate the effect on quality of life on a 4-point scale from 0 (not at all) to 3 (very much); total scores range from 0 to 30, with lower scores indicating better health-related quality of life.

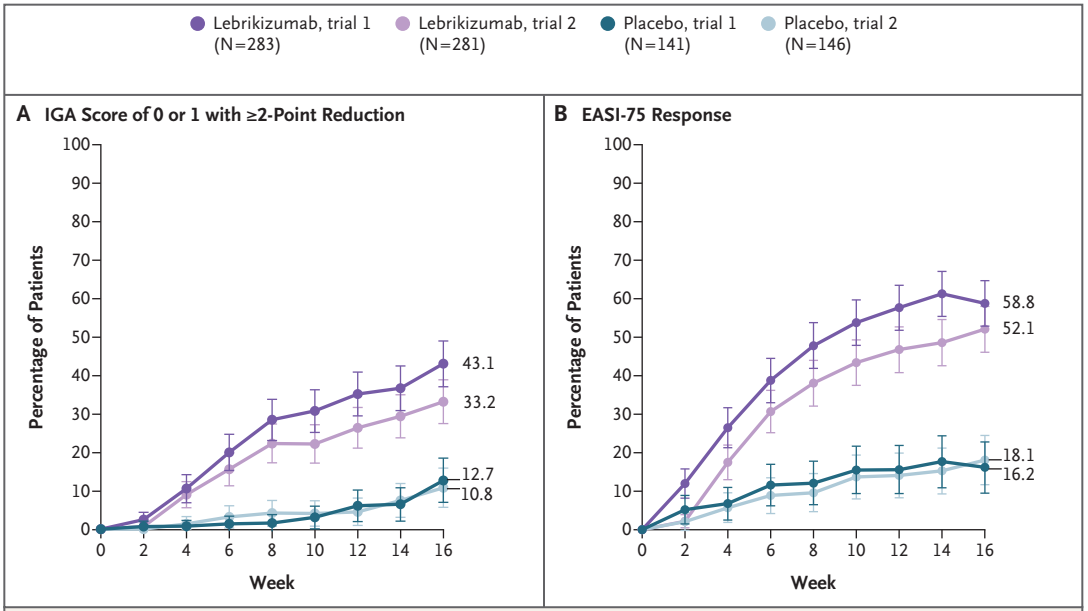


**Figure 1. Time Course for Outcomes of IGA Response and EASI-75 Response in Trial 1 (Intention-to-Treat Population) and Trial 2 (Modified Intention-to-Treat Population).**

The primary outcome was an Investigator's Global Assessment (IGA) score of 0 or 1 (clear or almost clear skin), with a reduction (indicating improvement) of at least 2 points from baseline (Panel A). IGA scores, which are used to describe the overall appearance of atopic dermatitis lesions at a given time point, range from 0 to 4 (severe disease). The first secondary outcome was an Eczema Area and Severity Index–75 (EASI-75) response (defined as a ≥75% reduction from baseline in the EASI score [range, 0 to 72, with higher scores indicating worse severity]). In both panels, I bars indicate 95% confidence intervals. P<0.001 for all comparisons of lebrikizumab with placebo at week 16. Efficacy analyses in trial 1 (ADvocate1) were based on the intention-to-treat population (which included all the patients who had undergone randomization). Efficacy analyses in trial 2 (ADvocate2) were based on a modified intention-to-treat population that excluded data for 18 patients from a single trial site because some or all of the trial participants did not meet the eligibility criterion of having moderate-to-severe atopic dermatitis.

placebo groups than in the lebrikizumab groups (14.9% vs. 7.1% in trial 1 and 11.0% vs. 7.8% in trial 2). Reasons for discontinuation in trial 1 included protocol deviation (in 3.5% of the patients in the placebo group and in 2.1% of those in the lebrikizumab group), loss to follow-up (in 0.7% and 1.4%, respectively), and withdrawal by the patient (in 4.3% and 1.1%). Reasons for discontinuation in trial 2 included adverse events (in 2.7% of the patients in the placebo group and in 2.1% of those in the lebrikizumab group), protocol deviation (in none in the placebo group and in 2.1% in the lebrikizumab group), withdrawal by the patient (in 3.4% and 1.4%, respectively), and reasons associated with the coronavirus disease 2019 pandemic (in 0.7% and 1.4%).

