Dermatol Ther (Heidelb) (2024) 14:1145–1160
https://doi.org/10.1007/s13555-024-01158-4

ORIGINAL RESEARCH

Lebrikizumab Provides Rapid Clinical Responses Across All Eczema Area and Severity Index Body Regions and Clinical Signs in Adolescents and Adults with Moderate-to-Severe Atopic Dermatitis

Eric L. Simpson · Marjolein de Bruin-Weller · H. Chih-ho Hong · Delphine Staumont-Sallé · Andrew Blauvelt · Kilian Eyerich · Melinda Gooderham · Mona Shahriari · Lotus Mallbris · Amber Reck Atwater · Maria Jose Rueda · Yuxin Ding · Zhuqing Liu · Helena Agell · Jonathan I. Silverberg

Received: February 16, 2024 / Accepted: April 3, 2024 / Published online: May 3, 2024

ABSTRACT

Introduction: Atopic dermatitis (AD) affects multiple areas of the body, some of which may be more refractory to treatment. We evaluated improvements in the Eczema Area and Severity Index (EASI) by body region and clinical signs for each body region in lebrikizumab-treated patients with moderate-to-severe AD.

Methods: ADvocate 1 and ADvocate 2 compared lebrikizumab 250 mg as monotherapy every 2 weeks versus placebo for 16 weeks. Efficacy measures included EASI, which rates the extent and severity of four clinical signs (erythema, edema/papulation, excoriation, lichenification) in four body regions (head/neck, upper extremities, trunk, lower extremities). Analyses are post hoc.

Results: Mean baseline EASI, body region EASI subscores, and the severity of clinical signs were consistent across both studies (EASI ranging from 16.0 to 72.0). At week 16 in both studies, patients treated with lebrikizumab showed sig-

Prior presentation: This manuscript is based on work that has been previously presented at the Fall Clinical Dermatology Conference in Las Vegas, NV, 20–23 October 2022; Maui Derm Hawaii 19th Annual Meeting in Maui, Hawaii, 23–27 January 2023; and the Fall Clinical Dermatology Conference in Las Vegas, NV, October 19–22, 2023.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-024-01158-4.

E. L. Simpson (✉)
Oregon Health and Science University, 3303 S. Bond Avenue, Portland, OR 97239, USA
e-mail: simpsone@ohsu.edu

M. de Bruin-Weller
University Medical Center Utrecht, Utrecht, The Netherlands

H. C. Hong
University of British Columbia and Probity Medical Research, Surrey, BC, Canada

D. Staumont-Sallé
Service de Dermatologie, CHU Lille, Univ Lille, INSERM U1286, Lille Inflammation Translational Research Institute (INFINITE), 59000 Lille, France

A. Blauvelt
Oregon Medical Research Center, Portland, OR, USA

K. Eyerich
University of Freiburg, Freiburg, Germany

M. Gooderham
SKiN Centre for Dermatology, Peterborough, ON, Canada

nificantly greater percent improvement in EASI across all body regions versus placebo ($p \leq 0.001$), with improvements as early as week 2. In ADvocate 1, all clinical signs significantly improved across all body regions at week 16 with lebrikizumab (51.4–71.6% improvement) versus placebo (23.1–43.5%, $p \leq 0.001$), with significant improvements as early as week 2 for all signs. Significant improvements for all clinical signs at week 16 were also seen in ADvocate 2 for lebrikizumab (53.5–75.6%) versus placebo (28.5–41.2%, $p \leq 0.001$) and as early as week 2 for all body regions and signs except head/neck erythema and lower extremity erythema, edema/papulation, and lichenification, which showed significant improvement by week 4.
Conclusions: Lebrikizumab as monotherapy consistently and rapidly reduced the extent of involvement and severity of AD in all EASI clinical signs and body regions, including the head and neck region and clinical sign of lichenification, compared with placebo.
Trial Registration: ClinicalTrials.gov identifier: ADvocate 1 (NCT04146363) and ADvocate 2 (NCT04178967).

Keywords: Atopic dermatitis; Anatomical regions; Clinical signs; Lebrikizumab

Key Summary Points

Why carry out the study?

Atopic dermatitis (AD) affects multiple areas of the body, some of which may be more refractory to treatment

Characterizing response patterns across specific body regions and clinical signs enhances assessment of treatment response, guides treatment decisions, and helps with discussion of treatment expectations

Here, we evaluated the efficacy of lebrikizumab in patients with moderate-to-severe AD across four body regions; we also determined how Eczema Area and Severity Index (EASI) clinical signs of disease were impacted

What was learned from the study?

In both studies, patients treated with lebrikizumab showed statistically significant improvements in EASI subscores as early as week 2 across all body regions versus placebo

A significantly higher proportion of patients treated with lebrikizumab achieved EASI 100 at week 16 versus placebo

All clinical signs were improved in all body regions, with significant improvements demonstrated as early as weeks 2 and 4

M. Shahriari
Yale University School of Medicine, New Haven, CT, USA

L. Mallbris · A. R. Atwater · M. J. Rueda · Y. Ding · Z. Liu
Eli Lilly and Company, Indianapolis, IN, USA

H. Agell
Almirall S.A., Barcelona, Spain

J. I. Silverberg
Department of Dermatology, George Washington University School of Medicine and Health, Washington, DC, USA

DIGITAL FEATURES

This article is published with digital features, including an animation, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.25533682

INTRODUCTION

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease with varying signs, including erythema, induration, excoriation, and lichenification, which can affect different body areas that may respond differently to therapy. Visible lesions on the head and neck or fingers and hands adversely affect patients' quality of life more than lesions on other areas of the body [1]. Head and neck erythema in particular can have a profound impact on patients as it is difficult to conceal and its treatment can be challenging as prolonged use of topical corticosteroids can lead to perioral dermatitis, skin atrophy, and steroid withdrawal [2].

The Eczema Area and Severity Index (EASI) is commonly used to assess severity for four clinical signs of AD (erythema, edema/papulation, excoriation, lichenification) across four body regions (head/neck, upper extremities, trunk, lower extremities) in aggregate, yielding an overall score of 0 (no AD) to 72 (most severe AD). Improvement of baseline EASI by ≥ 75% (EASI 75) is an established and clinically meaningful endpoint used in AD clinical trials [3–5]. Response patterns of clinical improvement of AD have been characterized across body regions and clinical signs using EASI in patients treated with dupilumab [6, 7] and abrocitinib [8], which enhances clinician understanding of treatment responses and helps effectively communicate treatment expectations to patients who may have concerns about specific body areas that cause the most physical or mental burden.

Lebrikizumab is a monoclonal antibody that binds with high affinity and slow off-rate to interleukin (IL)-13, the primary cytokine in the pathogenesis of AD [9–11], thereby blocking downstream effects of IL-13 with high potency [12]. In completed phase 2 and 3 clinical trials, lebrikizumab as monotherapy and in combination with topical corticosteroids improved signs and symptoms of AD in adolescent and adult patients [13–16]. The primary aims of this analysis were to evaluate the efficacy of lebrikizumab across body regions and to determine how clinical signs were affected by lebrikizumab in patients with moderate-to-severe AD.

METHODS

Study Design

Data for this analysis are from two identically designed, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trials in the lebrikizumab AD clinical program, ADvocate 1 (NCT04146363) and ADvocate 2 (NCT04178967) (Fig. 1) [15]. Eligible patients with moderate-to-severe AD (adolescents ≥ 12 to < 18 years weighing ≥ 40 kg and adults [≥ 18 years], with EASI ≥ 16, Investigator Global Assessment [IGA] ≥ 3, ≥ 10% of total body surface area affected, chronic AD for ≥ 1 year, and for whom topical treatment was inadequate or inadvisable) were randomized 2:1 to lebrikizumab 250 mg every 2 weeks with a 500-mg loading dose at week 0 and week 2, or placebo. Data from the 16-week placebo-controlled period of each study are presented here. Studies were conducted in accordance with the Declaration of Helsinki and the International Council for the Harmonization of Good Clinical Practice Guideline and approved by individual institutional review boards at each participating study center. All patients provided written informed consent.

