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ORIGINAL RESEARCH

Lebrikizumab Improves Quality of Life and Patient-Reported Symptoms of Anxiety and Depression in Patients with Moderate-to-Severe Atopic Dermatitis

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin disease for which signs and symptoms have a negative impact on a patient's quality of life (QoL) and mental health. Here, we assess the impact of lebrikizumab on QoL and mental health after 16 weeks of treatment in patients with moderate-to-severe AD.

Methods: Data were analyzed over 16 weeks from two separate phase 3, randomized, placebo-controlled, monotherapy trials (ADvocate1 and ADvocate2). Patient-reported outcomes were assessed using the following measures: Dermatology Life Quality Index (DLQI), EQ-5D-5L visual analogue scale (VAS), EQ-5D-5L index scores (UK and US), Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety, and PROMIS Depression.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-024-01199-9.

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Results: Treatment with lebrikizumab 250 mg every 2 weeks in two studies led to statistically significant improvements (based on nominal *p* values) versus placebo in DLQI since week 4 (the first timepoint assessed) for the following measures: change from baseline in DLQI total score (ADvocate1 −7.8 vs −2.8; ADvocate2 −7.3 vs −3.9), proportion of patients with DLQI ≥ 4-point improvement (ADvocate1 69.5% vs 36.2%; ADvocate2 60.5% vs 42.6%), DLQI total score ≤ 5 (ADvocate1 36.7% vs 8.8%; ADvocate2 29.6% vs 10.8%), and DLQI (0, 1) (ADvocate1 12.3% vs 1.7%; ADvocate2 9.2% vs 1.7%). Improvements in DLQI measures, EQ-5D-5L index scores (UK and US), and EQ-5D-5L VAS were sustained through week 16. Additionally, lebrikizumab improved PROMIS Anxiety and PROMIS Depression scores, and improvements were higher in patients with at least a mild score (≥ 55) versus placebo for PROMIS Anxiety (ADvocate1 −7.43 vs −1.51; ADvocate2 −4.95 vs −0.82) and PROMIS Depression (ADvocate1 −7.42 vs −2.46; ADvocate2 −4.28 vs −2.00).

Conclusions: Treatment with monotherapy 250 mg lebrikizumab for 16 weeks provided clinically meaningful improvements in outcomes related to QoL and mental health for patients with moderate-to-severe AD. Lebrikizumab-treated patients reported improvements in DLQI as early as week 4, the first measure since baseline.

Trial Registration: ClinicalTrials.gov Registration NCT04146363 (ADvocate1) and NCT04178967 (ADvocate2).

Keywords: Anxiety; Atopic dermatitis; Depression; Lebrikizumab; Mental health; Quality of life

Key Summary Points

There is an unmet need for data on disease control by reducing itch and associated impacts on QoL and mental health, such as anxiety and depression.

This article reports patient-reported outcomes related to quality of life and mental health, measured in the first 16 weeks of lebrikizumab monotherapy treatment, in patients with moderate-to-severe AD enrolled in the phase 3 ADvocate1 and ADvocate2 studies.

Clinically meaningful improvements in patient-reported outcomes related to quality of life and mental health were reported after 16 weeks of treatment with lebrikizumab monotherapy in the clinical trials ADvocate1 and ADvocate2.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritus and skin lesions [1–4]. At present, the global prevalence of AD is 20% in children and 2–7% in adults [5]. The onset of AD is usually early childhood diagnosed in 90% of patients with AD by 5 years of age and in 17% of patients by post-adolescence, often persisting into adulthood [5–10].

Symptoms of moderate-to-severe AD, such as increased itch and sleep disturbance due to itch, can have a detrimental impact on quality of life (QoL) and mental health [3, 11–18]. Emotional distress and impaired physical and social functioning are among some of the main factors negatively affecting QoL in patients with AD [3, 18]. Furthermore, approximately 30% of patients with AD reported anxiety or depression [19, 20].

Topical medications are currently the first line of anti-inflammatory therapy for patients with AD. However, they are often inadequate at controlling symptoms in patients with moderate-to-severe AD [4, 21–25]. Several systemic treatments,

such as Janus kinase inhibitors and biologics, have recently become available for the treatment of moderate-to-severe AD [26–28]. The primary endpoints of AD clinical studies focus on cutaneous signs and symptoms, and the impact of AD on patients' QoL and mental health is not always reported [29]. Therefore, there is an unmet need for data on disease control by reducing itch and associated impacts on QoL and mental health, such as anxiety and depression [29].

Lebrikizumab is an IgG4 monoclonal antibody that binds with high affinity and slow off-rate to interleukin (IL)-13 and selectively inhibits IL-13 signaling through the IL-4 receptor alpha (IL-4Rα)/IL-13 receptor alpha 1 (IL-13Rα1) pathway, thereby blocking the downstream effects of IL-13 with high potency. Blockade of IL-13 signaling is expected to be of benefit in IL-13-dominant diseases, such as AD [30–33]. The safety and efficacy of lebrikizumab has been demonstrated in two phase 3 monotherapy studies [34] (ADvocate1 and ADvocate2) in patients with moderate-to-severe AD.

This article reports patient-reported outcomes (PROs) related to QoL and mental health, measured in the first 16 weeks of lebrikizumab monotherapy treatment, in patients with moderate-to-severe AD enrolled in the phase 3 ADvocate1 and ADvocate2 studies.

METHODS

Study Design

ADvocate1 (NCT04146363) and ADvocate2 (NCT04178967) were identically designed 52-week randomized, double-blind, parallel-group, placebo-controlled, monotherapy phase 3 trials [34]. Eligible patients included adults (≥ 18 years old) and adolescents (≥ 12 to < 18 years old and weighing ≥ 40 kg) with moderate-to-severe AD who met Eczema Area and Severity Index (EASI) score of ≥ 16, Investigator's Global Assessment (IGA) score of ≥ 3, body surface area of ≥ 10%, and had chronic AD for more than 1 year. This manuscript focuses on patients in the induction treatment period from week 0 to week 16.