### PRIMARY EFFICACY OUTCOME

In both trials, a significantly higher percentage of patients in the lebrikizumab group than in the placebo group had a primary outcome response (IGA score of 0 or 1, with a reduction of ≥2 points from baseline) at week 16. In trial 1, a primary outcome response occurred in 43.1% of the patients in the lebrikizumab group, as compared with 12.7% of those in the placebo group (P<0.001); in trial 2, the corresponding percentages were 33.2% and 10.8% (P<0.001) (Fig. 1A).

### KEY SECONDARY EFFICACY OUTCOMES

A higher percentage of patients had an EASI-75 response at week 16 in the lebrikizumab group than in the placebo group in both trials. In trial 1, an EASI-75 response occurred in 58.8% of the patients in the lebrikizumab group, as compared with 16.2% of those in the placebo group (P<0.001); in trial 2, the corresponding percentages were 52.1% and 18.1% (P<0.001) (Fig. 1B). An EASI-90 response at week 16 was observed in 38.3% of the patients in the lebrikizumab group and in 9.0% of those in the placebo group in

trial 1 and in 30.7% and 9.5%, respectively, in trial 2 (P<0.001 for both comparisons).

In both trials, significantly higher percentages of patients in the lebrikizumab group than in the placebo group had a reduction in the Pruritus NRS score of at least 4 points from baseline at week 16 (P<0.001 for both comparisons) and a reduction in the Sleep-Loss Scale score of at least 2 points from baseline at week 16 (P<0.001 for both comparisons). Significantly higher percentages of patients in the lebrikizumab group than in the placebo group in both trials had an IGA response (score of 0 or 1 with a reduction of ≥2 points) at week 4 and a reduction in the Pruritus NRS score of at least 4 points at week 4. A significantly higher percentage of patients in the lebrikizumab group than in the placebo group had a reduction in the Pruritus NRS score of at least 4 points at week 2 in trial 1 (P=0.02) but not in trial 2. This was the only secondary end point that did not meet the threshold for significance as compared with placebo. Table 2 shows all the secondary outcomes according to the FDA multiplicity control strategy. Table S7 shows outcomes according to the European Medicines Agency multiplicity control strategy. All the other outcomes consistently favored lebrikizumab over placebo (Figs. S6 and S7).

#### USE OF RESCUE MEDICATION

The percentage of patients who used rescue medication was approximately 3 times as high in the placebo group as in the lebrikizumab group in trial 1 and approximately 2 times as high in the placebo group as in the lebrikizumab group in trial 2 (Table S3). Patients in the placebo groups received rescue therapy earlier than those in the lebrikizumab groups.

#### SAFETY ASSESSMENTS

Adverse events during the induction period were reported in 129 of 282 patients (45.7%) who received lebrikizumab and in 73 of 141 patients (51.8%) who received placebo in trial 1 and in 150 of 281 (53.4%) and 96 of 145 (66.2%), respectively, in trial 2 (Table 3). Most adverse events were mild-to-moderate in severity, and the incidence of trial discontinuation due to adverse events was low. The incidence of injection-site reactions among patients who received lebrikizumab was 1.1% in trial 1 and 2.1% in trial 2 — results similar to those among patients who received placebo.

The most common adverse event (occurring in ≥5% of the patients who received lebrikizumab and consistently reported with higher frequency than in the placebo group) was conjunctivitis (in 7.4% vs. 2.8% of the patients in trial 1 and in 7.5% vs. 2.1% in trial 2) (Table 3). Conjunctivitis was a clinically relevant event, given that the incidence of conjunctivitis events was higher with lebrikizumab than with placebo. These events were mostly mild or moderate in severity. One lebrikizumab-treated patient in trial 2 discontinued treatment owing to conjunctivitis, and another patient in the lebrikizumab group in trial 2 discontinued treatment owing to keratitis. Approximately 20% of the patients in the intention-to-treat population in trial 1 and in the modified intention-to-treat population in trial 2 reported a history of conjunctivitis. No cancers were reported in trial 1. In trial 2, nonmelanoma skin cancer developed in 0.4% of the patients in the lebrikizumab group and in 1.4% of those in the placebo group.

