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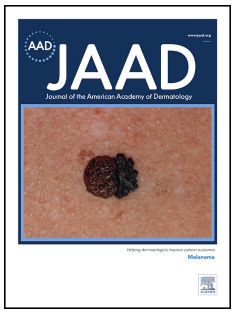

The efficacy of longer-term lebrikizumab treatment in patients with moderate-to-severe atopic dermatitis who did not meet protocol-defined response criteria at week 16 in two randomized controlled clinical trials

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ABSTRACT

Background: Lebrikizumab demonstrated statistically significant improvements in patients with moderate-to-severe atopic dermatitis at week 16 with a durable response up to week 52.

Objective: To investigate the efficacy of lebrikizumab-treated patients at 52 weeks who did not achieve the ADvocate1 and ADvocate2 protocol-defined response criteria (≥75% improvement in the Eczema Area and Severity Index [EASI 75] or Investigator Global Assessment [IGA] 0/1 with ≥2-point improvement without rescue medication) after 16 weeks.

Methods: This analysis includes observed data for patients who received lebrikizumab every 2 weeks during the induction period, did not achieve the protocol-defined response, and subsequently received open-label lebrikizumab treatment.

Results: At week 16, 38.1% of lebrikizumab-treated patients entered the escape arm due to not achieving the response criteria. However, most of these patients had achieved ≥50% improvement in EASI (58.1%) by week 16. At week 52, 36.1% achieved IGA 0/1 with ≥2-point improvement, 75.5% achieved EASI 75, 44.2% achieved ≥90% improvement in EASI, and 66.4% reported ≥4-point Pruritus Numeric Rating Scale improvement.

Limitations: This analysis assesses patients receiving open-label treatment with concomitant topical therapy allowed.

Conclusion: Lebrikizumab-treated patients not achieving the protocol-defined response at week 16 can benefit from the continuation of longer-term therapy.

CAPSULE SUMMARY

- In clinical trials, not all patients with moderate-to-severe atopic dermatitis achieve a protocol-defined response to treatment with biologics within the first 16 weeks of therapy.
- Healthcare providers may consider continuing treatment with lebrikizumab past 16 weeks even if patients do not meet initial, restrictive response thresholds defined in clinical trials.

KEYWORDS: atopic dermatitis (atopic eczema), clinical trials, immunology, lebrikizumab, pruritus, quality of life, therapeutics

INTRODUCTION

Biologic therapies for moderate-to-severe atopic dermatitis (AD) are often recommended for patients who fail topical treatments such as topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), topical phosphodiesterase 4 inhibitors, and topical Janus kinase inhibitors or who cannot sustain response or continue being treated with systemic immunosuppressive therapies such as cyclosporine (approved in the European Union for severe AD)[1, 2]. Though many patients benefit from treatment with biologics, some patients in clinical trials do not meet the protocol-defined response criteria (typically defined as ≥75% improvement in the Eczema Area and Severity Index from baseline [EASI 75] and/or an Investigator's Global Assessment of 0 or 1 [IGA 0/1]) within the first 16 weeks of monotherapy treatment[3-5]. In clinical practice, providers may resort to combination therapy to increase the degree of response in these patients[2, 6]. The use of multiple therapies, however, is associated with non-adherence, potential safety concerns, inconvenience, and financial burden[7-9]. Due to these concerns and the differences between the definition of response in clinical trials and clinical practice, continuation of monotherapy biologic treatment beyond week 16 may be considered. This becomes especially relevant if clinical trials define per protocol non-response as not meeting a specific endpoint despite a patient achieving other potentially clinically meaningful responses (e.g., EASI 50).