Outcomes

Efficacy was assessed using EASI [17, 18], ranging from 0 to 72. The amount of involvement for each body region (head/neck, upper extremities, trunk, lower extremities) is evaluated and assigned an area score as follows: 1 (1–9%), 2 (10–29%), 3 (30–49%), 4 (50–69%), 5 (70–89%), and 6 (90–100%). Next, each body region is assessed individually for severity of four clinical signs (erythema, edema/papulation, excoriation, lichenification) on a scale of 0 (no involvement) to 3 (severe involvement); half points can be used between scores 1 and 3. Additionally, each body region is assigned a multiplier (age ≥ 8 years old): head/neck (0.1),

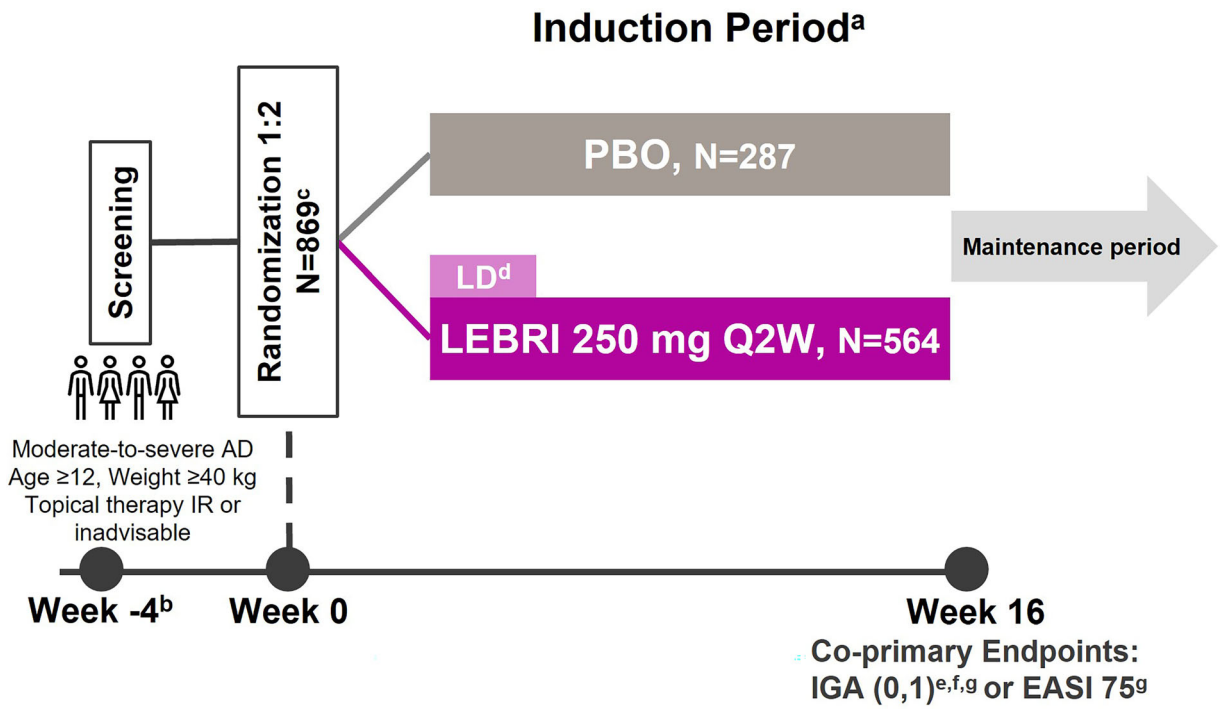

Fig. 1 Study design. Induction period of ADvocate 1 and ADvocate 2. *AD* atopic dermatitis, *EASI 75* reduction of ≥ 75% in Eczema Area and Severity Index, *IGA (0,1)* Investigator's Global Assessment (clear or almost clear), *IR* inadequate response, *LD* loading dose, *LEBRI* lebrikizumab, *N* number of patients in the analysis population, *PBO* placebo, *Q2W* every 2 weeks. [a]Use of topical/systemic treatments for AD prohibited; [b]≤ 30-day screening period; [c]424 patients (ADvocate 1) and 445 patients (ADvocate 2) with moderate-to-severe AD; [d]500-mg loading dose at week 0 and week 2; [e]IGA (0,1) with ≥ 2-point improvement from baseline; [f]United States Food and Drug Administration primary endpoint; [g]European Medicines Agency co-primary endpoint

upper extremities (0.2), trunk (0.3), lower extremities (0.4). Finally, the body region severity score is multiplied by the area score and the multiplier, and body region subscores are added together for the total EASI. Categories of AD severity based on EASI are defined as clear: 0; almost clear: 0.1–1.0; mild: 1.1–7.0; moderate: 7.1–21.0; severe: 21.1–50.0; or very severe: 50.1–72.0 [18]. We analyzed the EASI total score across both studies, the four region subscores, and the severity of each clinical sign for the four body regions. We also analyzed the proportion of patients who achieved 100% clearance overall (EASI 100) and for each body region.

Statistical Analysis

Efficacy analyses in ADvocate 1 were based on the intent-to-treat population (all randomized patients). In ADvocate 2, a total of 18 patients from a single study site were excluded from the intent-to-treat population since some or all the study participants' eligibility criteria could not be confirmed to have moderate-to-severe AD. Thus the efficacy analyses in ADvocate 2 were based on the modified intent-to-treat population. To better understand the baseline severity of AD of patients entering the studies, the distribution of individual baseline EASI is presented for the pooled modified intent-to-treat population from ADvocate 1 and ADvocate 2.

In this post hoc analysis, EASI improvement was evaluated for each study via change from baseline to week 16 for each body region subscore and for each clinical sign by body region using the mixed-effects model of repeated measures. EASI least squares mean change from baseline was converted to percent change from baseline by dividing the baseline mean for each

body region and for each clinical sign in each body region. For continuous variables, data after rescue therapy (topical or systemic) and discontinuation of treatment were considered missing. To provide a visual presentation of EASI improvement, the changes in EASI total score from baseline to week 16 were animated in a rainfall plot by treatment arms, with EASI percent change from baseline intervals (< 50%, 50–75%, 75–90%, ≥ 90%) indicated by different colors. Observed data up to rescue medication use or treatment discontinuation were plotted in the animation.

To analyze the proportion of patients who achieved 100% clearance, Cochran-Mantel-Haenszel test compared lebrikizumab treatment versus placebo for overall EASI 100 and within patients whose baseline subscore was > 0 for each body region's 100% clearance. For these categorical variables, data after rescue therapy (topical or systemic) or treatment discontinuation and any intermittent missing data were analyzed as non-response. The analyses reported here were not controlled for type I error or multiplicity; therefore, nominal *p*-values are reported. The statistical results were confirmed through replicate statistical programming, validation, and quality reviews.

RESULTS

A total of 424 and 427 patients were enrolled in ADvocate 1 and ADvocate 2, respectively. Patient demographics and disease characteristics were similar across both trials and treatment groups (Table 1). Mean age was approximately 36 years across both studies, and 13.0% and 11.0% of patients were ≥ 12 to < 18 years old in ADvocate 1 and ADvocate 2, respectively (Table 1). The mean percentage of body surface area affected ranged from 45.3 to 47.8% across treatment groups, and most patients (≥ 89.7%) were affected in each body region. Baseline mean EASI total scores between treatment arms were numerically comparable for ADvocate 1 (placebo, 31.0; lebrikizumab 28.8) and ADvocate 2 (placebo, 29.6; lebrikizumab, 29.7), as were EASI body region subscores (Table 1) and EASI clinical signs by body region (Table 2).