Adverse events that were reported with a lower incidence among patients receiving lebrikizumab than among those who received placebo included atopic dermatitis exacerbation (6.0% vs. 21.3% in trial 1 and 10.3% vs. 26.9% in trial 2) and skin infection (2.8% vs. 5.7% in trial 1 and 1.4% vs. 6.2% in trial 2). Herpes infections were reported in 3.2% of the patients who received lebrikizumab and in 4.3% of those who received placebo in trial 1 and in 2.8% and 4.8%, respectively, in trial 2. No parasitic infections or confirmed opportunistic infections (according to the definitions of Winthrop et al.[38] and defined with the use of the *Medical Dictionary for Regulatory Activities*, version 24.1, preferred terms from the system organ class for infections and infestations) were reported.

Patients who were treated with lebrikizumab had small increases from baseline in the mean blood eosinophil count ($0.13\times10^3$ per cubic millimeter, vs. $-0.04\times10^3$ per cubic millimeter in the placebo group in trial 1; and $0.16\times10^3$ per cubic millimeter vs. $0.01\times10^3$ per cubic millimeter in trial 2). No eosinophil-related disorders were reported.

## DISCUSSION

We conducted two identically designed phase 3 trials, ADvocate1 and ADvocate2, to evaluate the

**Table 2. Efficacy Outcomes in Trial 1 (Intention-to-Treat Population) and Trial 2 (Modified Intention-to-Treat Population).***

| Outcome | Trial 1 | | | | Trial 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo (N = 141) | Lebrikizumab (N = 283) | Difference (95% CI) | P Value | Placebo (N = 146) | Lebrikizumab (N = 281) | Difference (95% CI) | P Value |
| | *percent of patients* | | *percentage points* | | *percent of patients* | | *percentage points* | |
| **Primary outcome** | | | | | | | | |
| IGA score of 0 or 1 with reduction of ≥2 points from baseline at wk 16 | 12.7 | 43.1 | 29.7 (21.6 to 37.8) | <0.001 | 10.8 | 33.2 | 21.9 (14.2 to 29.6) | <0.001 |
| **Key secondary outcomes** | | | | | | | | |
| EASI-75 response at wk 16 | 16.2 | 58.8 | 42.0 (33.3 to 50.6) | <0.001 | 18.1 | 52.1 | 33.3 (24.4 to 42.2) | <0.001 |
| EASI-90 response at wk 16 | 9.0 | 38.3 | 28.8 (21.3 to 36.3) | <0.001 | 9.5 | 30.7 | 20.7 (13.3 to 28.1) | <0.001 |
| Reduction of ≥4 points in the Pruritus NRS score from baseline at wk 16† | 13.0 | 45.9 | 32.9 (24.6 to 41.3) | <0.001 | 11.5 | 39.8 | 28.3 (20.0 to 36.5) | <0.001 |
| IGA score of 0 or 1 with reduction of ≥2 points from baseline at wk 16 among adults‡ | 11.3 | 42.2 | 30.8 (22.1 to 39.4) | <0.001 | 11.5 | 31.8 | 20.4 (12.3 to 28.6) | <0.001 |
| Reduction of ≥2 points in the Sleep-Loss Scale from baseline at wk 16§ | 4.7 | 39.0 | 34.6 (26.2 to 43.0) | <0.001 | 8.2 | 28.0 | 18.9 (9.6 to 28.1) | <0.001 |
| IGA score of 0 or 1 with reduction of ≥2 points from baseline at wk 4 | 0.8 | 10.6 | 9.6 (5.7 to 13.6) | <0.001 | 1.4 | 9.0 | 8.1 (4.1 to 12.0) | 0.002 |
| Reduction of ≥4 points in the Pruritus NRS score from baseline at wk 4† | 2.3 | 21.5 | 19.3 (13.7 to 25.0) | <0.001 | 3.0 | 16.8 | 13.2 (7.7 to 18.7) | <0.001 |
| Reduction of ≥4 points in the Pruritus NRS score from baseline at wk 2† | 0.9 | 6.1 | 5.3 (1.9 to 8.6) | 0.02 | 0.7 | 3.6 | 2.7 (−0.1 to 5.4) | — |

* P values are reported for primary and key secondary outcomes up to the first outcome that was not significant, according to the multiplicity control strategy of the Food and Drug Administration. EASI-75 denotes a 75% reduction in the EASI score, and EASI-90 a 90% reduction in the EASI score.

† The analyses of a reduction of at least 4 points in the Pruritus NRS score from baseline at weeks 16, 4, and 2 were assessed only in patients who had a score of at least 4 at baseline. In trial 1, the analysis population included 130 in the placebo group and 263 in the lebrikizumab group; in trial 2, the analysis population included 134 and 253 patients, respectively.