Lebrikizumab is a monoclonal antibody that binds with high affinity and slow off-rate to interleukin (IL)-13, thereby blocking the downstream effects of IL-13 with high potency[10]. ADvocate1 and ADvocate2 are identically designed, phase 3, randomized, double-blinded, placebo-controlled, monotherapy studies that evaluated the efficacy and safety of lebrikizumab in patients with moderate-to-severe AD. In ADvocate1 and ADvocate2, the proportions of patients treated with monotherapy lebrikizumab every 2 weeks (Q2W) who achieved the primary endpoint (IGA 0/1, with ≥2-point improvement and without rescue medication use) during the first 16 weeks were 43.1% ($p<0.001$) and 33.2% ($p<0.001$), respectively, with 58.8% ($p<0.001$)

and 52.1% ($p<0.001$) of patients achieving EASI 75[5]. Most adverse events were mild or moderate in severity and did not lead to trial discontinuation[5]. Patients who met the protocol-defined response criteria at week 16 and entered the maintenance period showed a similarly durable response whether they were treated with lebrikizumab Q2W or lebrikizumab every 4 weeks (Q4W) for an additional 36 weeks (52 total weeks of treatment)[11]. Lebrikizumab-treated patients who did not meet the protocol-defined response criteria at week 16 entered an escape arm where they received open-label lebrikizumab Q2W for an additional 36 weeks where topical therapies (e.g., TCS) were optional.

We report the results at week 52 for patients who continued treatment with lebrikizumab Q2W after not achieving the protocol-defined response criteria during the first 16 weeks of treatment.

METHODS

Trial design

The details of ADvocate1 (NCT04146363) and ADvocate2 (NCT04178967) were previously reported[5, 11] (**Mendeley supplemental figure I**). ADvocate1 and ADvocate2 were initiated on 24 September 2019 and 29 October 2019, respectively (**Mendeley supplemental table I**).

Both trials were approved by the applicable ethics review boards at each of the 171 sites in North America, Europe, and the Asia-Pacific region, and were performed in accordance with the Declaration of Helsinki, Council for International Organizations of Medical Sciences, and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent to participate in the trials.

Trial population

Eligible patients included adults and adolescents (≥12 to <18 years of age and weighing ≥40 kg) with chronic AD that was present for ≥1 year before the screening visit. Baseline requirements included: EASI ≥16, IGA ≥3, ≥10% body surface area (BSA) of AD involvement, and a history of inadequate response to topical medications or determination that topical treatments were otherwise medically inadvisable. Patients were not permitted to have received treatment of immunosuppressive or immunomodulating drugs within 4 weeks prior to the baseline visit. Patients with a history of prior treatment with dupilumab or tralokinumab were excluded. Treatment with other biologics was restricted prior to the baseline visit. These exclusions and restrictions were included to reduce the number of confounding factors while evaluating the monotherapy efficacy of lebrikizumab.

Treatment protocol

Eligible patients were randomized 2:1 to receive either 250 mg of subcutaneous lebrikizumab (with two, 500 mg loading doses at weeks 0 and 2) or placebo Q2W. At week 16, patients who did not meet the protocol-defined response criteria (EASI 75 or IGA 0/1 with ≥2-point improvement) or used any rescue medication (including topical therapy) were assigned to an escape arm to receive lebrikizumab 250 mg Q2W as open-label treatment through week 52 with optional topical therapy allowed for rescue. Patients who received systemic rescue medication during the induction period were required to washout for five half-lives before initiating treatment in the escape arm. Patients who received lebrikizumab during the induction period were administered blinded loading doses of placebo to maintain the treatment blind from the induction period. Patients in the escape arm who did not achieve or maintain ≥50% improvement in EASI from baseline (EASI 50) after 8 weeks of treatment were terminated from the trial.

While in the escape arm, intermittent use of topical rescue medications for symptoms of AD was permitted. Patients requiring short-term systemic rescue medication for symptoms of AD were assessed on a case-by-case basis and discussed with the medical monitor prior to initiating treatment. Patients requiring long-term systemic treatment for symptoms of AD were discontinued from the trial. Use of rescue medication was assessed at each study visit.

Outcome measures

This article reports the following endpoints for patients treated with lebrikizumab during the induction period who were assigned to the escape arm at week 16: IGA 0/1 with ≥2-point improvement, EASI 75, ≥90% improvement in EASI from baseline (EASI 90), EASI % improvement from baseline, Pruritus Numeric Rating Scale (NRS) ≥4-point improvement, Sleep-Loss Scale ≥2-point improvement, and Dermatology Life Quality Index (DLQI) ≥4-point improvement (**Mendeley supplemental table II**). Summary safety data from week 16 to week 52 are also reported for this subset of patients.