EASI Total Scores from Week 0 to Week 16

The distribution of baseline EASI in pooled data from the two studies ranged from 16.0 (minimum required for study entry) to 72.0 (Fig. 2). Based on the EASI categories of disease severity, most patients had severe disease (EASI 21.1–50.0; 67.3% and 63.7% in the placebo and lebrikizumab treatment groups, respectively); 8.0% and 7.5% of patients, respectively, had very severe disease (EASI > 50.1). Change in EASI total score for individual patients treated with lebrikizumab and placebo from week 0 to week 16 in ADvocate 1 and ADvocate 2 is shown in an animation rainfall plot (animation) and at week 16 (Fig. 3). The animation and figure visually show individual patients as they progress through percentage improvement in EASI from < 50 to 50–75%, 75–90%, and ≥ 90%. At week 16 of ADvocate 1, 10.6% of lebrikizumab-treated patients and 0.0% of placebo-treated patients achieved EASI 100 ($p < 0.001$); at week 16 of ADvocate 2, 10.3% versus 0.7% of lebrikizumab- and placebo-treated patients, respectively, achieved EASI 100 ($p < 0.001$).

Supplementary file1 (MP4 18068 KB)

EASI Body Regions

Lebrikizumab improved EASI across all body regions as early as week 2 versus placebo in both ADvocate 1 and ADvocate 2 (Fig. 4). At week 16 of ADvocate 1, patients treated with lebrikizumab showed statistically significant improvement in EASI across all body regions versus placebo (head/neck, 68.2% vs. 35.1%; upper extremities, 71.3% vs. 31.9%; trunk, 74.3% vs. 37.1%; lower extremities, 71.4% vs. 34.8%; $p \leq 0.001$ for all comparisons) (Fig. 4a). Similar improvements in lebrikizumab versus placebo were noted at week 16 of ADvocate 2 (head/neck, 66.8% vs. 37.3%; upper extremities, 70.9% vs. 33.7%; trunk, 74.9% vs. 40.2%; lower extremities, 75.3% vs. 42.7%; $p < 0.001$ for all comparisons) (Fig. 4b).

At week 16 of ADvocate 1, a greater proportion of patients treated with lebrikizumab achieved 100% clearance for each body region versus placebo (head/neck: 33.0% vs. 10.6%;

Table 1 Baseline demographics and disease characteristics

	ADvocate 1		ADvocate 2	
	Placebo (*N* = 141)	**Lebrikizumab 250 mg Q2W (*N* = 283)**	**Placebo (*N* = 146)**	**Lebrikizumab 250 mg Q2W (*N* = 281)**
Age, years, mean (SD)	34.2 (16.4)	36.1 (17.8)	35.3 (17.2)	36.6 (16.8)
Adult (≥ 18 years), *n* (%)	123 (87.2)	246 (86.9)	129 (88.4)	251 (89.3)
Adolescent (≥ 12 to < 18 years), *n* (%)[a]	18 (12.8)	37 (13.1)	17 (11.6)	30 (10.7)
Female, *n* (%)	73 (51.8)	141 (49.8)	75 (51.4)	136 (48.4)
Region, *n* (%)				
US	62 (44.0)	128 (45.2)	60 (41.1)	107 (38.1)
Europe	46 (32.6)	92 (32.5)	38 (26.0)	76 (27.0)
Rest of world	33 (23.4)	63 (22.3)	48 (32.9)	98 (34.9)
Race, *n* (%)				
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/African American	16 (11.3)	33 (11.7)	10 (6.8)	25 (8.9)
BMI, kg/m^2, mean (SD)	27.8 (7.2)	26.3 (5.8)	26.3 (6.3)	26.7 (6.6)
% Body surface area, mean (SD)	47.8 (23.9)	45.3 (22.5)	46.0 (21.1)	46.1 (22.6)
Body regions affected, *n* (%)				
Head/neck	131 (92.9)	263 (92.9)	131 (89.7)	253 (90.0)
Upper extremities	139 (98.6)	283 (100)	140 (95.9)	278 (98.9)
Trunk	138 (97.9)	269 (95.1)	144 (98.6)	267 (95.0)
Lower extremities	137 (97.2)	274 (96.8)	138 (94.5)	275 (97.9)
EASI, mean (SD) [range]	31.0 (12.9) [16.3–67.2]	28.8 (11.3) [16.0–72.0]	29.6 (10.8) [16.0–65.3]	29.7 (12.0) [16.0–69.6]
Head/neck[b]	2.7 (1.7)	2.4 (1.5)	2.7 (1.7)	2.6 (1.6)
Upper extremities[b]	6.8 (3.1)	6.7 (2.9)	6.5 (2.7)	6.4 (2.8)
Trunk[b]	9.3 (4.7)	8.2 (4.0)	8.7 (4.2)	8.6 (4.3)
Lower extremities[b]	12.2 (6.3)	11.6 (6.1)	11.7 (5.6)	12.1 (6.1)

BMI body mass index, *EASI* Eczema Area and Severity Index, *Q2W* every 2 weeks, *SD* standard deviation

[a]Weight ≥ 40 kg

[b]Ranges for body region subscores are: head/neck (0–7.2); upper extremities (0–14.4); trunk (0–21.6); lower extremities (0–28.8)

Table 2 Baseline mean EASI subscores for each clinical sign and for body region

	ADvocate 1		ADvocate 2	
	Placebo (N = 141)	Lebrikizumab 250 mg Q2W (N = 283)	Placebo (N = 146)	Lebrikizumab 250 mg Q2W (N = 281)
Erythema (range 0–3)				
Head/neck	2.2 (0.8)	2.1 (0.7)	2.1 (0.7)	2.1 (0.7)
Trunk	2.3 (0.6)	2.2 (0.6)	2.2 (0.6)	2.2 (0.6)
Upper extremities	2.5 (0.5)	2.4 (0.5)	2.4 (0.6)	2.3 (0.5)
Lower extremities	2.3 (0.6)	2.3 (0.6)	2.3 (0.5)	2.3 (0.6)
Edema/papulation (range 0–3)				
Head/neck	1.9 (0.8)	1.9 (0.7)	1.9 (0.7)	1.9 (0.7)
Trunk	2.1 (0.6)	2.1 (0.6)	2.1 (0.5)	2.1 (0.6)
Upper extremities	2.3 (0.6)	2.2 (0.5)	2.3 (0.5)	2.2 (0.6)
Lower extremities	2.2 (0.6)	2.1 (0.7)	2.2 (0.5)	2.2 (0.6)
Excoriation (range 0–3)				
Head/neck	1.6 (0.9)	1.5 (0.8)	1.6 (0.8)	1.7 (0.8)
Trunk	1.9 (0.7)	1.9 (0.7)	1.9 (0.7)	2.0 (0.7)
Upper extremities	2.2 (0.6)	2.1 (0.7)	2.1 (0.7)	2.2 (0.6)
Lower extremities	2.1 (0.7)	2.0 (0.7)	2.1 (0.6)	2.2 (0.7)
Lichenification (range 0–3)				
Head/neck	1.8 (0.8)	1.8 (0.8)	1.8 (0.8)	1.9 (0.8)
Trunk	2.0 (0.7)	1.9 (0.7)	1.9 (0.7)	2.0 (0.6)
Upper extremities	2.2 (0.6)	2.2 (0.6)	2.3 (0.6)	2.3 (0.6)
Lower extremities	2.1 (0.7)	2.1 (0.7)	2.1 (0.7)	2.2 (0.6)

Data are mean (SD)
EASI Eczema Area and Severity Index, *Q2W* every 2 weeks, *SD* standard deviation

upper extremities: 23.0% vs. 2.1%; trunk: 34.3% vs. 7.2%; lower extremities: 28.9% vs. 6.5%; $p < 0.001$ for all comparisons) (Fig. 5a). Lebrikizumab-treated patients achieved EASI 100 most rapidly and at significantly higher proportions than placebo-treated patients in the head/neck (15.4% vs. 3.8%; $p \leq 0.001$) and lower extremities (9.6% vs. 3.6%; $p \leq 0.05$) by week 4, and then trunk (18.9% vs. 6.5%; $p \leq 0.001$) and upper extremities (7.4% vs. 2.1%; $p \leq 0.05$) by week 6 (Fig. 5a). In ADvocate 2 at week 16, significantly greater proportions of patients treated with lebrikizumab achieved 100% clearance for each body region (head/neck: 29.1% vs. 10.9%; upper extremities: 19.6% vs. 4.2%; trunk: 28.6% vs. 9.1%; lower extremities: 20.1% vs. 8.3%; $p < 0.001$ for all comparisons) (Fig. 5b).

