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Lebrikizumab Improved Itch Symptoms and Reduced Itch Interference on Sleep over 52 Weeks in Patients with Moderate-to-Severe Atopic Dermatitis in Two Phase 3 Trials

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Keywords
Atopic dermatitis · Itch · Patient-reported outcomes · Sleep loss

Abstract

Introduction: Lebrikizumab significantly reduced itch and itch interference on sleep in patients with moderate-to-severe atopic dermatitis (AD) at week 16 in two phase 3 trials. We investigated itch reduction and the efficacy of improving itch interference on sleep in lebrikizumab-treated patients over 52 weeks. ***Methods:*** At week 16 in ADvocate1 and ADvocate2, patients who met protocol-defined response criteria to lebrikizumab 250 mg every 2 weeks (Q2W) were re-randomized 2:2:1 to lebrikizumab Q2W, lebrikizumab 250 mg every 4 weeks (Q4W), or placebo Q2W to week 52; patients who did not achieve protocol-defined response continued open-label lebrikizumab Q2W. The Pruritus Numeric Rating Scale (NRS) evaluated the worst itch intensity over the previous 24 h in daily electronic diaries; the Sleep-Loss Scale measured the interference of itch on sleep over the last night. For week 16 responders, data after systemic rescue medication or discontinuation due to lack of efficacy were imputed with non-responder imputation; data after topical corticosteroid usage and discontinuation due to other reasons were set as missing; all missing data were imputed with multiple imputation. Descriptive statistics using observed data are reported for week 16 by non-responders. ***Results:*** At week 52 among patients who met week-16 protocol-defined response criteria, 73.4% and 71.8% receiving lebrikizumab Q4W and Q2W, respectively, reported ≥3-point improvement in the Pruritus NRS. Mean percent improvement from baseline to week 52 in the Pruritus NRS was 59.9% and 59.6% with lebrikizumab Q4W and Q2W, respectively. For patients who did not achieve a week-16 protocol-defined response,

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73.3% achieved ≥3-point improvement on the Pruritus NRS at week 52, with mean percent improvement from baseline to week 52 of 59.2%. At week 52 in responders, ≥1-point improvement in the Sleep-Loss Scale was achieved by 77.9% and 78.9% of patients receiving lebrikizumab Q4W and Q2W, respectively, with a mean percent improvement from baseline to week 52 of 64.4% and 65.9%. For week-16 non-responders, 86.1% of patients achieved ≥1-point improvement in the Sleep-Loss Scale at week 52, with a mean percent improvement of 74.9%. ***Conclusion:*** These findings indicate that lebrikizumab is an effective AD treatment to reduce itch and improve sleep loss due to itch over the long term for both patients who did and did not meet protocol-defined response criteria at week 16.

Introduction

Itch is the most common symptom of atopic dermatitis (AD) [1] and has an important role in psychosocial well-being [2] as constant itch can be associated with depression, anxiety, and suicidal ideation [3, 4]. Sleep disturbance, largely resulting from itching, often occurs in AD [2, 5–8] and has a negative impact on health-related quality of life (QoL), work productivity, and mental health [1, 9]. Treatments that lead to rapid and sustained control of itch and sleep disturbance due to itch are important for providing prompt relief to patients with AD.

Lebrikizumab is a novel monoclonal antibody that binds with high affinity and a slow off-rate to interleukin-13, the key cytokine in the skin of patients with AD [10], thereby blocking downstream effects of interleukin-13 with high potency [11–13]. Lebrikizumab monotherapy improved signs and symptoms of AD at week 16 in adolescent and adult patients in two phase 3 randomized, double-blind, placebo-controlled studies (ADvocate1 and ADvocate2), including improvements in itch and sleep loss due to itch [14, 15]. Reports of pooled data from these studies showed that most lebrikizumab-treated patients who met the protocol-defined response criteria at week 16 maintained a ≥4-point improvement in the Pruritus Numeric Rating Scale (NRS) at week 52 [16]. Additionally, the majority of patients who did not achieve protocol-defined response criteria at week 16 reported ≥4-point improvement in the Pruritus NRS at week 52 [17]. The aim of the current analysis was to further investigate the reduction of itch and of the interference of itch on sleep over 52 weeks in ADvocate1 and ADvocate2 in both patient populations.

Methods

The study designs of ADvocate1 (NCT04146363) and ADvocate2 (NCT04178967) have previously been reported [14]. Briefly, they were identically designed, 52-week, randomized, double-blind, placebo-controlled, parallel-group phase 3 trials evaluating the efficacy and safety of lebrikizumab monotherapy in adults and adolescents with moderate-to-severe AD. Both trials comprised a 16-week induction treatment period and a 36-week maintenance treatment period (Fig. 1). During the 16-week induction period, patients were randomized 2:1 to receive lebrikizumab 250 mg every 2 weeks (Q2W) (loading dose of 500 mg given at baseline and week 2) or placebo. This analysis focuses on patients who were randomized to lebrikizumab during the induction period. At week 16, the protocol-defined response was the achievement of the Investigator's Global Assessment (IGA) of 0 or 1 with ≥2-point improvement or ≥75% improvement in the Eczema Area and Severity Index (EASI-75), without the use of rescue medication (including topical). Lebrikizumab was discontinued in patients who required systemic rescue therapy. Patients who responded to lebrikizumab 250 mg Q2W were re-randomized 2:2:1 to receive lebrikizumab 250 mg Q2W, lebrikizumab 250 mg every 4 weeks (Q4W), or placebo Q2W (lebrikizumab withdrawal) for 36 additional weeks (maintenance treatment period) to week 52. Patients who did not meet protocol-defined response criteria for lebrikizumab 250 mg Q2W in the first 16 weeks continued with open-label lebrikizumab 250 mg Q2W in the escape arm (Fig. 1). During the 36-week maintenance treatment period, week 16 responders who did not maintain ≥50% reduction in EASI score (EASI-50) from baseline were also assigned to the escape arm. Once in the escape arm, patients who did not achieve EASI-50 after ≥8 weeks of treatment were discontinued from the study. Intermittent use of topical rescue medications for AD was permitted during the maintenance period as was short-term (≤30 days) systemic treatment for AD symptoms, as assessed on a case-by-case basis. Short-term systemic rescue treatments included systemic corticosteroids and conventional systemic therapies such as cyclosporine; antihistamines were not considered systemic rescue treatments. Patients who required long-term systemic treatment were discontinued from the study. Both studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by individual institutional review boards at each participating study center. All patients provided written informed consent.