Eligible patients were randomly assigned 2:1 to either lebrikizumab 250 mg (loading dose of 500 mg given at baseline and week 2) or placebo by subcutaneous (SC) injection every 2 weeks (Q2W) until week 16. Both studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The studies were approved by the appropriate institutional review boards or ethics committee situated across the 100 study sites in the USA, Canada, Europe, and the Asia/Pacific area.

Patient-Reported Measures Related to QoL and Mental Health

In both studies, Dermatology Life Quality Index (DLQI) was measured at baseline and weeks 4, 8, 12, and 16. All other outcomes (EQ-5D, Patient-Reported Outcomes Measurement Information System [PROMIS] Anxiety, and PROMIS Depression) were measured at baseline and week 16.

DLQI

DLQI is a patient-reported, 10-item, QoL questionnaire in patients > 16 years old that evaluates six domains over the previous 7 days, including daily activities, symptoms and feelings, leisure, work and school, personal relationships, and treatment. Responses are categorized into four scores of 0, 1, 2, and 3 corresponding to "not at all," "a little," "a lot," and "very much." Unanswered (or "not relevant") responses are scored as 0 [35], giving a possible total score range from 0 (no impact of skin disease on QoL) to 30 (maximum impact on QoL). A DLQI total score of 0 to 1 (DLQI 0/1) is considered as having no effect on a patient's health-related QoL [36], a DLQI total score ≤ 5 is considered as having a small effect on a patient's health-related QoL [37], and a DLQI ≥ 4-point improvement from baseline is known as the minimal clinically important difference [37]. Patients analyzed in this group were > 16 years old. Children's Dermatology Life Quality Index (cDLQI) were reported and collected for patients < 17 years old, but data were not included in this study because of limited sample size.

EQ-5D-5L

The EQ5D-5L is a patient-reported tool used to measure health-related QoL. The descriptive system is composed of several domains, which include usual activities, mobility, self-care, pain or discomfort, anxiety, or depression. Each domain is scored according to five levels, including "no problems," "slight problems," "moderate problems," "severe problems," and "extreme problems." The EQ-5D-5L visual analogue scale (VAS) measure reports the respondent's self-rated health on a vertical VAS where the endpoints are labeled as "best imaginable health state" (100) and "worst imaginable health state" (0). The EQ-5D-5L UK Health State Index and the EQ-5D-5L US Health State Index are derived from the EQ-5D-5L measure. Patients included in the analyses of this measure include a combination of adolescents and adults.

PROMIS Anxiety and PROMIS Depression

The PROMIS measures used in this study include the Anxiety and Depression short forms, which are self-reported and comprised of eight questions per measure that assess a patient's symptoms over the previous week [38]. PROMIS Anxiety and Depression scales were used for subjects aged > 17 years. The PROMIS Anxiety scale assesses the following items (PROMIS Anxiety 2019): self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). The PROMIS Depression scale assesses the following items (PROMIS Depression 2019): self-reported negative mood (sadness, guilt), views of self (self-criticism, worthlessness), social cognition (loneliness, interpersonal alienation), and decreased positive affect and engagement (loss of interest, meaning, and purpose). The response scale ranges from 1 = "Never," 2 = "Rarely," 3 = "Sometimes," 4 = "Often," to 5 = "Almost always." Total raw scores (1 to 5) are converted to T-scores ranging from 0 to 100, with higher scores representing greater anxiety or depression, where symptoms are categorized as normal (T-scores of < 55), mild (T-scores of ≥ 55 to < 60), moderate (T-scores of ≥ 60 to < 70), or severe (T-score of ≥ 70).

Subpopulation: PROMIS Anxiety and PROMIS Depression

In both studies, a subpopulation of patients who reported at least mild anxiety and/or depression at baseline (T-scores ≥ 55) were analyzed further.

Statistical Analysis

Analyses in ADvocate1 used the intent-to-treat (ITT) population (all randomized patients). In ADvocate2, a total of 18 patients from a single study site were excluded from the ITT population since some or all the study participants did not meet the eligibility criteria of having moderate-to-severe AD. Thus, analyses in ADvocate2 used the modified intent-to-treat (mITT) population.

The analysis of binary endpoints, DLQI (0, 1), DLQI total score ≤ 5, and DLQI ≥ 4-point improvement, was based on a Cochran–Mantel–Haenszel test adjusted by the following stratification factors: geographic region (USA vs EU vs rest of world), age (adolescent patients that completed DLQI 16 to < 18 years vs adults ≥ 18 years), and disease severity (IGA 3 vs 4). Data collected after rescue treatment or treatment discontinuation were considered as missing and were imputed by non-responder imputation (NRI). Additionally, as the data were collected at multiple visits for DLQI, change from baseline of DLQI was analyzed using mixed-model repeated measure (MMRM).

The analysis of continuous endpoints (EQ-5D, PROMIS Anxiety, and PROMIS Depression) was based on analysis of covariance (ANCOVA) with treatment group, baseline value, and stratification factors, and last observation carry forward was used for imputation for these endpoints.

There is no multiplicity control. All p values reported are nominal. Analyses were performed using SAS, Version 9.4 (SAS Institute).

RESULTS

Baseline Demographics and Disease Characteristics

A total of 424 and 427 patients were randomized to treatment in ADvocate1 and ADvocate2, respectively. Baseline demographics and clinical characteristics are presented in Table 1. QoL and PROMIS baseline mean scores were similar between placebo and lebrikizumab groups and across both studies.

Impact of Lebrikizumab on PROs Related to QoL and Mental Health

Clinically relevant improvements were reported in patients after 16 weeks of treatment with lebrikizumab 250 mg Q2W compared to placebo for DLQI, EQ-5D-5L VAS and index scores (UK and US), PROMIS Anxiety, and PROMIS Depression in ADvocate1 and ADvocate2.