Statistical analysis

This analysis reports the ADvocate1 and ADvocate2 52-week pooled results of lebrikizumab-treated patients who were part of the escape population. This population includes lebrikizumab-treated patients who did not meet the protocol-defined response criteria at week 16, were assigned to the escape arm, and received ≥1 dose of lebrikizumab during the escape arm. Patients treated with either topical or systemic rescue medication during the induction period were assigned to the escape arm and are included in this analysis.

The primary analysis for efficacy outcomes reported in this manuscript uses as observed values at each time point with no imputation for missing values (**Figure 1**). An additional efficacy analysis was performed where data after treatment discontinuation due to lack of efficacy were imputed with nonresponder imputation (NRI) and data after treatment discontinuation due to other reasons and other missing data were imputed with multiple imputation (MI; **Mendeley supplemental figure III**). Differences in baseline demographics and disease characteristics between Week 16 per protocol responders and Week 16 per protocol nonresponders were not tested for statistical significance.

RESULTS

Patient disposition

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. Of 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 continue receiving lebrikizumab Q2W (**Mendeley supplemental figure II**). Sixteen of these patients were incorrectly assigned to the escape arm and 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. At week 52, 68.4% (n=147) of these patients completed the trial, 20.5% (n=44) discontinued due to lack of efficacy, and 4.7% (n=10) withdrew from the study.

Baseline demographics and disease characteristics

The baseline demographics and disease characteristics for this population were generally comparable to the subset of lebrikizumab-treated patients who met the protocol-defined response criteria at week 16 with a few exceptions (**Table I**)[11]. A numerically higher proportion of patients were male, Asian, from the rest of the world (i.e., not from the United States or Europe), and/or presented with a greater baseline IGA severity compared with per protocol responders at week 16.

The mean (standard deviation [SD]) baseline EASI score in this population was 29.9 (11.4). The proportions of patients with moderate versus severe disease were 55.3% and 44.7%, respectively, as measured by IGA. The mean (SD) BSA affected was 47.6% (23.3). Despite not achieving the protocol-defined response criteria at week 16, 58.1% (n=125) of patients entered the escape arm with at least an EASI 50.

Efficacy and Safety

At week 52, 36.1% (53/147) of lebrikizumab-treated patients who did not achieve the protocol-defined response criteria at week 16 achieved IGA 0/1 with ≥2-point improvement. In the same population, 75.5% (111/147) achieved EASI 75 and 44.2% (65/147) achieved EASI 90. The mean EASI percent change from baseline was -83.0%. Most patients reported a ≥4-point improvement on the Pruritus NRS (66.4%, 83/125) and ≥2-point improvement on the Sleep-Loss Scale (68.2%, 60/88) at week 52. At total of 89.1% (98/110) of patients also reported ≥4-point improvement in the DLQI.

Figure I shows the time course of response for IGA 0/1, EASI 75, EASI 90, and Pruritus NRS using as observed analysis. Over the course of maintenance treatment, a rapid increase in the proportion of patients achieving EASI 75 occurred between week 16 (10.2%, 22/215) and week 24 (57.6%, 118/205), and this response continued to increase through week 52 (75.5%, 111/147). Additional time course analyses were also performed using a combined NRI/MI methodology (**Mendeley supplemental figure III**). Using the combined NRI/MI methodology, the proportions of patients to achieve IGA 0/1 with ≥2-point improvement, EASI 75, and EASI 90 at week 52 were 28.4%, 57.7%, and 33.6%, respectively. Approximately 50% of patients reported ≥4-point improvement in Pruritus NRS at week 52.

Most patients who showed a partial response at week 16 (defined as ≥EASI 50 and <EASI 75) achieved EASI 75 at week 24 (65.0%, 65/100) and week 52 (80.5%, 62/77). Many patients who had not achieved EASI 50 by week 16 did achieve EASI 75 at week 24 (38.6%, 32/83) and week 52 (61.8%, 34/55) when continuing treatment with lebrikizumab (**Mendeley supplemental table III**).