ADvocate1 and ADvocate2 included adults and adolescents (aged ≥12 to <18 years; weight ≥40 kg) with

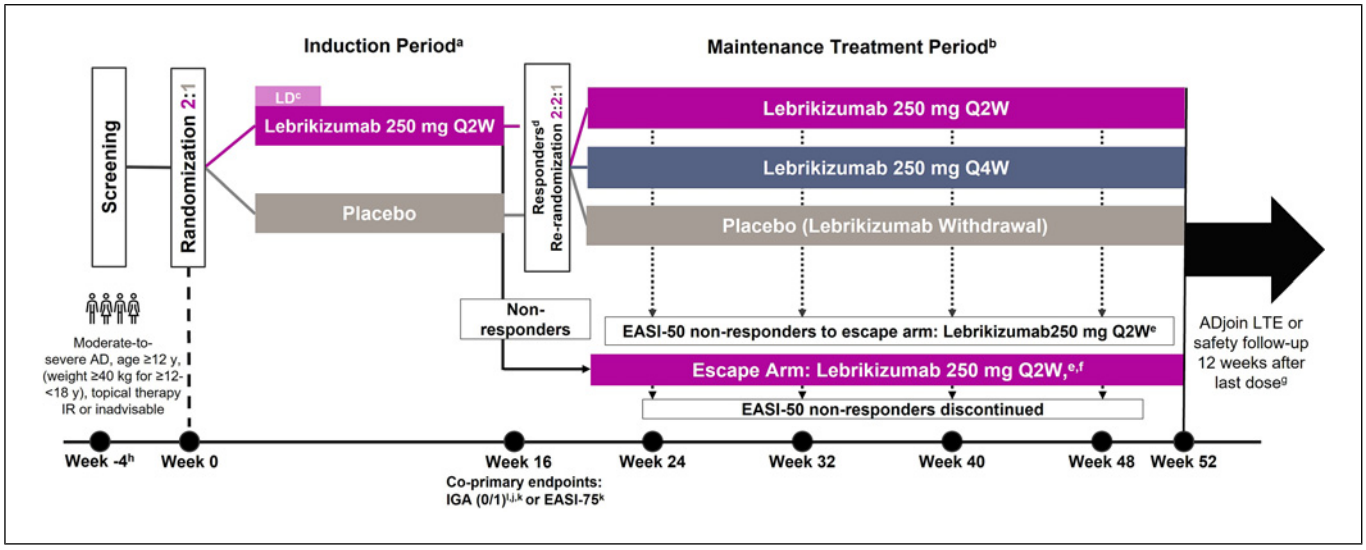

Fig. 1. Study design of ADvocate1 and ADvocate2. [a]Use of topical/systemic treatments for AD was prohibited. Patients who used rescue therapy (including topical) during the induction period were considered non-responders. [b]Use of intermittent topical rescue medications for AD was permitted. Responders who received placebo during induction and were re-randomized to lebrikizumab received an LD of either 500 mg given at week 16 or 500 mg given at weeks 16 and 18. [c]An LD of lebrikizumab 500 mg was given at weeks 0 and 2. [d]Responders were patients who achieved an IGA 0/1 with a ≥2-point improvement from baseline or EASI-75, without use of rescue medication. [e]Maintenance of response was assessed by EASI-50. Patients receiving systemic rescue medication were required to washout for five half-lives before initiating treatment in the escape arm. [f]Patients eligible for the escape arm at week 16 received a blinded LD at weeks 16 and 18, based on their prior treatment assignment. [g]Patients who completed ADvocate1 and ADvocate2 were offered participation in the ADjoin study; otherwise, patients participated in a safety follow-up visit 12 weeks after their last dose. [h]Screening period of ≤30 days. [i]IGA 0/1 with ≥2-point improvement from baseline. [j]Primary endpoint for the US Food and Drug Administration. [k]Co-primary endpoint for the European Medicines Agency. AD, atopic dermatitis; EASI-50, Eczema Area and Severity Index ≥50% reduction; EASI-75, Eczema Area and Severity Index ≥75% reduction; IGA 0/1, Investigator's Global Assessment of 0 or 1 (clear or almost clear); IR, inadequate responder; LD, loading dose; LTE, long-term extension; Q2W, every 2 weeks; Q4W, every 4 weeks.

moderate-to-severe AD, defined as an EASI score ≥16, IGA score ≥3, and percent body surface area involvement ≥10%. There were no inclusion criteria regarding itch severity. Before randomization, patients were required to complete daily electronic diary entries for pruritus and sleep loss due to itch for a minimum of 4 of 7 days; these scores were used to calculate the baseline mean scores. Itch and the extent of itch interference on sleep were recorded in daily electronic diaries during the studies.

Itch was measured using the Pruritus NRS, a daily, patient-reported, single-item, 11-point scale. Patients rated their worst itch intensity over the past 24 h (0 = no itch to 10 = worst itch imaginable). The minimum clinically important difference (MCID) for the Pruritus NRS is 3 points [18]. The extent of itch interference on sleep was assessed using the Sleep-Loss Scale. Patients rated the extent of itch interference on their sleep over the previous night using a 5-point Likert scale (0 = not at all to 4 = unable to sleep). The Sleep-Loss Scale has an MCID of 1 point [19].

Statistical Analysis

This analysis reports pooled data from the 36-week maintenance treatment periods of ADvocate1 and ADvocate2 for two populations: (1) patients who responded to lebrikizumab treatment at week 16, who were re-randomized to maintenance treatment as described above, and (2) patients who did not meet the protocol-defined response criteria at week 16 and entered the escape arm.