‡ In trial 1, the analysis population included 123 adults in the placebo group and 246 in the lebrikizumab group; in trial 2, the analysis population included 129 and 251 adults, respectively.

§ The analysis of a reduction of at least 2 points in the Sleep-Loss Scale score from baseline to week 16 was assessed only in patients who had a score of at least 2 at baseline. In trial 1, the analysis population included 91 patients in the placebo group and 195 in the lebrikizumab group; in trial 2, the analysis population included 97 and 161 patients, respectively.

**Table 3. Adverse Events through Week 16 in Trial 1 (Safety Population) and Trial 2 (Modified Safety Population).***

| Event | Trial 1 | | Trial 2 | |
|---|---|---|---|---|
| | Placebo (N=141) | Lebrikizumab (N=282) | Placebo (N=145) | Lebrikizumab (N=281) |
| | *number of patients (percent)* | | | |
| Adverse event | 73 (51.8) | 129 (45.7) | 96 (66.2) | 150 (53.4) |
| Adverse events according to severity | | | | |
| Mild | 34 (24.1) | 78 (27.7) | 40 (27.6) | 73 (26.0) |
| Moderate | 32 (22.7) | 45 (16.0) | 49 (33.8) | 70 (24.9) |
| Severe | 7 (5.0) | 6 (2.1) | 7 (4.8) | 7 (2.5) |
| Serious adverse event†‡ | 1 (0.7) | 6 (2.1) | 4 (2.8) | 2 (0.7) |
| Death | 0 | 0 | 1 (0.7) | 0 |
| Adverse event leading to discontinuation of placebo or lebrikizumab‡ | 1 (0.7) | 3 (1.1) | 4 (2.8) | 9 (3.2) |
| Adverse events reported in ≥5% of the patients in a lebrikizumab group | | | | |
| Conjunctivitis§ | 4 (2.8) | 21 (7.4) | 3 (2.1) | 21 (7.5) |
| Exacerbation of atopic dermatitis | 30 (21.3) | 17 (6.0) | 39 (26.9) | 29 (10.3) |
| Nasopharyngitis | 4 (2.8) | 11 (3.9) | 3 (2.1) | 14 (5.0) |
| Headache | 2 (1.4) | 9 (3.2) | 6 (4.1) | 14 (5.0) |
| Adverse events of clinical interest | | | | |
| Infection¶ | 28 (19.9) | 61 (21.6) | 30 (20.7) | 65 (23.1) |
| Skin infection | 8 (5.7) | 8 (2.8) | 9 (6.2) | 4 (1.4) |
| Potential opportunistic infection‖ | 1 (0.7) | 1 (0.4) | 1 (0.7) | 3 (1.1) |
| Herpes infection** | 6 (4.3) | 9 (3.2) | 7 (4.8) | 8 (2.8) |
| Eosinophilia | 3 (2.1) | 1 (0.4) | 0 | 3 (1.1) |
| Eosinophil-related disorder†† | 0 | 0 | 0 | 0 |
| Injection-site reaction‡‡ | 3 (2.1) | 3 (1.1) | 1 (0.7) | 6 (2.1) |
| Cancer§§ | 0 | 0 | 2 (1.4) | 1 (0.4) |
| Nonmelanoma skin cancer | 0 | 0 | 2 (1.4) | 1 (0.4) |
| Other cancer | 0 | 0 | 0 | 0 |

* Safety analyses were conducted in the safety population in trial 1 (all the patients who had undergone randomization and had received at least one dose of lebrikizumab or placebo) and in the modified safety population in trial 2 (which excluded data for 18 patients from a single trial site because some or all of the trial participants did not meet the eligibility criterion of having moderate-to-severe atopic dermatitis).

† A full listing of serious adverse events is provided in Table S6.

‡ Deaths are also included as serious adverse events and as adverse events leading to the discontinuation of lebrikizumab or placebo.

§ Conjunctivitis is reported here as a single preferred term only.

¶ Infections were defined with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 24.1, preferred terms from the system organ class for infections and infestations.

‖ Potential opportunistic infections, according to the definition of Winthrop et al.[38] and listed in MedDRA, that were reported in both trials included eczema herpeticum, herpes zoster infection, and herpes simplex infection. A blinded medical review was completed, and all potential opportunistic infections were assessed as not opportunistic according to the definition of Winthrop et al.[38]

** Herpes infections included the MedDRA preferred terms of oral herpes, herpes zoster, genital herpes, and herpes simplex infections.