DLQI

Treatment with lebrikizumab 250 mg in two monotherapy studies (ADvocate1, $N=283$; ADvocate2, $N=281$) led to early improvements in DLQI compared to placebo (ADvocate1, $N=141$; ADvocate2, $N=146$). In both studies, at week 4, the first time that DLQI was reported since baseline, lebrikizumab-treated patients showed improvements from baseline versus placebo-treated patients in DLQI total score (ADvocate1: least squares mean [LSM] of −7.8 vs −2.8, $p<0.001$; ADvocate2: LSM of −7.3 vs −3.9, $p<0.001$); the percentage of patients with DLQI ≥ 4-point improvement (ADvocate1: 69.5% vs 36.2%, $p<0.001$; ADvocate2: 60.5% vs 42.6%, $p=0.001$; Supplementary Material Fig. S1 shows NRI/MI data); the percentage of patients with DLQI total score ≤ 5, which accounts for little-to-no effect (ADvocate1: 36.7% vs 8.8%, $p<0.001$; ADvocate2: 29.6% vs 10.8%, $p<0.001$; Supplementary Material Fig. S2 shows NRI/MI data); and the percentage of patients with DLQI (0,1) (ADvocate1: 12.3% vs 1.7%, $p<0.001$; ADvocate2: 9.2% vs 1.7%, $p=0.006$), respectively (Fig. 1a–h).

In both studies, lebrikizumab-treated patients showed continued significant improvements up to week 16 versus placebo-treated patients in LSM change from baseline DLQI total score (ADvocate1: −9.9 vs −4.4; ADvocate2: −9.4 vs −5.0), DLQI ≥ 4-point improvement (ADvocate1: 71.2% vs 29.3%, $p<0.0001$; ADvocate2: 62.3% vs 31.3%, $p<0.0001$; Supplementary Material Fig. S1 shows NRI/MI data), DLQI total score ≤ 5 (ADvocate1: 51.2% vs 14.2%, $p<0.001$; ADvocate2: 43.2% vs 16.7%, $p<0.001$; Supplementary Material Fig. S2 shows NRI/MI data), and DLQI (0,1) (ADvocate1: 26.3% vs 4.2%, $p<0.001$; ADvocate2: 16.1% vs 7.7%, $p=0.035$), respectively (Fig. 1a–h).

EQ-5D-5L

At week 16, significant improvements in EQ-5D-5L VAS were reported in patients treated with lebrikizumab compared to placebo, LSM change from baseline (CFB) of 10.4 vs 2.1 ($p<0.001$) in ADvocate1 (Fig. 2a) and 9.7 vs 5.2 ($p=0.0053$) in ADvocate2 (Fig. 2b), respectively. At week 16, lebrikizumab 250 mg treatment resulted in improvements ($p<0.001$) in the EQ-5D-5L health state index score compared with placebo for both the UK algorithm (Fig. 2c, d) and the US algorithm (Fig. 2e, f) in ADvocate1 and ADvocate2.

PROMIS Anxiety and PROMIS Depression

In ADvocate1 and ADvocate2, 58.9% and 53.8% of lebrikizumab-treated patients reported PROMIS Anxiety scores that were categorized as "normal" at baseline compared to 56.9% and 54.3% in placebo-treated patients, respectively, as assessed by PROMIS Anxiety. Likewise, in ADvocate1 and ADvocate2, 67.1% and 64.9% of lebrikizumab-treated patients reported PROMIS Depression scores that were categorized as "normal" at baseline compared to 71.5% and 62.8% of placebo-treated patients, respectively, as assessed by PROMIS Depression (Table 1). Patients treated with lebrikizumab in ADvocate1 and ADvocate2, respectively,

Table 1 Baseline demographics and disease characteristics in ADvocate1 and ADvocate2 patient population

Characteristic	ADvocate1		ADvocate2	
	Placebo Q2W (*N* = 141)	Lebrikizumab 250 mg Q2W (*N* = 283)	Placebo Q2W (*N* = 146)	Lebrikizumab 250 mg Q2W (*N* = 281)
Baseline demographics				
Age (years)	34.2 (16.4)	36.1 (17.8)	35.3 (17.2)	36.6 (16.8)
Adolescents (≥ 12 to < 18 years), *N* (%)	18 (12.8)	37 (13.1)	17 (11.6)	30 (10.7)
Adults (≥ 18 years), *N* (%)	123 (87.2)	246 (86.9)	129 (88.4)	251 (89.3)
Female, *N* (%)	73 (51.8)	141 (49.8)	75 (51.4)	136 (48.4)
Race, *N* (%)				
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)
White	93 (66.0)	196 (69.3)	85 (58.2)	168 (59.8)
Weight, kg	79.0 (22.7)	77.0 (19.7)	76.0 (21.1)	76.7 (20.5)
Ethnicity*, *N* (%)				
Hispanic/Latino	16 (25.8)	23 (18.0)	12 (20.0)	27 (25.2)
BMI, kg/m^2	27.8 (7.2)	26.6 (5.8)	26.3 (6.3)	26.7 (6.6)
Geographic region, *N* (%)				
USA	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)
Prior systemic treatment, *N* (%)	85 (60.3)	144 (50.9)	81 (55.5)	156 (55.5)
Baseline disease characteristics				
IGA (3), *N* (%)	83 (58.9)	170 (60.1)	95 (65.1)	175 (62.3)
IGA (4) *N* (%)	58 (41.1)	113 (39.9)	51 (34.9)	106 (37.7)
EASI	31.0 (12.9)	28.8 (11.3)	29.6 (10.8)	29.7 (12.0)
BSA affected	47.8 (23.9)	45.3 (22.5)	46.0 (21.1)	46.1 (22.6)
Pruritus NRS	7.3 (1.7)	7.2 (1.9)	7.2 (1.9)	7.1 (1.9)
Sleep-Loss due to itch	2.3 (1.0)	2.3 (1.0)	2.2 (0.9)	2.2 (0.9)
DLQI [*N*]	15.7 (7.2) [121]	15.3 (7.4) [239]	15.9 (7.6) [118]	15.4 (7.0) [218]
EQ-5D-5L Health State Index (UK) [*N*]	0.6 (0.25) [141]	0.6 (0.24) [282]	0.6 (0.27) [145]	0.7 (0.24) [277]