In ADvocate1, efficacy and patient-reported outcome analyses used the maintenance primary population, which included all patients who received lebrikizumab Q2W during the 16-week induction period who met the criteria for response to study drug and were subsequently re-randomized to lebrikizumab Q2W, lebrikizumab Q4W, or placebo (lebrikizumab withdrawal) at week 16. To be included in the maintenance primary population, patients must have received ≥1 dose of study treatment in the 36-week maintenance treatment period. Similar populations were used in ADvocate2 analyses; however, the eligibility criteria of having moderate-to-severe AD could not be

Table 1. Baseline demographics and disease characteristics

	Patients who met protocol-defined response criteria at week 16[a] (*N* = 291)			Patients who did not meet protocol-defined response criteria at week 16[a] (*N* = 215)
	lebrikizumab withdrawal (*N* = 60)	lebrikizumab 250 mg Q4W (*N* = 118)	lebrikizumab 250 mg Q2W (*N* = 113)	open-label lebrikizumab 250 mg Q2W (*N* = 215)
Baseline demographics				
Age, years	33.8 (16.6)	35.8 (17.3)	36.1 (17.0)	36.6 (17.6)
Adolescents (≥12 to <18 years),[b] *n* (%)	8 (13.3)	17 (14.4)	13 (11.5)	23 (10.7)
Adults (≥18 years), *n* (%)	52 (86.7)	101 (85.6)	100 (88.5)	192 (89.3)
Female, *n* (%)	36 (60.0)	69 (58.5)	53 (46.9)	88 (40.9)
Geographic region, *n* (%)				
USA	22 (36.7)	51 (43.2)	44 (38.9)	81 (37.7)
Europe	18 (30.0)	38 (32.2)	40 (35.4)	59 (27.4)
Rest of world	20 (33.3)	29 (24.6)	29 (25.7)	75 (34.9)
Race,[c] *n* (%)				
White	33 (55.0)	86 (72.9)	80 (70.8)	124 (57.7)
Asian	15 (25.0)	17 (14.4)	19 (16.8)	58 (27.0)
Black/African American	8 (13.3)	12 (10.2)	9 (8.0)	23 (10.7)
Body mass index, kg/m^2	25.3 (4.8)	26.2 (5.9)	26.3 (6.9)	27.0 (6.2)
Disease duration since AD onset, years	20.4 (14.9)	22.6 (14.8)	21.7 (14.2)	21.9 (15.3)

	Patients who met protocol-defined response criteria at week 16[a] (*N* = 291)						Patients who did not meet protocol-defined response criteria at week 16[a] (*N* = 215)	
	lebrikizumab withdrawal (*N* = 60)		lebrikizumab 250 mg Q4W (*N* = 118)		lebrikizumab 250 mg Q2W (*N* = 113)		open-label lebrikizumab 250 mg Q2W (*N* = 215)	
Disease characteristics	Baseline	Week 16	Baseline	Week 16	Baseline	Week 16	Baseline	Week 16
IGA, *n* (%)								
3 (moderate)	37 (61.7)	1 (1.7)	78 (66.1)	8 (6.8)	70 (61.9)	4 (3.5)	119 (55.3)	99 (46.0)
4 (severe)	23 (38.3)	0	40 (33.9)	0	43 (38.1)	0	96 (44.7)	20 (9.3)
EASI	28.9 (11.2)	2.3 (2.2)	28.8 (12.6)	2.4 (2.5)	29.5 (10.8)	2.5 (2.6)	29.9 (11.4)	15.1 (10.8)
BSA % involvement	42.9 (22.4)	4.9 (5.7)	43.9 (23.2)	5.7 (6.9)	45.3 (20.6)	5.5 (6.6)	47.6 (23.3)	28.7 (21.1)
Pruritus NRS	7.5 (1.8)	3.4 (2.4)	7.0 (2.1)	2.6 (2.1)	7.2 (1.7)	2.8 (2.2)	7.3 (1.9)	4.8 (2.5)
≥3, *n* (%)	59 (100)	31 (53.4)	111 (95.7)	45 (39.5)	110 (99.1)	49 (45.4)	206 (95.8)	155 (73.5)
≥4, *n* (%)	57 (96.6)	24 (41.4)	107 (92.2)	24 (21.1)	108 (97.3)	32 (29.6)	198 (94.3)	129 (61.1)
Sleep-Loss Scale	2.3 (1.1)	0.8 (1.0)	2.1 (1.0)	0.7 (0.8)	2.3 (0.9)	0.8 (0.9)	2.3 (0.9)	1.3 (1.0)
≥1, *n* (%)	50 (86.2)	23 (39.7)	98 (85.2)	44 (38.9)	104 (93.7)	46 (42.6)	196 (91.2)	147 (69.7)
≥2, *n* (%)	37 (63.8)	10 (17.2)	64 (55.7)	12 (10.6)	79 (71.2)	17 (15.7)	148 (70.5)	68 (32.2)

Data are presented as mean (standard deviation) unless otherwise stated. AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, Numeric Rating Scale; Q2W, every 2 weeks; Q4W, every 4 weeks. [a]Protocol-defined response was the achievement of an IGA score of 0 or 1 with ≥2-point improvement or ≥75% improvement in the EASI score, without use of rescue medication (including topical). [b]Patients weighed ≥40 kg. [c]Additional races reported were American Indian or Alaska Native, Native Hawaiian, or other Pacific Islander, multiple, and other.