In the escape arm population, 52.6% of patients reported a treatment-emergent adverse event (TEAE) with most events being mild (47.8%) or moderate (41.6%) in severity. A serious adverse event was reported in 4.2% of patients, and 2.3% of patients discontinued study treatment due to a TEAE (**Mendeley supplemental table IV**).

306

307 **Rescue therapy**

308

309 While in the escape arm, 29.3% (n=63) of lebrikizumab-treated patients used ≥1 rescue
310 medication **(Mendeley supplemental table V)**. The predominance of rescue therapy consisted
311 of topical therapy (28.8%; n=62) with a low proportion of patients requiring systemic rescue
312 therapy (2.8%; n=6). The proportions of patients using low-to-moderate potency TCS, high
313 potency TCS, and TCI were 16.7% (n=36), 15.8% (n=34), and 5.6% (n=12), respectively. Of the
314 6 patients reporting systemic rescue therapy use, 1 patient used cyclosporine and 5 patients
315 used systemic corticosteroids including prednisolone, prednisone, and triamcinolone.
316 Of the patients in the escape arm who achieved EASI 75 at week 52 (N=111), 27.9%
317 (n=31) used ≥1 rescue medication. No patient used systemic rescue therapy.

DISCUSSION

In the ADvocate1 and ADvocate2 trials, most patients not achieving the protocol-defined response criteria at week 16 had already achieved clinically meaningful efficacy (i.e., EASI 50) by that time point. In the patients who continued lebrikizumab Q2W, many achieved EASI 75 well before week 52, with the largest increase in EASI 75 responses occurring between week 16 and week 24. In addition to physician-assessed skin clearance, patient-reported outcomes such as itch and itch interference on sleep also showed improvement up to week 52. These results are noteworthy in a chronic, heterogeneous, and unstable disease such as AD where long-term disease control is as equally important as short-term efficacy. The level of stringent response defined in clinical trials differs from the definition of response in clinical practice and, therefore, these data may assist clinicians in therapeutic decision-making for patients who show improvement with lebrikizumab after 16 weeks of induction treatment but have not yet reached an optimal response. In addition, due to the established heterogeneity of AD, some patients may benefit from a prolonged induction period with lebrikizumab Q2W.

A numerically, but not statistically higher proportion of patients who did not meet response criteria at week 16 (i.e., the population for this analysis) were male, Asian, from the rest of the world (i.e., not from the United States or Europe), and/or had a higher baseline IGA compared to patients who achieved response criteria at week 16. Similar differences in baseline demographics and disease characteristics were seen in an analysis of patients who did not respond optimally during initial dupilumab treatment[12], indicating that these differences are not unique to lebrikizumab. The proportions of patients who were initial per protocol nonresponders and subsequently achieved IGA 0/1 or EASI 75 after 52 weeks of treatment with lebrikizumab appear comparable to data reported for dupilumab[12] and were greater than results reported for tralokinumab[13]. Certain patients may require more time to respond to biologic treatment due to differing endotypes across age groups, races, ethnicities, immunoglobulin E levels, or filaggrin

mutation status[14] along with the severity of systemic inflammation[15]. Understanding baseline demographics and disease characteristics may help to individualize the approach to treatment with lebrikizumab and provide more precise counseling as to when patients may expect to see treatment results.

Although the proportion of patients using rescue medication in this population was higher when compared to per protocol lebrikizumab responders at week 16, the use of rescue medication was still relatively low (<30%). This suggests that rescue medication alone was not the primary driver of the efficacy response in lebrikizumab-treated patients. The predominance of treatment discontinuations in the escape arm were due to lack of efficacy (**Mendeley supplemental figure II**). This was largely dictated by the protocol requirement to terminate patients from the trial who did not achieve or maintain EASI 50 after 8 weeks of treatment following assignment to the escape arm.