Table 1 continued

Characteristic	ADvocate1		ADvocate2	
	Placebo Q2W (*N* = 141)	Lebrikizumab 250 mg Q2W (*N* = 283)	Placebo Q2W (*N* = 146)	Lebrikizumab 250 mg Q2W (*N* = 281)
EQ-5D-5L Health State Index (US) [*N*]	0.7 (0.17) [141]	0.7 (0.17) [282]	0.7 (0.18) [145]	0.8 (0.16) [277]
EQ-5D-5L VAS [*N*]	67.0 (22.23) [141]	68.2 (21.99) [282]	68.6 (21.62) [145]	66.7 (20.71) [277]
PROMIS Anxiety score [*N*]	54.3 (9.3) [122]	52.9 (10.1) [244]	55.0 (10.4) [128]	54.4 (8.9) [246]
Normal (< 55), *n* (%)	70 (56.9)	145 (58.9)	70 (54.3)	135 (53.8)
Mild (55 to < 60), *n* (%)	22 (17.9)	43 (17.5)	19 (14.7)	46 (18.3)
Moderate (60 to < 70), *n* (%)	22 (17.9)	46 (18.7)	28 (21.7)	49 (19.5)
Severe (≥ 70), *n* (%)	8 (6.5)	10 (4.1)	11 (8.5)	16 (6.4)
PROMIS Depression score [*N*]	50.0 (9.2) [122]	49.8 (10.0) [244]	51.2 (10.4) [127]	51.3 (9.2) [246]
Normal (< 55), *n* (%)	88 (71.5)	165 (67.1)	81 (62.8)	163 (64.9)
Mild (55 to < 60), *n* (%)	13 (10.6)	43 (17.5)	15 (11.6)	36 (14.3)
Moderate (60 to < 70), *n* (%)	20 (16.3)	31 (12.6)	26 (20.2)	41 (16.3)
Severe (≥ 70), *n* (%)	1 (0.8)	5 (2.0)	5 (3.9)	6 (2.4)
PROMIS Anxiety score, subset with scores ≥ 55 at baseline [*N*]	63.0 (5.74) [52]	62.4 (6.11) [99]	64.0 (6.87) [58]	62.1 (5.56) [111]
PROMIS Depression score, subset with scores ≥ 55 at baseline [*N*]	62.0 (4.68) [34]	61.4 (5.57) [79]	62.5 (5.96) [46]	61.4 (5.24) [83]

Data are mean (standard deviation), unless otherwise indicated

IGA, EASI, Pruritus NRS, Sleep-Loss due to itch, BSA affected, EQ-5D-5L VAS Score, EQ-5D-5L Health State Index (UK), and EQ-5D-5L Health State Index (US) include a combination of adults and adolescent patients

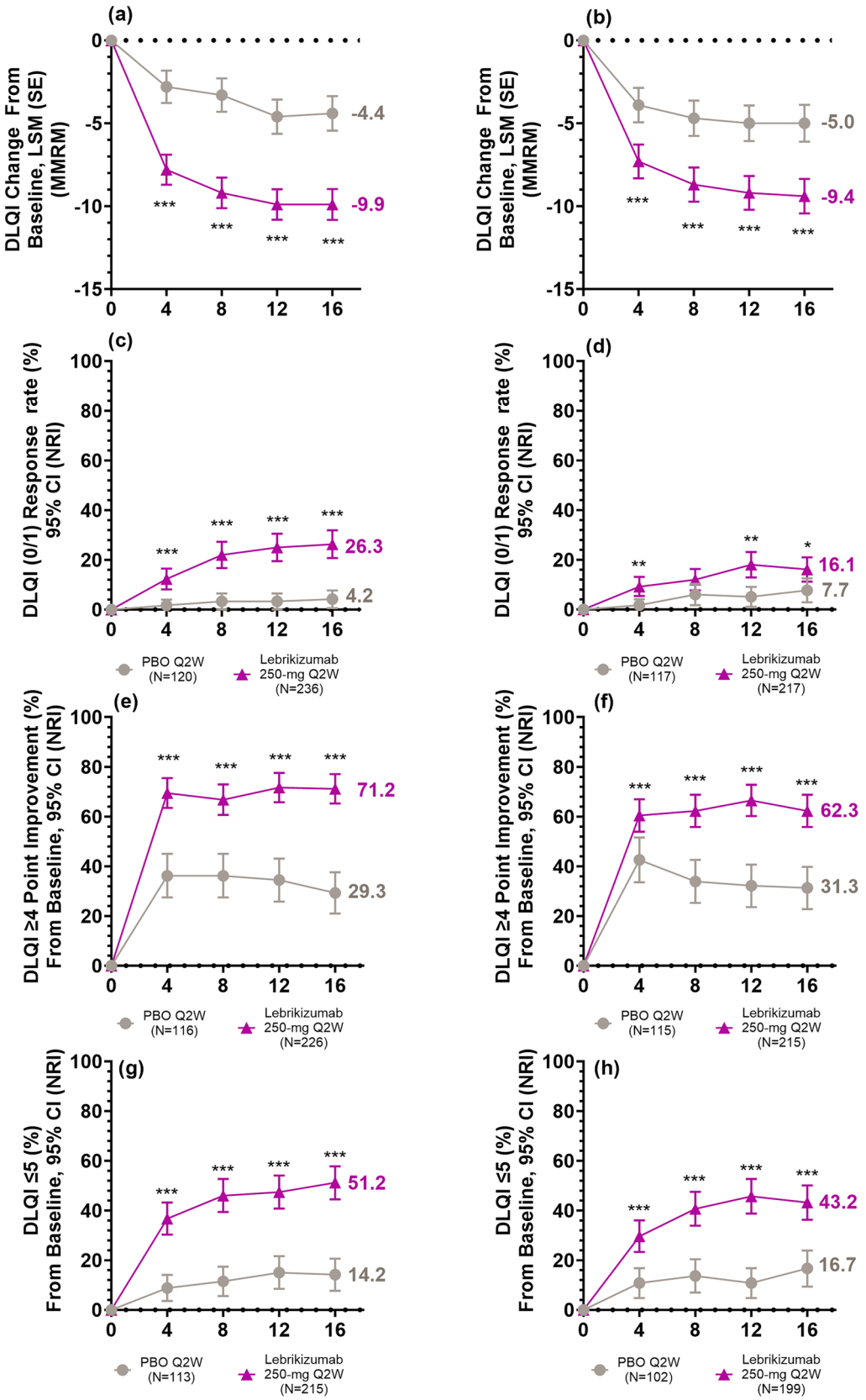
Patients > 16 years old responded to DLQI