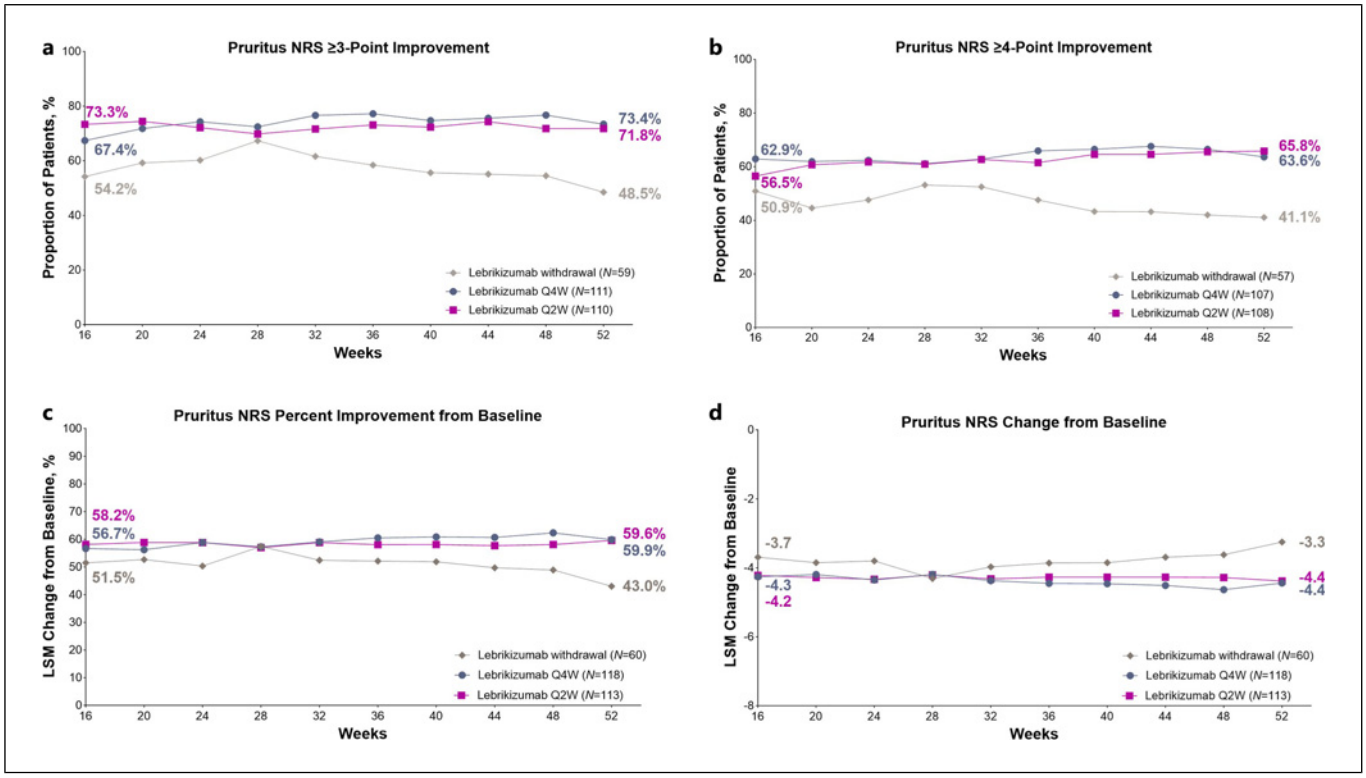

Fig. 2. Improvements in the Pruritus NRS score from week 16 to week 52 in patients who achieved a protocol-defined response[a] at week 16: ≥3-point improvement in patients with a baseline Pruritus NRS score ≥3 (**a**); ≥4-point improvement in patients with a baseline Pruritus NRS score ≥4 (**b**); percent improvement from baseline (**c**); and change from baseline (**d**). [a]Protocol-defined response was the achievement of an Investigator's Global Assessment score of 0 or 1 with a ≥2-point improvement or ≥75% improvement in the Eczema Area and Severity Index score, without use of rescue medication (including topical). LSM, least-squares mean; NRS, Numeric Rating Scale; Q2W, every 2 weeks; Q4W, every 4 weeks.

confirmed for 18 patients from a single study site. Of these 18 patients, 14 entered the maintenance period as part of the primary population and were excluded from maintenance analyses. Thus, efficacy and patient-reported outcome analyses in ADvocate2 were performed on the modified maintenance primary population.

For analysis of the Pruritus NRS and Sleep-Loss Scale, the baseline mean was the prorated average of the daily scores in the week before the first injection and was considered missing if a patient had ≤3 responses. During the maintenance treatment period, if the patient had ≥1 daily score, the weekly mean was the prorated average of daily scores within the given week. For Pruritus NRS, we report the proportion of patients who achieved ≥3-point and ≥4-point improvement as well as percent change from baseline and least square mean change from baseline. For the Sleep-Loss Scale, we report the proportion of patients who achieved ≥1-point and ≥2-point improvement and percent change from baseline and least square mean change from baseline.

For the 36-week maintenance period of these studies among patients who met the protocol-defined response criteria to lebrikizumab at week 16, data after systemic rescue medication or discontinuation due to lack of efficacy were imputed with non-responder imputation; data after topical corticosteroid usage or discontinuation due to other reasons were set as missing. All missing data were imputed with multiple imputation. Categorical endpoints were analyzed with a Cochran-Mantel-Haenszel test adjusted by region and study. Continuous endpoints were analyzed with the use of analysis of covariance, with treatment group, baseline value, region, and study as fixed factors. For patients who did not meet protocol-defined response criteria at week 16, descriptive statistics using observed values were reported at each timepoint with no imputation for missing values. A summary of the baseline demographics and disease characteristics are presented for week 16 per-protocol responders and non-responders.