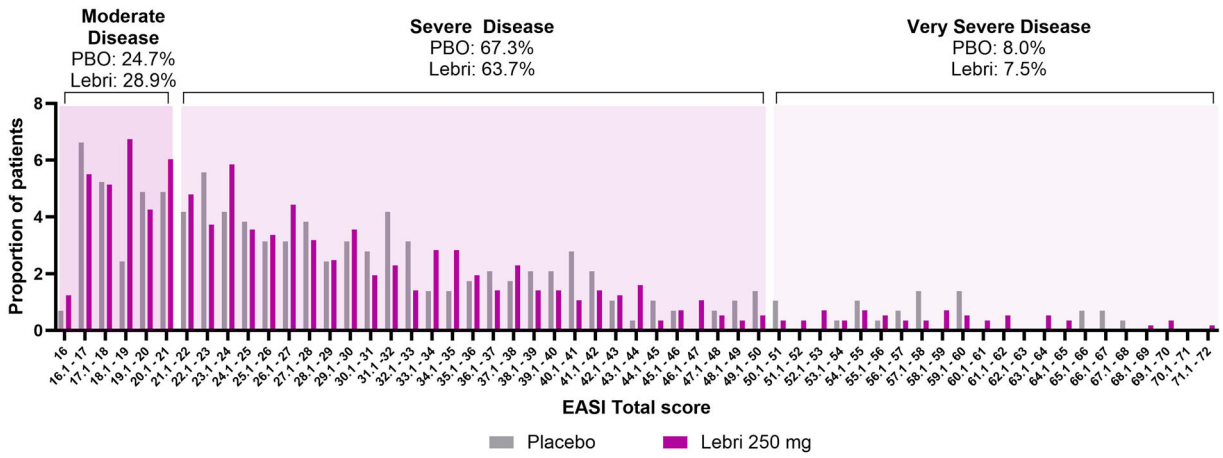

Fig. 2 Distribution of baseline EASI in individual patients from pooled data of ADvocate 1 and ADvocate 2. Categories of AD severity based on EASI are defined as: moderate: 7.1–21.0; severe: 21.1–50.0; very severe: 50.1–72. Note: While moderate AD is defined as 7.1 to 21.0, inclusion criteria for the study included EASI $\geq$ 16; therefore, no patients had EASI from 7.1 to $<$ 16

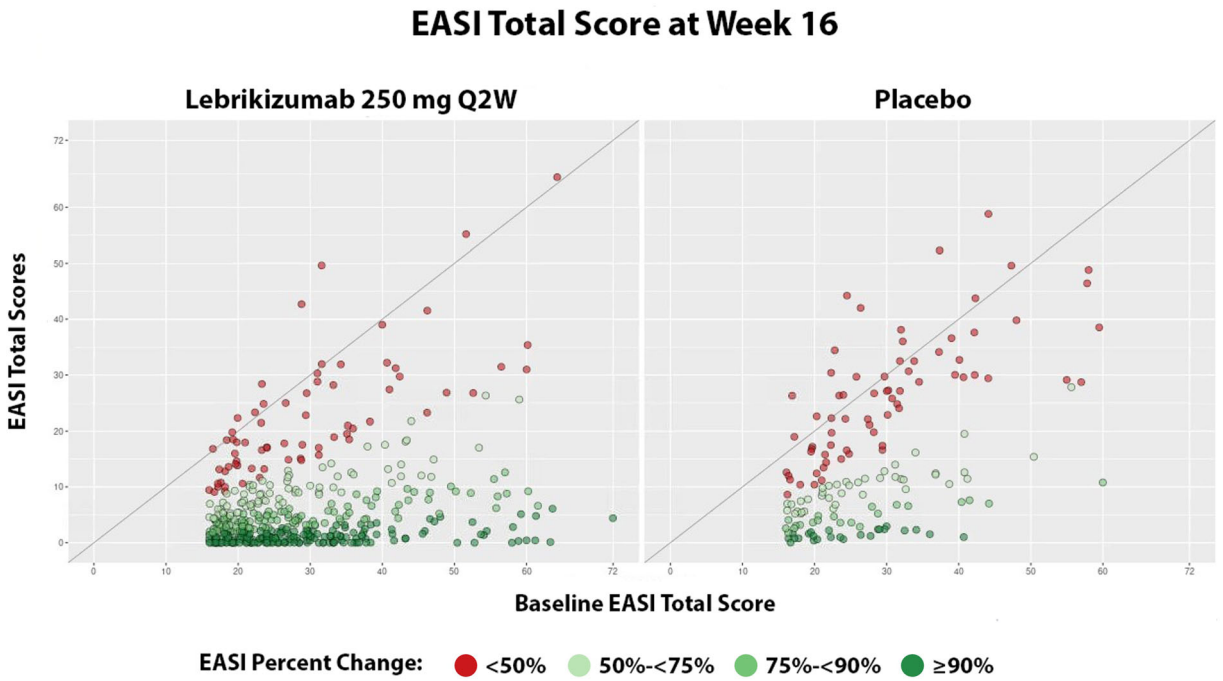

Fig. 3 EASI total score at week 16 in pooled data from ADvocate 1 and ADvocate 2 among patients treated with lebrikizumab 250 mg every 2 weeks and placebo. In the rainfall plot animation (see Supplement) changes in EASI total scores from baseline to week 16 are shown. Each dot represents an individual patient, and dot color is associated with a range of percentage improvement in EASI from $<$ 50%, 50–75%, 75–90%, and $\geq$ 90%

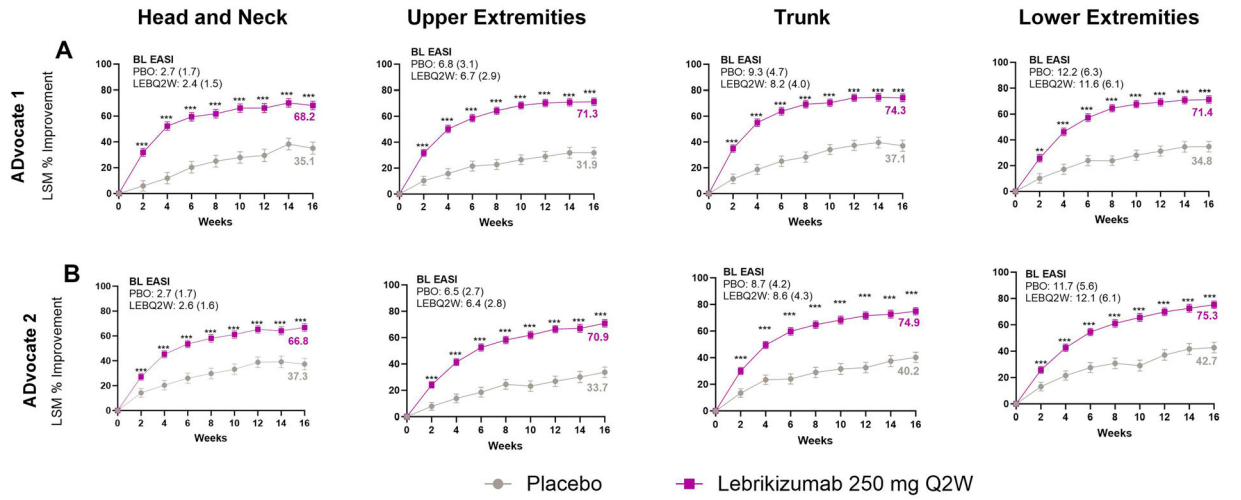

Fig. 4 Least squares mean percentage improvement in EASI by body region from baseline to week 16 in **A**) ADvocate 1 and **B**) ADvocate 2 in patients who had EASI body region sub-scores > 0 at baseline. Baseline EASI data are mean (SD). $^{*}p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$ vs. placebo. *BL* baseline, *EASI* Eczema Area and Severity Index, *LSM* least squares mean, *Q2W* every 2 weeks