Patients > 17 years old responded to PROMIS Anxiety and PROMIS Depression

BMI body mass index, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *NRS* numeric rating scale, *PROMIS* Patient-Reported Outcomes Measurement Information System, *Q2W* every 2 weeks, *VAS* visual analogue scale

*Ethnicity is reported for US sites only. The percentage reflects the percentage in population from US sites

reported PROMIS Anxiety symptoms that were categorized as mild (17.5% and 18.3%), moderate (18.7% and 19.5%), and severe (4.1% and 6.4%) at baseline compared to patients treated with placebo who reported PROMIS Anxiety symptoms that were categorized as mild (17.9% and 14.7%), moderate (17.9% and 21.7%), and severe (6.5% and 8.5%). Similarly, at baseline, lebrikizumab-treated patients reported PROMIS Depression scores that were mild (17.5% and 14.3%), moderate (12.6% and 16.3%), and severe (2.0% and 2.4%) at baseline compared to patients treated with placebo who reported PROMIS Depression scores that were categorized as mild (10.6% and 11.6%), moderate (16.3%


(a)
DLQI Change From Baseline, LSM (SE) (MMRM)
-4.4
-9.9
(b)
DLQI Change From Baseline, LSM (SE) (MMRM)
-5.0
-9.4
(c)
DLQI (0/1) Response rate (%) 95% CI (NRI)
26.3
4.2
PBO Q2W (N=120)
Lebrikizumab 250-mg Q2W (N=236)
(d)
DLQI (0/1) Response rate (%) 95% CI (NRI)
16.1
7.7
PBO Q2W (N=117)
Lebrikizumab 250-mg Q2W (N=217)
(e)
DLQI ≥4 Point Improvement (%) From Baseline, 95% CI (NRI)
71.2
29.3
PBO Q2W (N=116)
Lebrikizumab 250-mg Q2W (N=226)
(f)
DLQI ≥4 Point Improvement (%) From Baseline, 95% CI (NRI)
62.3
31.3
PBO Q2W (N=115)
Lebrikizumab 250-mg Q2W (N=215)
(g)
DLQI ≤5 (%) From Baseline, 95% CI (NRI)
51.2
14.2
PBO Q2W (N=113)
Lebrikizumab 250-mg Q2W (N=215)
(h)
DLQI ≤5 (%) From Baseline, 95% CI (NRI)
43.2
16.7
PBO Q2W (N=102)
Lebrikizumab 250-mg Q2W (N=199)

◂**Fig. 1** Least squares mean change in DLQI total score (**a**, **b**), percentage of patients with DLQI 0/1 (**c**, **d**), percentage of patients with DLQI ≥ 4-point improvement at baseline (**e**, **f**), and percentage of patients with DLQI ≤ 5 with ITT/mITT DLQI > 5 at baseline (**g**, **h**) response rate in ADvocate1 and in ADvocate2. *CI* confidence interval, *DLQI* Dermatology Life Quality Index, *ITT* intent-to-treat, *LSM* least squares mean, *mITT* modified intent-to-treat, *MMRM* mixed-model repeated measures, *NRI* non-responder imputation, *PBO* placebo, *Q2W* every 2 weeks, *SE* standard error. $^{*}p \le 0.05$, $^{**}p \le 0.01$, and $^{***}p \le 0.001$ denote analyses comparing lebrikizumab with placebo. For continuous endpoints, LSM and SE are from MMRM. For categorical endpoints, a non-responder imputation was applied to missing values. Note: Patients > 16 years old responded to DLQI

and 20.2%), and severe (0.8% and 3.9%) in ADvocate1 and ADvocate2, respectively.

After 16 weeks, lebrikizumab-treated patients showed significant improvements in PROMIS Anxiety scores versus placebo in ADvocate1 (CFB LSM of −3.91 vs −0.60, $p<0.001$; Fig. 3a) and ADvocate2 (CFB LSM of −3.18 vs −0.45, $p<0.001$; Fig. 3b). Likewise, there were significant improvements in PROMIS Depression scores in patients after 16 weeks of treatment with lebrikizumab 250 mg versus placebo in ADvocate1 (CFB LSM of −3.07 vs −0.37, $p<0.001$; Fig. 3c) and ADvocate2 (CFB LSM of −2.59 vs 0.16, $p<0.001$; Fig. 3d).

Subpopulation: PROMIS Anxiety and Depression

In ADvocate1 and ADvocate2, respectively, a total of 35.0% ($n=99/283$) and 39.5% ($n=111/281$) of lebrikizumab-treated patients, and 36.9% ($n=52/141$) and 30.7% ($n=58/146$) of placebo-treated patients had a PROMIS Anxiety score of ≥ 55 at baseline. A total of 27.9% ($n=79/283$) and 29.5 ($n=83/281$) of lebrikizumab-treated patients, and 24.1% ($n=34/141$) and 31.5% ($n=46/146$) of placebo-treated patients had a PROMIS Depression score of ≥ 55, at baseline, for both studies respectively. In both studies, after 16 weeks of treatment with lebrikizumab 250 mg, patients with a baseline PROMIS Anxiety score of ≥ 55, indicating at least mild impairment, reported significant improvements in anxiety score compared to placebo (ADvocate1: −7.43 vs −1.51, $p<0.001$; Fig. 4a. ADvocate2: −4.95 vs −0.82, $p<0.001$; Fig. 4b). Similarly, at week 16, significant improvements were reported in patients with a PROMIS Depression score of ≥ 55 at baseline in lebrikizumab-treated patients versus placebo in ADvocate1 (−7.42 vs −2.46, $p=0.002$; Fig. 4c), and in ADvocate2, numerical improvements were reported (−4.28 vs −2.00, $p=0.065$; Fig. 4d).