This analysis is limited by the lack of placebo control for the escape arm and the use of as observed results. In clinical practice, physicians will likely consider factors other than only IGA 0/1 and EASI 75 when determining efficacy at week 16. Based on the study eligibility criteria, these results are limited to patients not previously treated with biologics for moderate-to-severe AD. Additional studies are needed to determine the efficacy of lebrikizumab in these patients. ADvocate1 and ADvocate2 were not designed to evaluate statistically significant differences between patients who met the protocol defined response criteria and those who did not. Therefore, conclusions comparing the baseline demographics and disease characteristics between these two groups are limited. Finally, these trials did not provide information on dosing lebrikizumab Q4W in the escape arm.

CONCLUSION

368 Patients who did not achieve the protocol-defined response criteria at 16 weeks of treatment
369 with lebrikizumab can benefit from the continuation of longer-term therapy.
370

ABBREVIATIONS AND ACRONYMS

AD=atopic dermatitis; BSA=body surface area; DLQI=Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; EASI 50=at least 50% improvement in EASI from baseline; EASI 75=at least 75% improvement in EASI from baseline; EASI 90=at least 90% improvement in EASI from baseline; IGA=Investigator Global Assessment; IL=interleukin; NRS=Numeric Rating Scale; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation; TCI=topical calcineurin inhibitors; TCS=topical corticosteroids

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Role of the sponsor

Eli Lilly and Company was involved in the trial design, data collection, data analysis, and preparation of the manuscript.

Role of contributors

All authors participated in the interpretation of trial results and in the critical revision and approval of the final version of the manuscript. E. Guttman-Yassky, D. Rosmarin, and H.C. Hong were investigators in the trial. C. Xu conducted the statistical analysis.

Data availability

Lilly 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 United States 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, 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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447 **TABLES**
448
449 **Table I.** Baseline Demographics and Disease Characteristics
450

	All Randomized Patients	Patients Not Meeting Protocol-Defined Response Criteria at Week 16 with LEB Q2W[a]		Patients Meeting Protocol-Defined Response Criteria at Week 16 with LEB Q2W[a]	
Baseline demographics	**N=851**	**N=215**		**N=291**	
Age (years)	35.8 (17.1)	36.6 (17.3)		35.5 (17.0)	
Adults (≥18 years), n (%)	749 (88.0)	192 (89.3)		253 (86.9)	
Adolescents (≥12 to <18 years), n (%)	102 (12.0)	23 (10.7)		38 (13.1)	
Female, n (%)	425 (49.9)	88 (40.9)		158 (54.3)	
Race[b], n (%)					
White	542 (63.7)	124 (57.7)		199 (68.4)	
Asian	192 (22.6)	58 (27.0)		51 (17.5)	
Black/African American	84 (9.9)	23 (10.7)		29 (10.0)	
Weight[c] (kg)	77.1 (20.7)	78.8 (20.6)		74.8 (19.9)	
BMI[c] (kg/m^2)	26.8 (6.4)	27.0 (6.2)		26.0 (6.1)	
Geographic region, n (%)					
US	357 (42.0)	81 (37.7)		117 (40.2)	
Europe	252 (29.6)	59 (27.4)		96 (33.0)	
Rest of World	242 (28.4)	75 (34.9)		78 (26.8)	
Disease characteristics	**Week 0**	**Week 0**	**Week 16**	**Week 0**	**Week 16**
Duration since AD onset, years	21.6 (15.0)	21.9 (15.3)	-	21.8 (14.6)	-
IGA score, n (%)					
3, moderate	523 (61.5)	119 (55.3)	99 (46.0)	185 (63.6)	13 (4.5%)
4, severe	328 (38.5)	96 (44.7)	20 (9.3)	106 (36.4)	0
EASI	29.6 (11.7)	29.9 (11.4)	15.1 (10.8)	29.1 (11.6)	2.4 (2.5)
Pruritus NRS[d]	7.2 (1.9)	7.3 (1.9)	4.8 (2.5)	7.2 (1.9)	2.9 (2.2)
≥4, n (%)	780 (94.5)	198 (94.3)	129 (61.1)	272 (95.1)	80 (28.6)
Sleep-Loss Scale[e]	2.3 (1.0)	2.3 (0.9)	1.3 (1.0)	2.2 (1.0)	0.73 (0.9)
Percent of BSA affected[f]	46.1 (22.5)	47.6 (23.3)	28.7 (21.1)	44.2 (22.0)	5.5 (6.5)
DLQI[g]	15.5 (7.3)	16.2 (6.9)	8.4 (6.6)	14.9 (7.2)	4.1 (4.2)