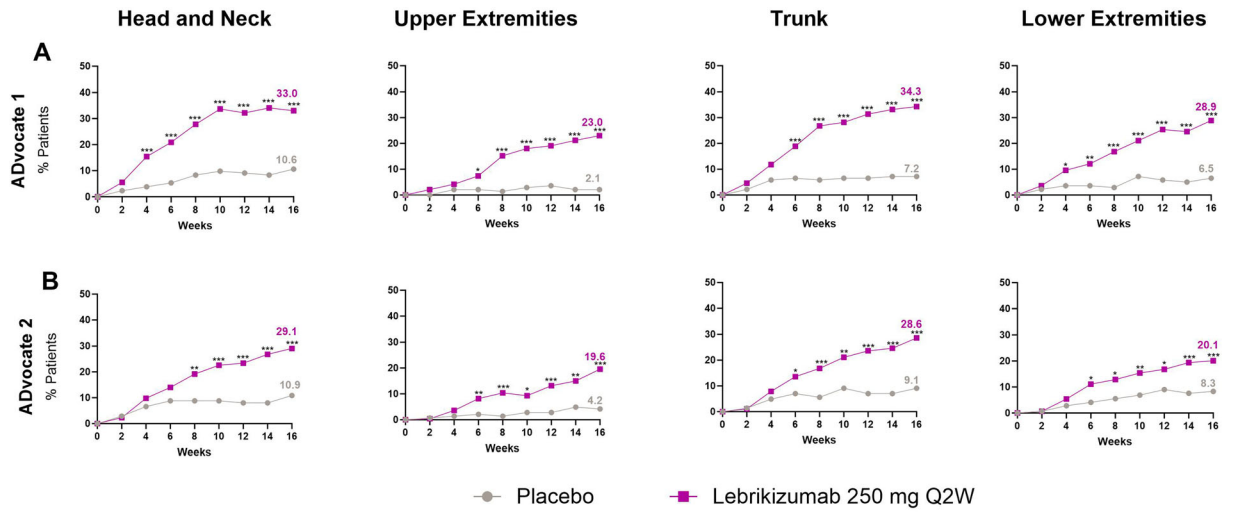

Fig. 5 Proportion of patients who achieved 100% clearance based on EASI by body region from baseline to week 16 in **A**) ADvocate 1 and **B**) ADvocate 2 in patients who had EASI body region sub-scores > 0 at baseline. $^{*}p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$ vs. placebo. *Q2W* every 2 weeks

EASI Clinical Signs in Each Body Region

Improvement in all clinical signs across all body regions showed statistical significance at week 16 in both studies ($p < 0.001$) (Figs. 6 and 7). For ADvocate 1, a statistically significant improvement from baseline in all four clinical signs was seen as early as week 2 with lebrikizumab treatment versus placebo for head/neck and trunk ($p < 0.001$), and for upper extremities and lower extremities ($p < 0.01$) (Fig. 6a). For ADvocate 2, a statistically significant improvement from baseline was seen for head/neck as early as week 2 for edema/papulation,

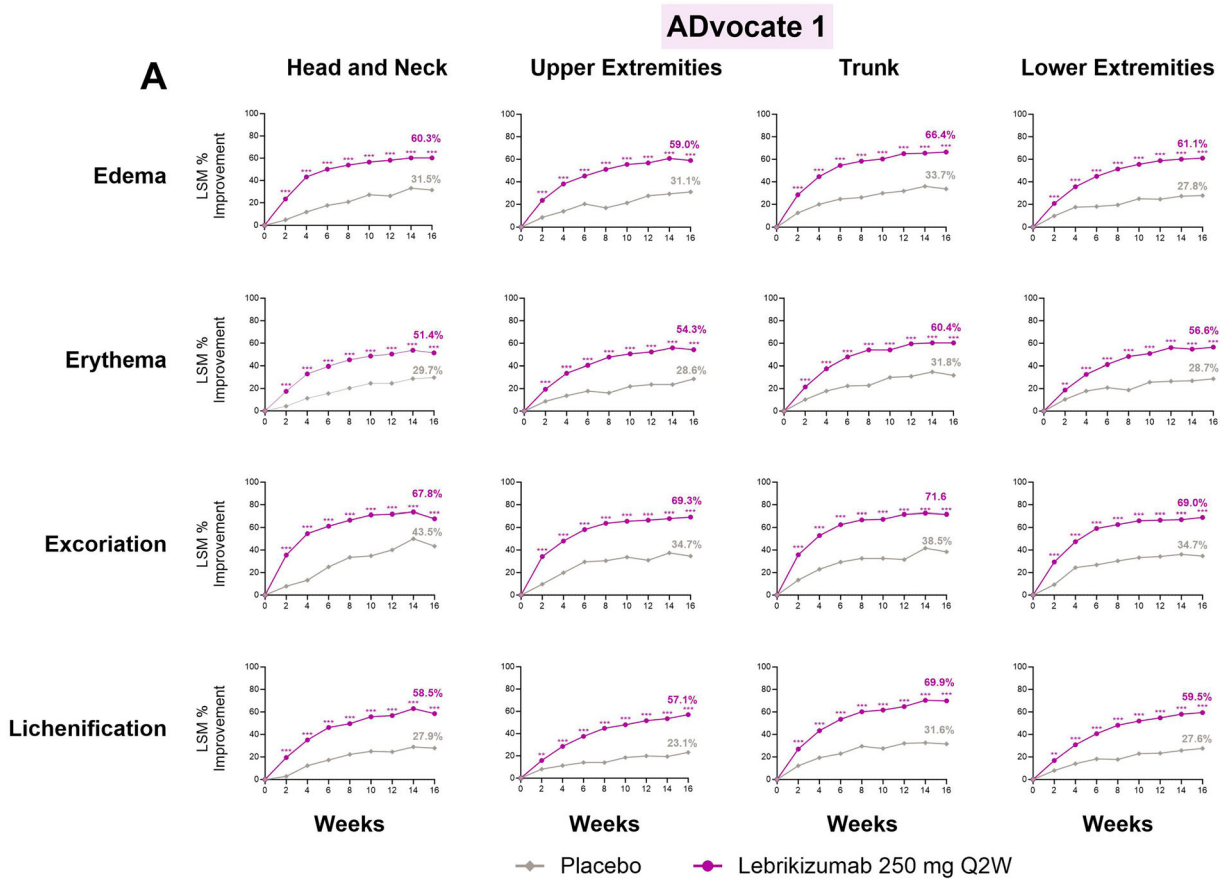

Fig. 6 Least squares mean percentage improvement in EASI clinical signs for each body region from baseline to week 16 in patients who had EASI body region subscores > 0 at baseline in (**A**) ADvocate 1 and (**B**) ADvocate 2. $^{*}p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$ vs. placebo. *LSM* least squares mean, *Q2W* every 2 weeks

excoriation, and lichenification, and as early as week 4 for erythema with lebrikizumab treatment versus placebo ($p < 0.05$). For trunk and upper extremities, statistically significant improvement for all four signs versus placebo was seen as early as week 2 ($p < 0.05$), and for lower extremities, improvement was seen by week 2 for excoriation ($p < 0.001$) and by week 4 for erythema, edema/papulation, and lichenification ($p < 0.001$) (Fig. 6b).