DISCUSSION

Long-term and effective treatment of AD requires consideration of disease burden and its impact on QoL and mental health in patients with AD. This is particularly relevant since approximately 30% of patients with AD report symptoms of anxiety or depression [19, 20, 25]. Patients with moderate-to-severe AD in this study reported a very large impact on QoL at baseline (mean DLQI > 15). Baseline PROMIS Anxiety and depression assessments showed that about half of clinical study patients had at least "mild" anxiety and about 40% had at least "mild" depression. Clinically meaningful improvements in PRO measures related to QoL and mental health were reported after 16 weeks of treatment with lebrikizumab monotherapy in the clinical trials ADvocate1 and ADvocate2. Similar improvements have been shown with other approved biologics/JAKs for moderate-to-severe AD [39–41].

Improvements in DLQI were reported as early as week 4, the first visit since baseline in which DLQI was assessed, in lebrikizumab-treated patients and maintained through week 16. Early improvements of QoL measures are expected to improve mental health-related symptoms, such as anxiety and depression [29]. Improvements in the DLQI (0, 1) and DLQI ≤ 5 endpoints after 16 weeks demonstrate the ability of lebrikizumab treatment to significantly improve QoL to levels of little-to-no impact on QoL, which is an ultimate goal for patients with AD [42]. In addition, patients treated with lebrikizumab in both studies reported significant improvements