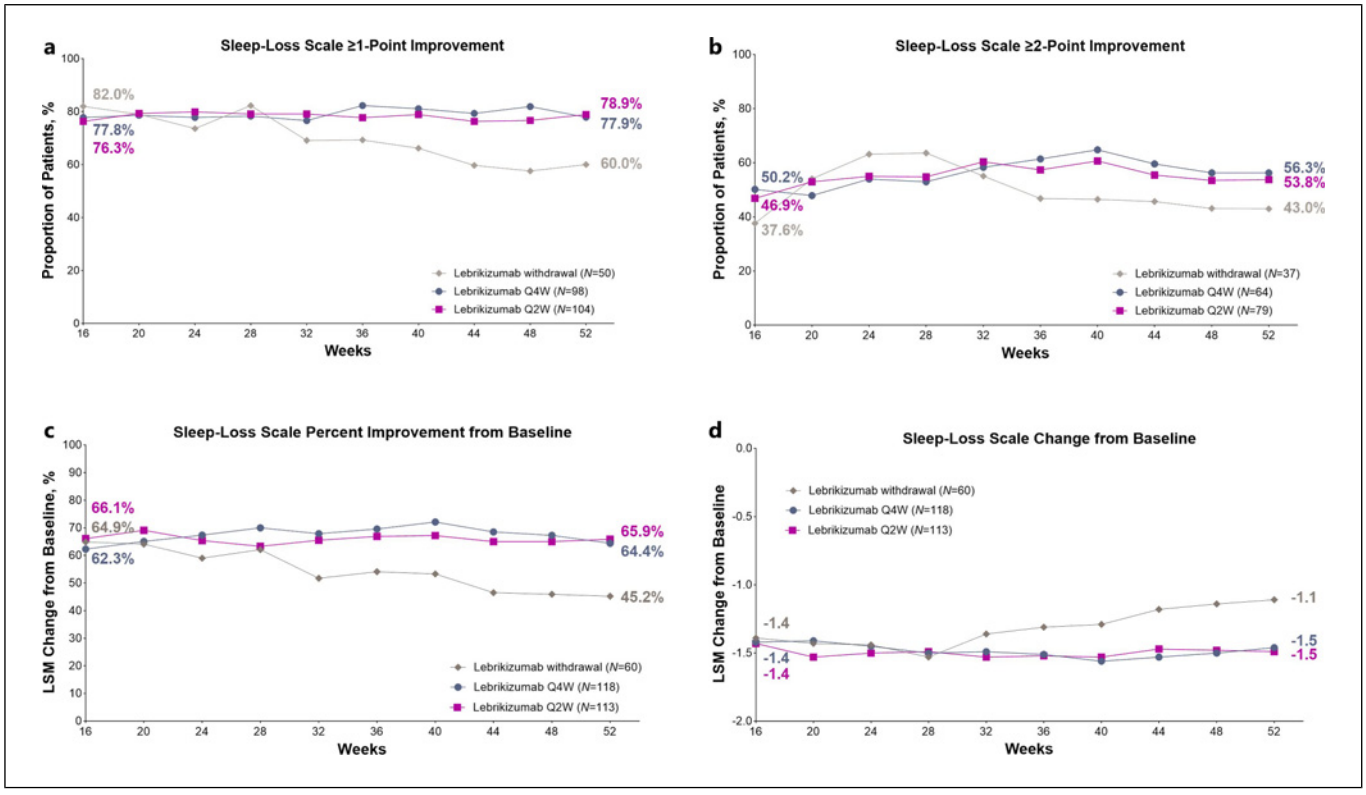

Fig. 3. Improvements in the Sleep-Loss Scale score from week 16 to week 52 in patients who achieved a protocol-defined response[a] at week 16: ≥1-point improvement in patients with a baseline Sleep-Loss Scale score ≥1 (**a**); ≥2-point improvement in patients with a baseline Sleep-Loss Scale score ≥2 (**b**); percent improvement from baseline (**c**); and change from baseline (**d**). [a]Protocol-defined response was the achievement of an Investigator's Global Assessment score of 0 or 1 with a ≥2-point improvement or ≥75% improvement in the Eczema Area and Severity Index score, without use of rescue medication (including topical). LSM, least-squares mean; Q2W, every 2 weeks; Q4W, every 4 weeks.

Results

In pooled results of ADvocate1 and ADvocate2, 564 patients were randomly assigned to lebrikizumab Q2W at week 0, and 92.6% (n = 522) of these patients completed the week 16 visit. Among patients treated with lebrikizumab, 291 (51.6%) achieved a protocol-defined response and were re-randomized at week 16 to receive maintenance-blinded treatment. Of these patients, 113 continued to receive lebrikizumab Q2W, 118 were assigned to lebrikizumab Q4W, and 60 were withdrawn from lebrikizumab and given a placebo. Among patients treated with lebrikizumab, 41.0% (n = 231) did not achieve the protocol-defined response criteria at week 16 and were assigned to the escape arm to receive open-label lebrikizumab Q2W. Sixteen of these patients were responders and were incorrectly assigned to the escape arm. These patients are not included in this analysis, resulting in a corrected proportion of 38.1% (n = 215) of patients who did not achieve the protocol-defined response criteria at week 16 and continued open-label lebrikizumab Q2W from weeks 16 to 52. Baseline demographics and disease characteristics were generally comparable, with a few exceptions, between patients who met the protocol-defined response criteria at week 16 and those who did not (Table 1). No patients exceeded 30 days of short-term systemic rescue treatment.

Patients Who Achieved Protocol-Defined Response Criteria

During the maintenance treatment period, among responders who continued treatment with lebrikizumab through 52 weeks, the proportion of patients with ≥3-point improvement (MCID) in the Pruritus NRS score was maintained from 67.4% at week 16 to 73.4% at week 52 with lebrikizumab Q4W and from 73.3% to 71.8%, respectively, with lebrikizumab Q2W (Fig. 2a). Similar trends were observed for ≥4-point improvement in the