DISCUSSION

In this analysis of two placebo-controlled, randomized, phase 3 trials in adolescent and adult patients with moderate-to-severe AD, baseline EASI scores are represented across the disease severity ranges of moderate, severe, and very severe. Lebrikizumab reduced the extent of involvement across all body regions, including the head/neck, as early as 2 weeks after initiating treatment, and response was maintained through week 16. Additionally, approximately one-third of lebrikizumab-treated patients achieved 100% clearance of the head/neck and trunk by week 16, and lebrikizumab improved all four clinical signs of disease across all body regions. Lebrikizumab showed efficacy for head/neck involvement, which can be difficult to treat, and improved lichenification in all regions.

While lebrikizumab was effective across all body regions, a progressive trend in the proportion of patients achieving EASI 100 was observed. Complete skin clearance of the

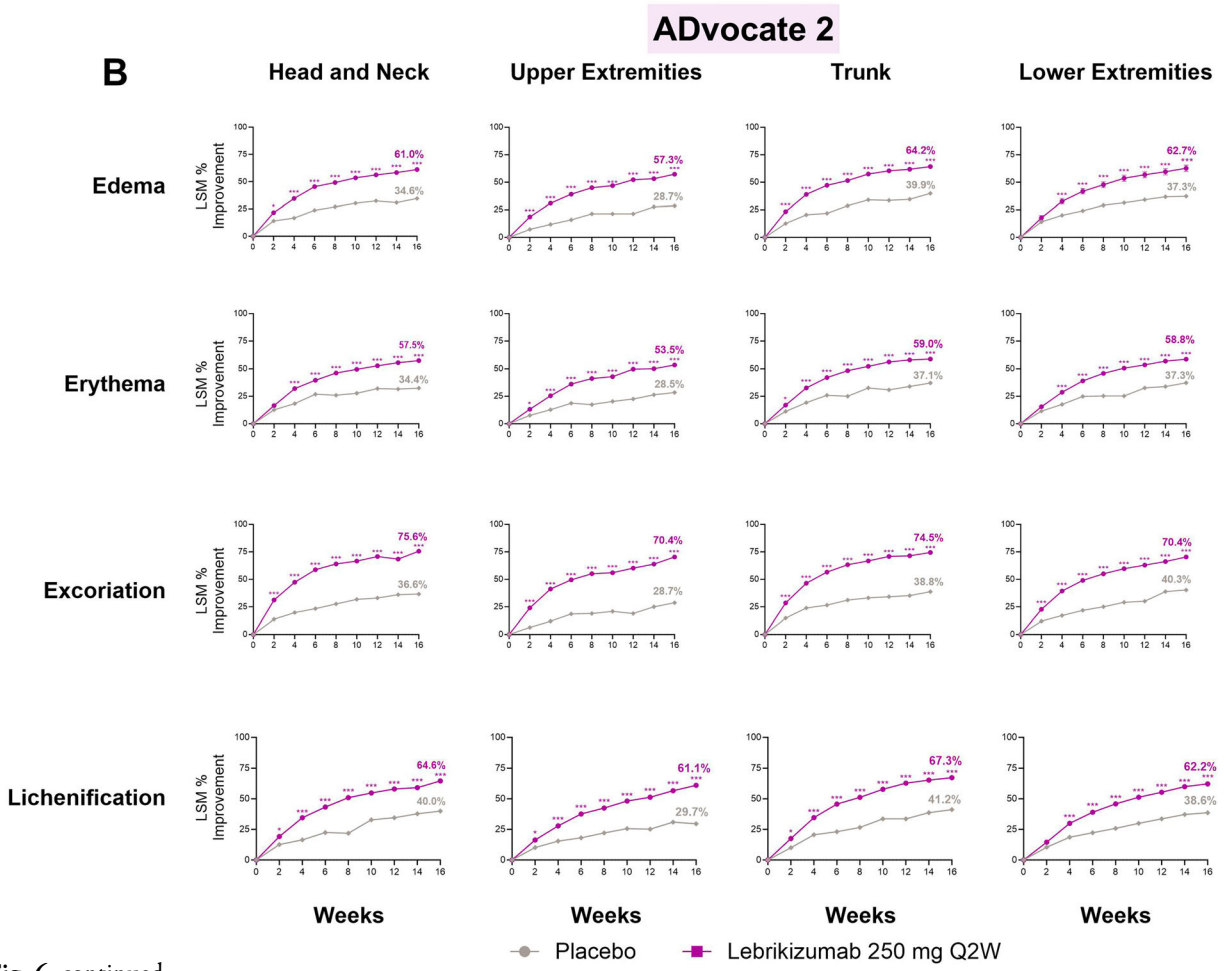

Fig. 6 continued

head/neck and lower extremity regions occurred earliest followed by the trunk and lower extremities. These findings can support healthcare professionals in discussions of treatment expectations with patients.

Real-world studies have shown that EASI head/neck subscores have a larger impact on quality of life than trunk and limb subscores [19], and the extent of facial involvement has been significantly correlated with lower quality of life [20]. The head and neck have historically been difficult to treat. The use of topical corticosteroids for treatment of head and neck AD is limited because of concerns about potential adverse events, including cutaneous atrophy, perioral dermatitis, and steroid withdrawal [2]. Other treatment options, such as topical calcineurin inhibitors and crisaborole, have been associated with a burning sensation and cutaneous irritation; therefore, local tolerability is a concern [21]. While studies of dupilumab using similar analyses to those herein have found improvement in the head/neck region by EASI, real-world cases of head/neck erythema adverse events have been reported with dupilumab [22, 23]. A recent analysis of treatment-emergent adverse events of facial, head, and neck erythema in four placebo-controlled lebrikizumab clinical trials for moderate-to-severe AD did not reveal a difference between lebrikizumab and placebo at week 16, while an analysis of all patients who received at least one dose of lebrikizumab in eight clinical trials showed that the incidence rate of adverse events of facial, head, and neck erythema did not increase with longer exposure to

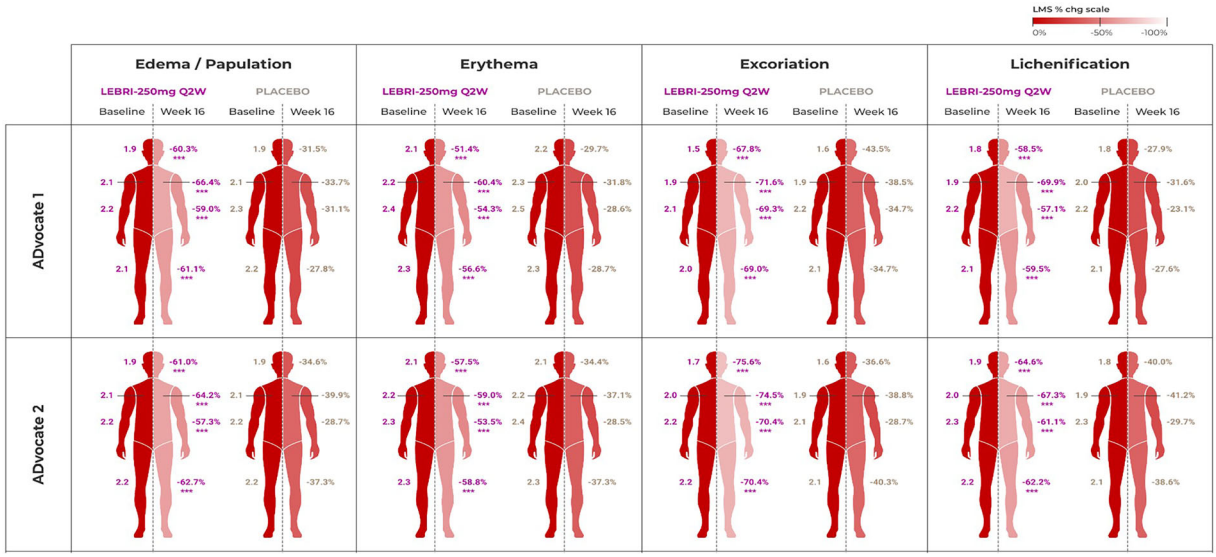

Fig. 7 Least squares mean percentage improvement in EASI clinical signs for each body region at week 16 in ADvocate 1 and ADvocate 2 in patients who had EASI body region sub-scores > 0 at baseline. ***$p \leq 0.001$ vs. placebo. *LEBRI* lebrikizumab, *LSM* least squares mean, *Q2W* every 2 weeks

lebrikizumab [24]. At this time, it is not definitively known whether lebrikizumab may be associated with head and neck erythema, as it has not been extensively utilized in the real-world setting.