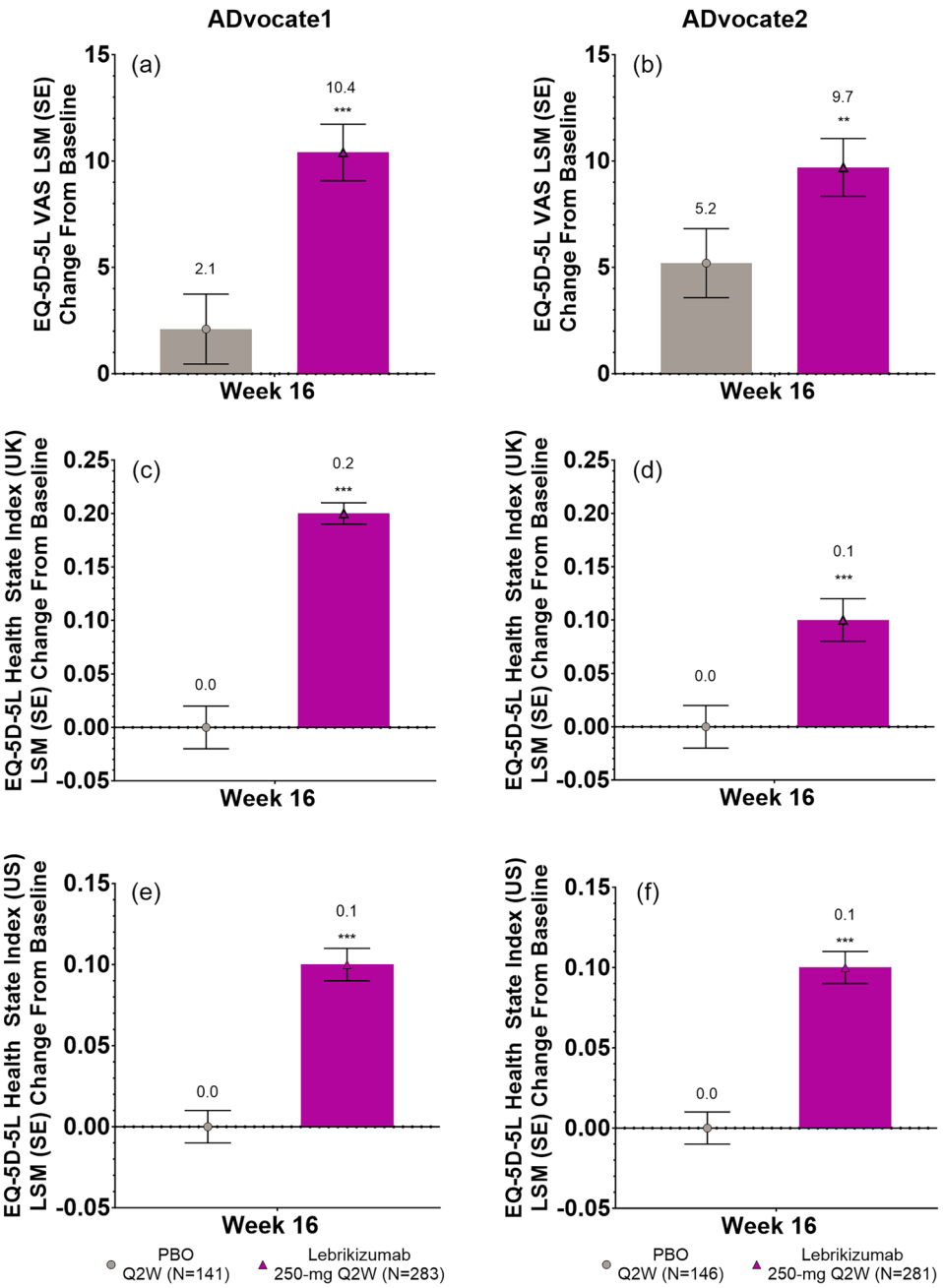


Fig. 2 Least squares mean change in EQ-5D-5L VAS Score (**a**, **b**), EQ-5D-5L UK Health State Index (**c**, **d**), and EQ-5D-5L US Health State Index (**e**, **f**) in ADvocate1 and in ADvocate2. *ANCOVA* analysis of covariance, *LSM* least squares mean, *LOCF* last observation carried forward, *PBO* placebo, *Q2W* every 2 weeks, *SE* standard error, *VAS*, visual analogue scale. $^{*}p \le 0.05$, $^{**}p \le 0.01$, and $^{***}p \le 0.001$ for analyses comparing lebrikizumab 250 mg with placebo. For continuous endpoints, LSM and SE are from ANCOVA with LOCF. EQ-5D-5L VAS Score, EQ-5D-5L Health State Index (UK), and EQ-5D-5L Health State Index (US) include analyses of adults and adolescents

in all three measures of the EQ-5D-5L, including the UK Health State Index, the US Health State Index, and VAS after 16 weeks. As such, treatment with lebrikizumab over 16 weeks demonstrated significant improvement across several QoL-related measures.

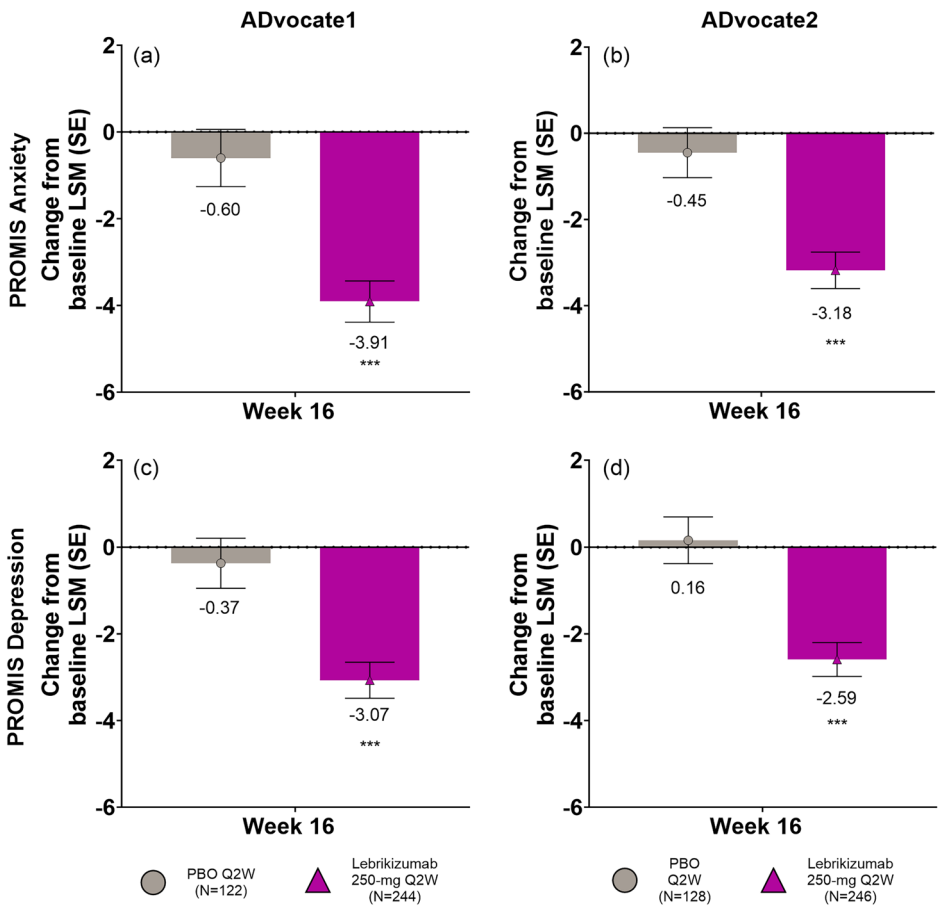


Fig. 3 Least squares mean change PROMIS Anxiety scores (**a**, **b**) and PROMIS Depression scores (**c**, **d**) from baseline in ADvocate1 (ITT) and ADvocate2 (mITT). *ANCOVA* analysis of covariance, *ITT* intent-to-treat, *LOCF* last observation carried forward, *LSM* least squares mean, *mITT* modified intent-to-treat, *PBO* placebo, *PROMIS* Patient-Reported Outcomes Measurement Information System, *Q2W* every 2 weeks, *SE* standard error. $^{*}p \le 0.05$, $^{**}p \le 0.01$, and $^{***}p \le 0.001$ for analyzes comparing lebrikizumab 250 mg with placebo. For continuous endpoints, LSM and SE are from ANCOVA with LOCF. Note: Patients > 17 years old responded to PROMIS Anxiety and PROMIS Depression

Limitations

These endpoints were reported early, after 16 weeks, and the long-term impact of lebrikizumab treatment on the mental health of patients should be explored. Additionally, in the subpopulation analyses, which included patients with at least mild symptoms of anxiety and depression, improvements for patients appeared higher compared to the overall population, which included patients that had scores that were considered normal on the PROMIS Anxiety and PROMIS Depression scales, and therefore results may have been diluted.