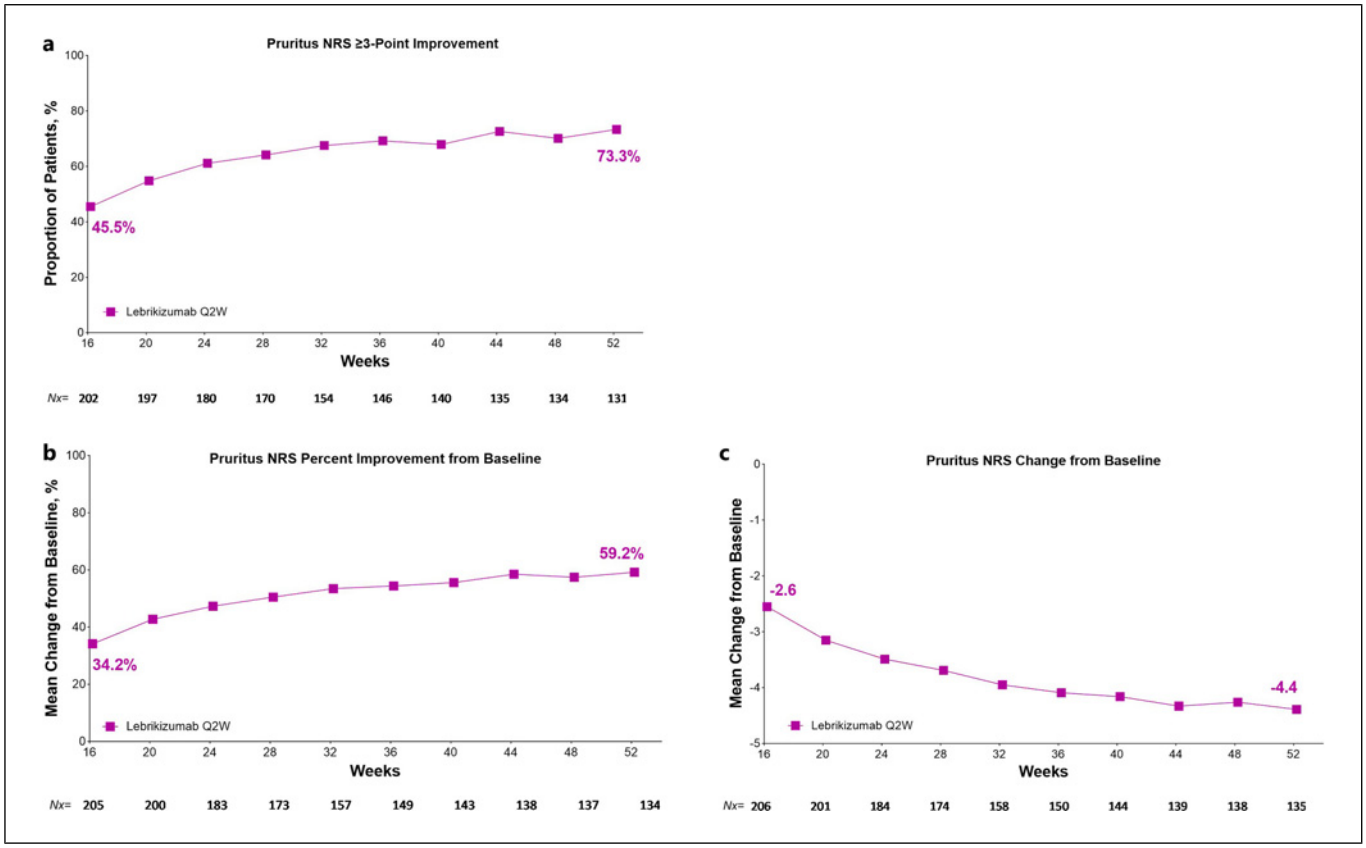

Fig. 4. Improvements in the Pruritus NRS score from week 16 to week 52 in patients who did not achieve a protocol-defined response[a] at week 16: ≥3-point improvement in patients with a baseline Pruritus NRS score ≥3 (**a**); percent improvement from baseline (**b**); and change from baseline (**c**). [a]Protocol-defined response was the achievement of an Investigator's Global Assessment score of 0 or 1 with a ≥2-point improvement or ≥75% improvement in the Eczema Area and Severity Index score, without use of rescue medication (including topical). LSM, least-squares mean; NRS, Numeric Rating Scale; Q2W, every 2 weeks.

Pruritus NRS score, in which improvement was maintained in 62.9% of patients at week 16 and 63.6% at week 52 with lebrikizumab Q4W and in 56.5% at week 16 and 65.8% at week 52 with lebrikizumab Q2W (Fig. 2b). Mean percent improvement from baseline for Pruritus NRS was maintained from 56.7% at week 16 to 59.9% at week 52 with lebrikizumab Q4W and from 58.2% to 59.6%, respectively, with lebrikizumab Q2W (Fig. 2c) as was mean change from baseline (Fig. 2d). Sustained improvements in itch were also observed among protocol-defined responders in the withdrawal arm (Fig. 2a–d), indicating durability of response to lebrikizumab.

For the Sleep-Loss Scale, the proportion of patients with ≥1-point improvement (MCID) was maintained from week 16 to week 52 for both lebrikizumab Q4W (77.8% to 77.9%) and lebrikizumab Q2W (76.3% to 78.9%) (Fig. 3a). Similarly, the proportion of patients with ≥2-point improvement in the Sleep-Loss Scale was maintained from week 16 to week 52 with lebrikizumab Q4W (50.2% to 56.3%) and lebrikizumab Q2W (46.9% to 53.8%) (Fig. 3b). Mean percent improvement from baseline for Sleep-Loss Scale was maintained from 62.3% at week 16 to 64.4% at week 52 with lebrikizumab Q4W and from 66.1% to 65.9%, respectively, with lebrikizumab Q2W (Fig. 3c), as was mean change from baseline (Fig. 3d). Sustained improvements in the Sleep-Loss Scale were also observed among protocol-defined responders in the withdrawal arm (Fig. 3a–d).