Note: Data are mean (standard deviation), unless otherwise indicated.

Abbreviations: AD=atopic dermatitis; BMI=body mass index; BSA=body surface area; DLQI=Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; EASI 75=at least 75% improvement in EASI from baseline; IGA=Investigator Global Assessment; LEB=lebrikizumab; N=number of patients in the analysis population; n=number of patients in the specified category; NRS=Numeric Rating Scale; Q2W=every 2 weeks; US=United States

Footnotes:

[a] Response was defined as achieving either EASI 75 or IGA 0/1 with ≥2-point improvement at week 16 without rescue medication.

[b] Additional races reported: American Indian or Alaska Native, Native Hawaiian or other, Pacific Islander, Multiple, and Other.

[c] N=849

[d] Pruritus NRS calculated for patients with non-missing data only: All randomized patients (N=825), per protocol nonresponders at week 0 (N=210) and week 16 (N=211), and per protocol responders at week 0 (N=286) and week 16 (N=280).

[e] Sleep-Loss Scale calculated for patients with non-missing data only: All randomized patients (N=823), per protocol nonresponders at week 0 (N=210) and week 16 (N=211), and per protocol responders at week 0 (N=284) and week 16 (N=279).

[f] N=851

[g] DLQI calculated for patients with non-missing data only: All randomized patients (N=696), per protocol nonresponders at week 0 (N=173) and week 16 (N=196), and per protocol responders at week 0 (N=235) and week 16 (N=257).

FIGURE LEGENDS

Figure I: Time Course of Response in Patients Who Did Not Meet the Protocol-Defined Response Criteria at Week 16