CONCLUSION

Treatment with lebrikizumab monotherapy over 16 weeks provided clinically meaningful QoL and mental health improvements compared to placebo in patients with moderate-to-severe AD. Lebrikizumab-treated patients reported improvements in DLQI as early as

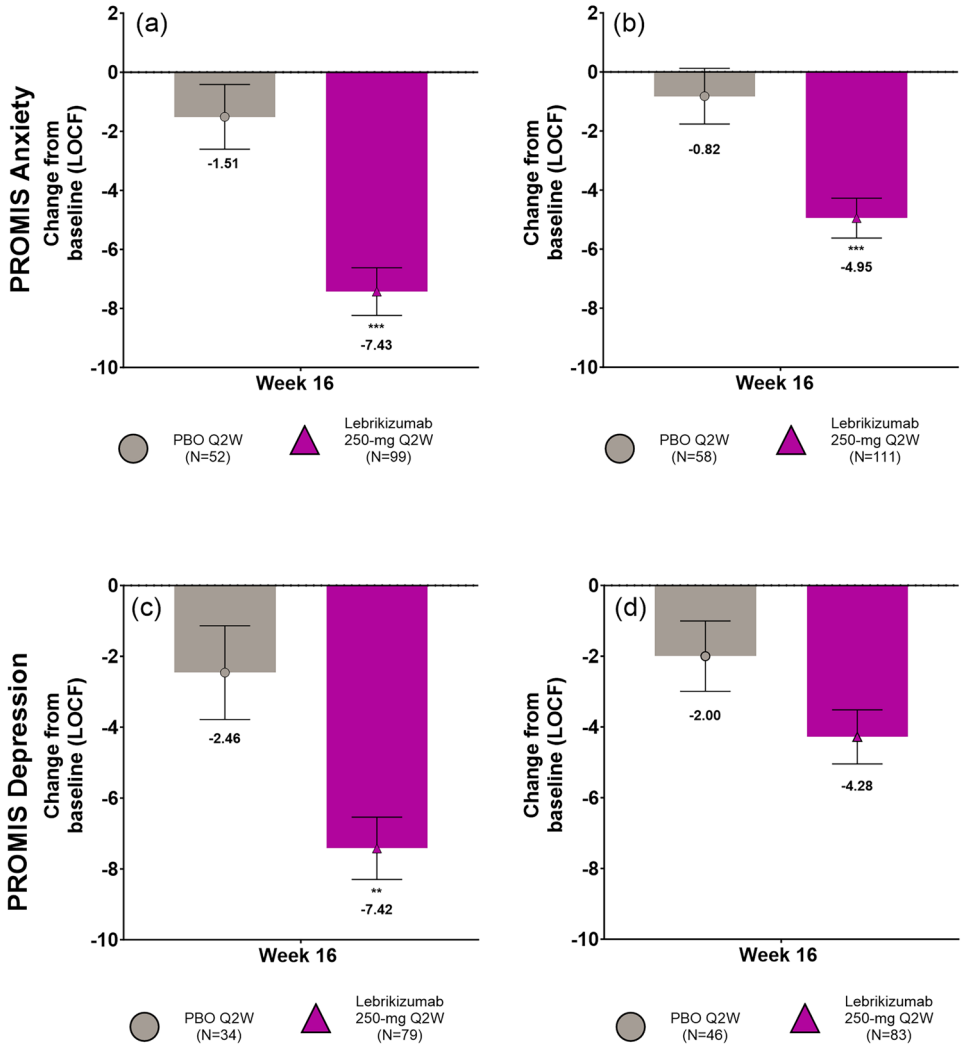


Fig. 4 Least squares mean change PROMIS Anxiety scores (**a**, **b**) and PROMIS Depression scores (**c**, **d**) in patients with baseline score of ≥ 55 in ADvocate1 (ITT) and ADvocate2 (mITT). *ANCOVA* analysis of covariance, *ITT* intent-to-treat, *LOCF* last observation carried forward, *LSM* least squares mean, *mITT* modified intent-to-treat, *PBO* placebo, *Q2W* every 2 weeks, *PROMIS* Patient-Reported Outcomes Measurement Information System, *SE* standard error. $^{*}p \le 0.05$, $^{**}p \le 0.01$, and $^{***}p \le 0.001$ for analyses comparing lebrikizumab 250 mg with placebo. For continuous endpoints, LSM and SE are from ANCOVA with LOCF analyses. Note: Patients > 17 years old responded to PROMIS Anxiety and PROMIS Depression

week 4, the first timepoint post-treatment where this PRO was measured.

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Data Availability. 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. Peter A. Lio has received grants as an investigator, honoraria for lecturing, and/or consulting fees from AbbVie, Arcutis, Almirall, Alphyn, Amyris, ASLAN, AOBiome, Bristol-Myers Squibb, Castle Biosciences, Concerto Biosci, Dermavant, Eli Lilly, Galderma, Hyphens Pharma, Incyte, Janssen, LEO Pharma, La Roche-Posay, Merck, Micreos, Pfizer, Pierre-Fabre, Regeneron/Sanofi-Genzyme, and UCB. April Armstrong has received research grants from AbbVie, BMS, Dermira, Janssen, Kyowa Hakko Kirin, Lilly, Novartis, and UCB; and has received personal fees from AbbVie, BI/Parexel, BMS, Celgene, Dermavant, Genentech, GSK, Janssen, Lilly, Menlo Therapeutics, Merck, Modernizing Medicine, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, Science 37, Sun Pharma, and Valeant. Jan Gutermuth received research grants and/or served as advisor/speaker for Janssen, Sanofi, LEO Pharma, Mylan, Lilly, Abbvie, and Pfizer. Howard Sofen has served as a clinical investigator for AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, Leo Pharma, Novartis, and Sun Pharma. Tiago Torres has received consultancy and/or speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Amgen, Almirall, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius-Kabi, Janssen, LEO Pharma, Eli Lilly, MSD, Mylan, Novartis, Pfizer, Samsung-Bioepis, Sanofi-Genzyme, Sandoz, and UCB. Esther Garcia Gil. is an employee of Almirall. Marta Casillas, Luna Sun, Evangeline Pierce, Hany Elmaraghy, Zach Dawson are employees and shareholders of Eli Lilly and Company. All authors meet the International Committee of Medical Journal Editors criteria for authorship for this article and have given their approval for this version to be published.

Ethical Approval. Informed consent was obtained from all patients before study procedures were initiated. For patients considered to be minors, the written consent of the parent or legal guardian, as well as the assent of the minor, was obtained. Both studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The studies were approved by the appropriate institutional review boards or ethics committee situated across the 100 study sites in the USA, Canada, Europe, and the Asia/Pacific area.

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