Patients Who Did Not Achieve Protocol-Defined Response Criteria

In the escape arm, the proportion of patients with ≥3-point improvement (MCID) in the Pruritus NRS increased from 45.5% at week 16 to 73.3% at week 52 (Fig. 4a). Mean percent change from baseline in the Pruritus NRS improved from 34.2% to 59.2% (Fig. 4b), and the Pruritus NRS score decreased by a mean of 1.8 points from week 16

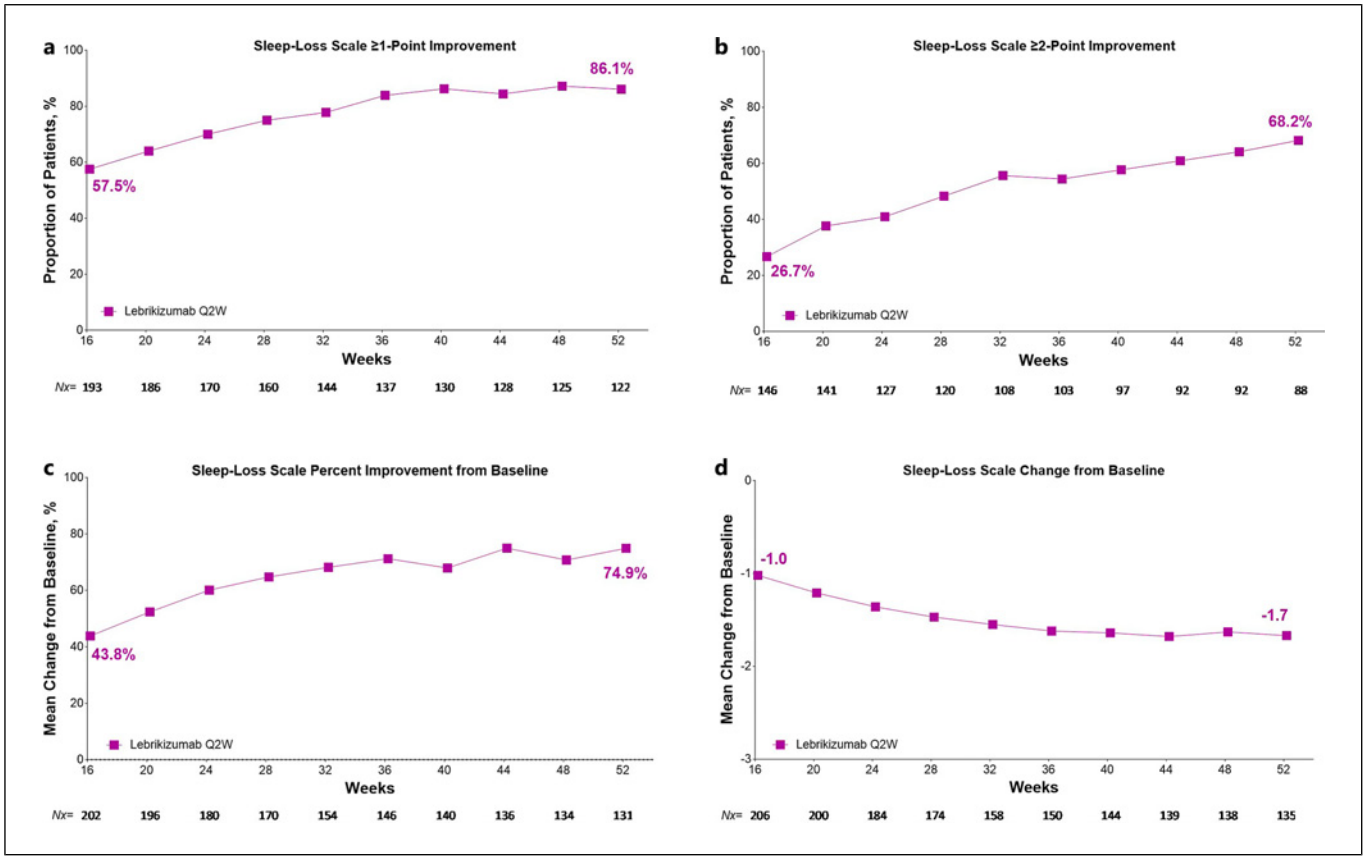

Fig. 5. Improvements in the Sleep-Loss Scale score from week 16 to week 52 in patients who did not achieve a protocol-defined response[a] at week 16: ≥1-point improvement in patients with a baseline Sleep-Loss Scale score ≥1 (**a**); ≥2-point improvement in patients with a baseline Sleep-Loss Scale score ≥2 (**b**); percent improvement from baseline (**c**); and change from baseline (**d**). [a]Protocol-defined response was the achievement of an Investigator's Global Assessment score of 0 or 1 with a ≥2-point improvement or ≥75% improvement in the Eczema Area and Severity Index score, without use of rescue medication (including topical). LSM, least-squares mean; Q2W, every 2 week.

to week 52 (Fig. 4c). For sleep loss due to itch, the proportion of patients with ≥1-point improvement (MCID) in the Sleep-Loss Scale score increased from 57.5% at week 16 to 86.1% at week 52 (Fig. 5a), and the proportion of patients with ≥2-point improvement increased from 26.7% at week 16 to 68.2% at week 52 (Fig. 5b). Mean percent change from baseline in the Sleep-Loss Scale score improved from 43.8% at week 16 to 74.9% at week 52, and the Sleep-Loss Scale mean score decreased by 0.7 points from week 16 to week 52.

Discussion

Itch and itch interference on sleep are significant components of the burden of disease for patients with moderate-to-severe AD, which cause a significant reduction in QoL. Previous analysis showed that both itch and itch interference on sleep were improved in adults and adolescents with moderate-to-severe AD treated with lebrikizumab monotherapy for up to 16 weeks in both the ADvocate1 and ADvocate2 clinical trials [14]. In the current analysis, patients who achieved protocol-defined response criteria at week 16 and were re-randomized to lebrikizumab showed sustained improvements in Pruritus NRS and Sleep-Loss Scale scores to week 52. Additionally, despite not achieving the protocol-defined response criteria at week 16, patients in the escape arm who continued lebrikizumab treatment achieved clinically relevant improvements in itch and itch interference on sleep with 73.3% and 86.1% achieving the MCIDs for the Pruritus NRS (3-point improvement) and Sleep-Loss Scale (1-point improvement), respectively, at week 52. Similar findings were reported showing

improvement in the frequency of patients achieving IGA 0/1, EASI 75, and EASI 90 who were treated with lebrikizumab after not meeting protocol-defined response at week 16 [17]. Even patients who were protocol-defined responders and re-randomized to placebo (lebrikizumab withdrawal) showed maintenance of response without receiving additional lebrikizumab, which warrants further testing of less frequent dosing [16].