†† Eosinophil-related adverse events included the MedDRA preferred terms of eosinophil count abnormal, eosinophil count increased, and eosinophil percentage increased.

‡‡ Injection-site reaction included the MedDRA preferred terms of injection-site pain, erythema, pruritus, edema, swelling, rash, dermatitis, infection, and reaction.

§§ Cancers were summarized separately as nonmelanoma skin cancer and cancer other than nonmelanoma skin cancer. Nonmelanoma skin cancer included the 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.

efficacy and safety of lebrikizumab monotherapy in adults and adolescents with moderate-to-severe atopic dermatitis. Lebrikizumab therapy led to improvements, as compared with placebo, with regard to the primary outcome and all the secondary outcomes at week 16, significantly improving skin clearance (as measured by the IGA and EASI), itch (as measured by the Pruritus NRS), and interference of itch with sleep (as measured by the Sleep-Loss Scale). The benefits of lebrikizumab therapy were observed with respect to all the secondary outcomes at week 2 and week 4, except for the Pruritus NRS score at week 2 in trial 2. These results show a rapid onset of action in multiple domains of the disease, such as skin clearance and itch. These results confirm the findings from the phase 2 trials of lebrikizumab (NCT02465606).[35,36]

Although 16 weeks of treatment with lebrikizumab is not sufficient to assess its long-term safety, the results from the induction period of these two trials suggest a safety profile that is consistent with findings in previous trials (e.g., NCT02465606).[35,36] Most adverse events during the induction period were nonserious and mild or moderate in severity, including a low incidence (≤2.5%) of injection-site reactions in both trials. The overall incidences of serious adverse events and trial discontinuations due to adverse events were low. Conjunctivitis was more frequently reported in lebrikizumab-treated patients than in patients who received placebo. A higher incidence of conjunctivitis has also been reported in patients treated with other interleukin-13– and interleukin-4–targeting biologic agents, such as dupilumab[39] and tralokinumab.[40] Although several theories have been proposed for the pathogenesis of conjunctivitis in patients with atopic dermatitis treated with this class of biologic agents, the mechanism remains unclear and warrants further study.[41,42]

Recently, it was postulated that conjunctival goblet-cell scarcity due to interleukin-13 and interleukin-4 inhibition affects homeostasis of the conjunctival mucosal surface, resulting in ocular adverse events.[43] The inhibition of only interleukin-13 appears to be associated with a lower incidence and severity of conjunctivitis than the inhibition of both interleukin-13 and interleukin-4 signaling.[43] Moreover, exacerbation of atopic dermatitis and skin infections were reported with lower frequency in the lebrikizumab groups than in the placebo groups in our trials, a finding that suggests a possible improvement of the skin-barrier function or restoration of a normal skin immune response in lebrikizumab-treated patients.

The results from these trials, together with the available evidence showing the associations of interleukin-13 and interleukin-13–producing cells with clinical severity scores for atopic dermatitis,[31,35,36,44-49] confirm the central role of interleukin-13 in the pathogenesis of this disease. As compared with dupilumab, which binds to the interleukin-4R$\alpha$ receptor subunit shared by the interleukin-4 and interleukin-13 receptor complexes, lebrikizumab and tralokinumab bind directly to interleukin-13.[30,50,51] In contrast to tralokinumab, lebrikizumab does not interfere with interleukin-13R$\alpha$2, which is part of the natural mechanism of the body for eliminating excess interleukin-13.[52] In vitro studies suggest that lebrikizumab has a higher binding affinity and slower rate of dissociation than tralokinumab.[32]

The induction period (16 weeks) in these trials limited the evaluations of efficacy and safety of longer-term treatment. More information from the maintenance period of these two clinical trials and a long-term extension study (ADjoin; NCT04392154) may be useful. Furthermore, data regarding a monotherapy may not always translate to real-life clinical settings. A separate clinical trial[53] was conducted to evaluate the safety and efficacy of lebrikizumab combined with topical glucocorticoids in patients with moderate-to-severe atopic dermatitis.

In two randomized, placebo-controlled, phase 3 trials, treatment with lebrikizumab led to significant improvements with regard to the signs and symptoms of moderate-to-severe atopic dermatitis in adults and adolescents.

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