Lichenification is usually more difficult to treat relative to other clinical signs of AD, and prevalence can vary among populations. A recent real-world analysis of disease severity at study enrollment found more severe lichenification in Black patients versus White patients for all body regions [25]. In this study, lichenification was nearly resolved across all body regions at week 16 with lebrikizumab treatment.

There are limitations to this study. The data presented here are from the initial 16-week period of the trials. This study also includes limitations inherent to post hoc analyses, such as the lack of a clear a priori hypothesis for testing.

CONCLUSIONS

Lebrikizumab as monotherapy consistently reduced the severity of AD and the extent of involvement across all body regions, including the head and neck, compared with placebo. Lebrikizumab also reduced the severity of all four clinical signs of AD, including lichenification, in all body regions. In addition, a significantly higher proportion of lebrikizumab-treated patients achieved EASI 100.

ACKNOWLEDGEMENTS

Eli Lilly and Company and Almirall S.A. would like to thank the clinical trial participants and their caregivers, without whom this work would not be possible.

Medical Writing, Editorial, and Other Assistance. Medical writing was provided by Kathy Oneacre, MA (Syneos Health, Morrisville, NC, USA), and editorial assistance was provided by Antonia Baldo (Syneos Health, Morrisville, NC, USA), both funded by Eli Lilly and Company.

Author Contributions. Eric Simpson, Marjolein de Bruin-Weller, Kilian Eyerich, Mona Shahriari, and Jonathan I Silverberg contributed to the interpretation of data and critical review

of the manuscript. Chih-ho Hong and Melinda Gooderham contributed to the acquisition of data and critical review of the manuscript. Delphine Staumont-Salle contributed to the analysis and interpretation of data and critical review of the manuscript. Andrew Blauvelt contributed to the acquisition, analysis, and interpretation of the data and critical review of the manuscript. Lotus Mallbris, Maria Jose Rueda, and Helen Agell contributed to the conception and design, analysis and interpretation of the data, and critical review of the manuscript. Amber Reck Atwater contributed to the conception and design, analysis and interpretation of the data, and drafting and critical review of the manuscript. Yuxin Ding and Zhuquing Liu contributed to the analysis and interpretation of the data and critical review of the manuscript.

Funding. These studies were funded by Dermira, Inc., a wholly owned subsidiary of Eli Lilly and Company. Almirall, S.A. has licensed the rights to develop and commercialize lebrikizumab for the treatment of dermatology indications, including atopic dermatitis, in Europe. Eli Lilly and Company has exclusive rights for the development and commercialization of lebrikizumab in the US and the rest of the world outside of Europe. Eli Lilly and Company funded the journal's Rapid Service and Open Access Fees.

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 US 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.

Declarations

Conflict of Interest. Eric Simpson: reports personal fees from AbbVie, Amgen, Arcutis, Areteia Therapeutics,, Bristol Myers Squibb – BMS, CorEvitas, Corvus, Dermira, Eli Lilly, Evelo Biosciences, FIDE, Forte Bio RX, Galderma, GlaxoSmithKline, Gilead Sciences, Impetus Healthcare, Incyte, Innovaderm Reche, Janssen, Johnson & Johnson, Kyowa Kirin Pharmaceutical Development, Leo, Merck, MJH holding (4/29/2021), NUMAB Therapeutics AG, Pfizer, Physicians World LLC, PRImE, Recludix Pharma, Regeneron, Roivant, Sanofi-Genzyme, Trevi therapeutics, Valeant; and grants (or serves as Principal investigator role) for AbbVie, Acrotech, Amgen, Arcutis, ASLAN, Castle, CorEvitas, Dermavant, Dermira, Incyte, Lilly, Kymab, Kyowa Kirin, National Jewish Health, Leo, Pfizer, Regeneron, Sanofi, Target, VeriSkin. Marjolein de Bruin-Weller: reports being a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Aslan, Amgen, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron, and Sanofi. H. Chih-ho Hong has been an investigator for and/or received honorarium from AbbVie, Amgen, Arcutis, Bausch Health, Boehringer-Ingelheim, Bristol-Meyers Squibb, Celgene, Cutanea, Dermira, Dermavant Sciences, DS Biopharma, Eli Lilly and Company, Galderma S.A., GSK, Incyte, Janssen, LEO Pharma, MedImmune, Merck, Mirimar, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, Sanofi-Genzyme, and UCB. Delphine Staumont-Sallé is speaker and/or advisory board member and/or investigator for AbbVie, Almirall S.A., Amgen, AstraZeneca, Eli Lilly and Company, Galderma S.A., Janssen, LEO Pharma, Novartis, Pfizer, Sanofi-Regeneron, and UCB. Andrew Blauvelt: has served as a speaker (received honoraria) for Eli Lilly and Company, Pfizer, and UCB, served as a scientific adviser (received honoraria) for AbbVie, Abcentra, Aclaris, Affibody, Aligos, Almirall, Alumis, Amgen, Anaptysbio, Apogee, Arcutis, Arena, Aslan, Athenex, Bluefin Biomedicine, Boehringer Ingelheim,