A 3-point improvement in the Pruritus NRS represents the MCID for itch [18], which is expected to lead to improvements in anxiety and depression and thus overall QoL in patients with moderate-to-severe AD. The current findings add support to previous studies of lebrikizumab monotherapy that have shown treatment benefit compared with placebo for patients with AD [14, 15] and suggest that this treatment benefit also applies to patients who do not meet protocol-defined response at week 16.

Itch is a key factor in AD that leads to sleep loss [20], which contributes to high disease burden and lower QoL [21]; this can affect normal daily activities and work productivity with a resultant high economic burden as well [8]. More than half of the patients treated with lebrikizumab in this analysis achieved the conservative ≥2-point improvement in the Sleep-Loss Scale and more than three-quarters achieved the clinically significant ≥1-point improvement at 52 weeks. Limitations of this analysis include the post hoc nature and the open-label treatment with lebrikizumab in the escape arm.

Conclusions

During the maintenance treatment period, lebrikizumab treatment demonstrated sustained improvements in the Pruritus NRS score and a durable reduction in itch interference on sleep through 52 weeks in patients with moderate-to-severe AD who were responders to lebrikizumab at the end of the 16-week induction period. Despite not achieving protocol-defined response criteria at week 16, most patients in the escape arm who continued with lebrikizumab had a clinically relevant improvement in itch and improvement in itch interference on sleep at week 52 as did patients in the lebrikizumab withdrawal arm.

Key Message

Lebrikizumab reduces itch and itch interference on sleep through 52 weeks for patients with moderate-to-severe AD.

Acknowledgments

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Statement of Ethics

This study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Both clinical trial protocols were approved by the Western Institutional Review Board (WIRB) (now WIRB-Copernicus Group [WCG]) on 19 September 2019 (ADvocate 1: IRB #AD04 20192332; IRB #ADvocate 2: AD05 20192344). Additionally, each participating center's Institutional Review Board or Ethics Committee approved the study. The list of investigator sites can be found in the primary results publication [14]; the list of individual ethics review boards can be found in the online supplementary materials (for all online suppl. material, see https://doi.org/10.1159/000547142). All patients provided written informed consent. No additional ethical approval was required to conduct the current post hoc analysis.

Conflict of Interest Statement

G.Y. has conducted clinical trials or received honoraria for serving as a member of the Scientific Advisory Board of Eli Lilly, TREVI, Novartis, Regeneron, Sanofi, Galderma, Pfizer, Bellus, Kiniksa, Escient, Arcutis, and LEO and received research funds from Pfizer, LEO, Novartis, and Eli Lilly. P.A.L. has received grants as an investigator, honoraria for lecturing, and/or consulting fees from AbbVie, AOBiome, Arbonne, Burt's Bees, Dermavant, Dermira, Eli Lilly and Company, Exeltis, Franklin Bioscience/Altus Labs, Incyte Corporation, IntraDerm, Johnson & Johnson, Kiniksa, La Roche-Posay/L'Oréal, LEO Pharma, Menlo Therapeutics, the National Eczema Association, Pfizer, Pierre Fabre, Realm Therapeutics, Regeneron/Sanofi Genzyme, Theraplex, TopMD, UCB Pharma, Unilever, and Verrica Pharmaceuticals. D.R. has as received honoraria as a consultant for AbbVie, Abcuro, AltruBio, Arena, Boehringer-Ingelheim, Bristol Meyers Squibb, Celgene, Concert, CSL Behring, Dermavant, Dermira, Incyte, Janssen, Kyowa Kirin, Lilly, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharmaceuticals, UCB, and VielaBio; has received research support from AbbVie, Amgen, Bristol Meyers Squibb, Celgene, Dermira, Galderma, Incyte, Janssen, Lilly, Merck, Novartis, Pfizer, and Regeneron Pharmaceuticals Inc.; and has served as a paid speaker for AbbVie, Amgen, Bristol Meyers Squibb, Celgene, Incyte, Janssen, Lilly, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi. F.J.L. has received consulting fees and/or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events; participated on advisory boards; and/or served as an investigator for AbbVie, Almirall, Amgen, Celgene, DS Biopharma, Eli Lilly and Company, Galderma, Incyte Corporation, Janssen-Cilag, Kiniksa Pharmaceuticals, LEO Pharma, Menlo

Therapeutics, Novartis, Pelpharma Handels GmbH, Pfizer, Sanofi, Trevi Therapeutics, and Vifor Pharma (now CSL Vifor). E.S.-B. has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from AbbVie, Novartis, Almirall, Leo, Sanofi, Pfizer, and Eli Lilly and Company. J.-M.C. is an investigator and/or has received consulting fees and/or speaker fees and/or has participated in Steering Committee from Eli Lilly and Company, AbbVie, Novartis, Galderma, BMS, Regeron/Sanofi Genzyme, Janssen, Almirall, Boehringer Ingelheim, LEO Pharma, and Amgen. L.B. is an employee of Alimirall S.A. H.C., M.C., E.P., and H.E. are employees and stockholders of Eli Lilly and Company. J.Z. has no conflicts to report. S.S. has been an Investigator for Dermasence, Galderma, Kiniksa Pharmaceuticals, Menlo Therapeutics, Trevi Therapeutics, Novartis, Sanofi, and Vanda Pharmaceuticals Inc. and has acted as a consultant, speaker, and/or served on advisory boards for AbbVie, Almirall, Beiersdorf, Bellus Health, Benevolent, Bionorica, Cara, Clexio, Escient, Galderma, Grünenthal, Kiniksa, Leo, Lilly, Menlo, Pfizer, Sanofi, Trevi, P.G. Unna Academy, and Vifor.

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Author Contributions

P.A.L., D.R., F.J.L., E.S.-B., J.-M.C., L.B., H.C., M.C., E.P., H.E., and S.S. participated in the interpretation of trial results and the critical revision and approval of the final version of the manuscript. G.Y. participated in the conception and design of the study, interpretation of trial results, and the critical revision and approval of the final version of the manuscript. J.Z. conducted the statistical analysis and participated in the critical revision and approval of the final version of the manuscript.

Data Availability Statement

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

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