Bristol Myers Squibb, Cara Therapeutics, CTI BioPharma, Dermavant, EcoR1, Eli Lilly and Company, Escient, Evelo, Evommune, Forte, Galderma, HighlightII Pharma, Incyte, InnoventBio, Janssen, Landos, Leo, Lipidio, Microbion, Merck, Monte Rosa Therapeutics, Nektar, Novartis, Overtone Therapeutics, Paragon, Pfizer, Q32 Bio, Rani, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, Takeda, TLL Pharmaceutical, TrialSpark, UCB Pharma, Union, Ventyx, Vibliome, and Xencor, and has acted as a clinical study investigator (institution has received clinical study funds) for AbbVie, Acelyrin, Allakos, Almirall, Alumis, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Concert, Dermavant, DermBiont, Eli Lilly and Company, Evelo, Evommune, Galderma, Incyte, Janssen, Leo, Merck, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, Takeda, UCB Pharma, and Ventyx. Kilian Eyerich is speaker and/or advisory board member for AbbVie, Almirall S.A., Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Incyte, Janssen, LEO Pharma, Pfizer, Sanofi, and UCB Pharma and holds shares of Dermagnostix and Dermagnostix R&D. Melinda Gooderham: has been an investigator, speaker and/or advisor for: AbbVie, Acelyrin, Amgen, Akros, Arcutis, Aristea, AnaptysBio, Apogee, Bausch Health, BMS, Boehringer Ingelheim, Cara, Dermira, Dermavant, Eli Lilly, Galderma, GSK, Incyte, InMagene, JAMP Pharma, Janssen, Kyowa Kirin, LEO Pharma, MedImmune, Meiji, Merck, Moonlake, Nimbus, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Sun Pharma, Tarsus, Takeda, UCB, Union and Ventyx. Mona Shahriari reports consulting for AbbVie, Amgen, Arcutis, Bristol Myers Squibb, Cara, Dermavant, Incyte, Janssen, Leo Pharma, Lilly USA, Novartis, Sanofi-Genzyme, Regeneron, UCB Disease State: Psoriasis, Atopic Dermatitis, Alopecia Areata, Hidradenitis Suppurativa; being a speaker for Abbvie, Arcutis, Bristol Myers Squibb, Lilly USA, Janssen, Dermavant, Leo Pharma, Pfizer, Sanofi-Genzyme, Regeneron, UCB Disease State: Psoriasis, Atopic Dermatitis, Alopecia Areata, Prurigo Nodularis and with regard to publications reports being consultant (honoraria) for AbbVie, Amgen, Arcutis, Bristol Myers Squibb, Dermavant, Galderma, Janssen, Leo Pharma, Lilly USA, Novartis, Ortho Dermatologics, Sanofi-Genzyme, Regeneron, UCB; being a speaker for Abbvie, Arcutis, Bristol Myers Squibb, Lilly USA, Janssen, Dermavant, Leo Pharma, Pfizer, UCB; and being an Investigator for AbbVie, CorEvitas Psoriasis and Atopic Dermatitis Registry, Dermira, Cara, Dermavant, Novartis, Union, Mindera. Lotus Mallbris, Amber Reck Atwater, Maria Jose Rueda, Yuxin Ding, and Zhuqing Liu are employees and stockholders of Eli Lilly and Company. Helena Agell is an employee of Almirall S.A. Jonathan I Silverberg: has received honoraria as a consultant and/or advisory board member for Abbvie, Aldena, Amgen, AObiome, Apollo, Arcutis, Arena, Asana, Aslan, Attovia, BioMX, Biosion, Bodewell, Boehringer-Ingelheim, Bristell-Meyers Squibb, Cara, Castle Biosciences, Celgene, Connect Biopharma, Corevitas, Dermavant, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Invea, Kiniksa, Leo Pharma, My-Or Diagnostics, Nektar, Novartis, Optum, Pfizer, RAPT, Recludix, Regeneron, Sanofi-Genzyme, Shaperon, TARGET-RWE, Union, UpToDate; speaker for Abbvie, Eli Lilly, Leo Pharma, Pfizer, Regeneron, Sanofi-Genzyme; institution received grants from Galderma, Incyte, Pfizer.

Ethical Approval. Studies were conducted in accordance with the Declaration of Helsinki and the International Council for the Harmonization of Good Clinical Practice Guideline and approved by individual institutional review boards at each participating study center. All patients provided written informed consent. Studies are registered at ClinicalTrials.gov: ADvocate 1 (NCT04146363) and ADvocate2 (NCT04178967).

REFERENCES

1. Lio PA, Wollenberg A, Thyssen JP, et al. Impact of atopic dermatitis lesion location on quality of life in adult patients in a real-world study. J Drugs Dermatol. 2020;19(10):943–8.

2. Hajar T, Leshem YA, Hanifin JM, The National Eczema Association Task Force, et al. A systematic review of topical corticosteroid withdrawal ("steroid addiction") in patients with atopic dermatitis and other dermatoses. J Am Acad Dermatol. 2015;72(3):541-9.e2.

3. Simpson EL, Lacour JP, Spelman L, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol. 2020;183(2):242–55.

4. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375(24):2335–48.

5. Silverberg JI, Toth D, Bieber T, et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol. 2021;184(3):450–63.

6. Blauvelt A, Rosmarin D, Bieber T, et al. Improvement of atopic dermatitis with dupilumab occurs equally well across different anatomical regions: data from phase III clinical trials. Br J Dermatol. 2019;181(1):196–7.

7. Simpson EL, Paller AS, Siegfried EC, et al. Dupilumab demonstrates rapid and consistent improvement in extent and signs of atopic dermatitis across all anatomical regions in pediatric patients 6 years of age and older. Dermatol Ther (Heidelb). 2021;11(5):1643–56.

8. Alexis A, de Bruin-Weller M, Weidinger S, et al. Rapidity of improvement in signs/symptoms of moderate-to-severe atopic dermatitis by body region with abrocitinib in the phase 3 JADE COMPARE study. Dermatol Ther (Heidelb). 2022;12(3):771–85.

9. Ratnarajah K, Le M, Muntyanu A, et al. Inhibition of IL-13: a new pathway for atopic dermatitis. J Cutan Med Surg. 2021;25(3):315–28.

10. Bieber T. Interleukin-13: targeting an underestimated cytokine in atopic dermatitis. Allergy. 2020;75:54–62.

11. Tsoi LC, Rodriguez E, Degenhardt F, et al. Atopic dermatitis is an IL-13-dominant disease with greater molecular heterogeneity compared to psoriasis. J Invest Dermatol. 2019;139(7):1480–9.

12. Okragly A, Ryuzoji A, Daniels M, Patel C, Benschop R. Comparison of the affinity and in vitro activity of lebrikizumab, tralokinumab, and cendakimab. Exp Dermatol. 2021;30(Suppl 1):3–43.

13. Guttman-Yassky E, Blauvelt A, Eichenfield LF, et al. Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a phase 2b randomized clinical trial. JAMA Dermatol. 2020;156(4):411–20.

14. Simpson EL, Gooderham M, Wollenberg A, et al. Efficacy and safety of lebrikizumab in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis: a randomized clinical trial (ADhere). JAMA Dermatol. 2023;159(2):182–91.

15. Silverberg JI, Guttman-Yassky E, Thaçi D, et al. Two phase 3 trials of lebrikizumab for moderate-to-severe atopic dermatitis. N Engl J Med. 2023;388:1080–91.

16. Blauvelt A, Thyssen JP, Guttman-Yassky E, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. Br J Dermatol. 2023;188(6):740–8.

17. Hanifin JM, Thurston M, Omoto TM, Cherill R, Tofte SJ, Graeber M, EASI Evaluator Group. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol. 2001;10(1):11–8.

18. Hanifin JM, Baghoomian W, Grinich E, Leshem YA, Jacobson M, Simpson EL. The eczema area and severity index-a practical guide. Dermatitis. 2022;33(3):187–92.

19. Ribero S, Puglisi B, Giura MT, et al. Head and neck severity index is associated to a significant

worsening of quality of life in atopic dermatitis patients. Exp Dermatol. 2021;30(11):1717–8.

20. Beikert FC, Langenbruch AK, Radtke MA, Kornek T, Purwins S, Augustin M. Willingness to pay and quality of life in patients with atopic dermatitis. Arch Dermatol Res. 2014;306(3):279–86.

21. Wollenberg A, Christen-Zäch S, Taieb A, et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol. 2020;34(12):2717–44.

22. Jo CE, Finstad A, Georgakopoulos JR, Piguet V, Yeung J, Drucker AM. Facial and neck erythema associated with dupilumab treatment: a systematic review. J Am Acad Dermatol. 2021;84(5):1339–47.

23. de Wijs LEM, Nguyen NT, Kunkeler ACM, et al. Clinical and histopathological characterization of paradoxical head and neck erythema in patients with atopic dermatitis treated with dupilumab: a case series. Br J Dermatol. 2020;183(4):745–9.

24. Murase J, Munera M, Hong C, et al. Lebrikizumab-treated patients with atopic dermatitis had no increase in treatment-emergent adverse events of facial, head, and neck erythema compared to placebo. SKIN J Cutan Med. 2023;7(6): s272.

25. Silverberg JI, Shi VY, Alexis A, et al. Racial and ethnic differences in sociodemographic, clinical, and treatment characteristics among patients with atopic dermatitis in the United States and Canada: real-world data from the CorEvitas atopic dermatitis registry. Dermatol Ther (Heidelb). 2023;13(9): 2045–61.