a) EASI 75

b) EASI 90

c) IGA 0/1 with ≥2-point improvement

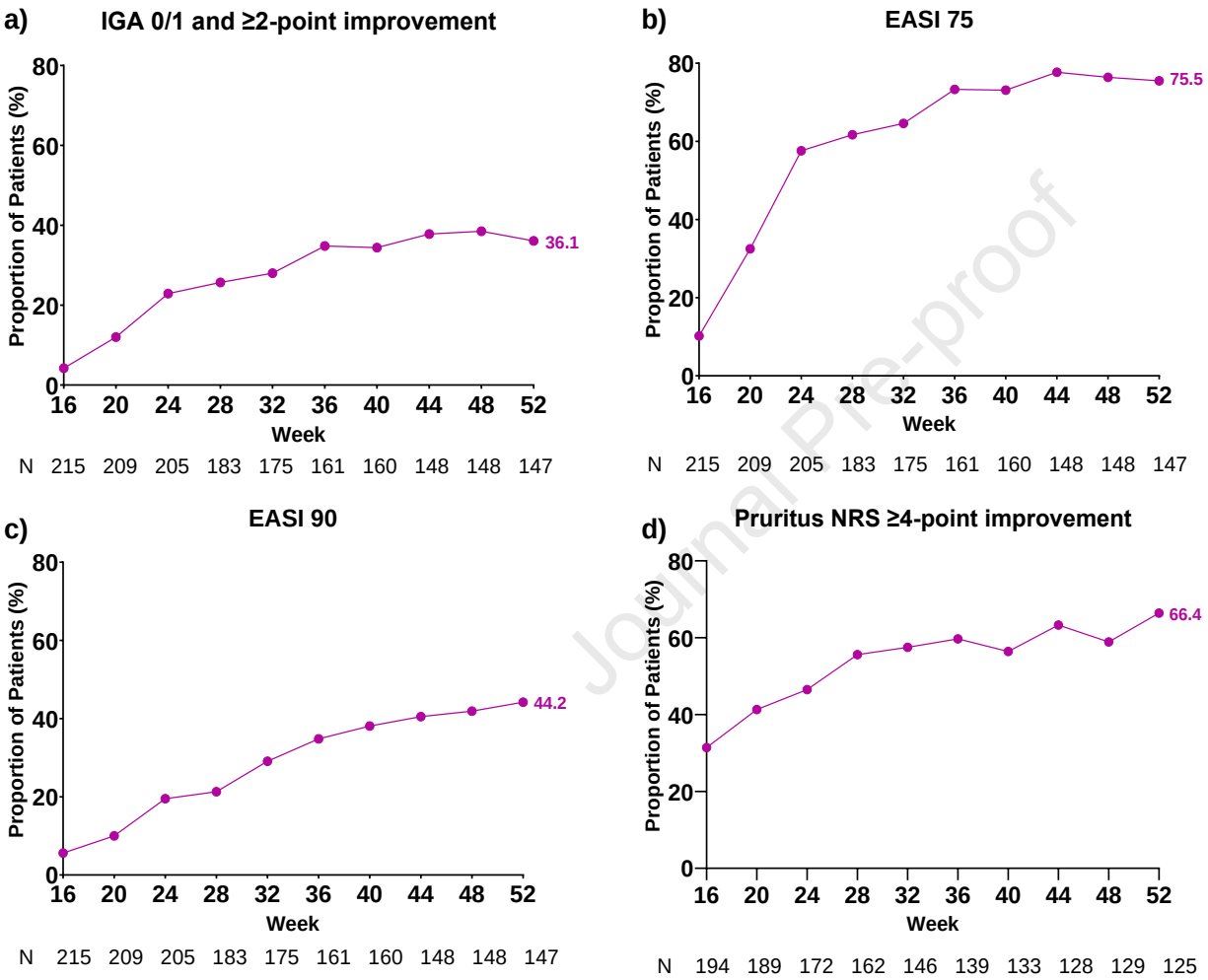
d) Pruritus NRS ≥4-point improvement

Notes: Data show as observed analysis. Response was defined as achieving either EASI 75 or IGA 0/1 with ≥2-point improvement at week 16 without rescue medication. The response rate for EASI 75 and IGA 0/1 with ≥2-point improvement does not start from 0 at week 16 since some patients achieved these endpoints with the use of rescue medication prior to week 16. Pruritus NRS ≥4-point improvement was only measured in patients with a baseline Pruritus NRS score of ≥4. Sixteen LEB-treated patients who met the protocol-defined response criteria at week 16 were incorrectly assigned to the escape arm; these patients were excluded from the analysis.

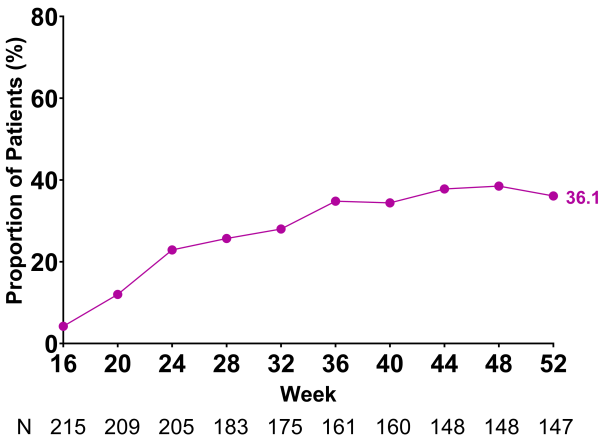
Abbreviations: EASI=Eczema Area and Severity Index; EASI 75=at least 75% improvement in EASI from baseline; EASI 90=at least 90% improvement in EASI from baseline; IGA=Investigator Global Assessment; LEB=lebrikizumab; NRS=Numeric Rating Scale

FIGURES

Figure I: Time Course of Response in Patients Who Did Not Meet the Protocol-Defined Response Criteria at Week 16

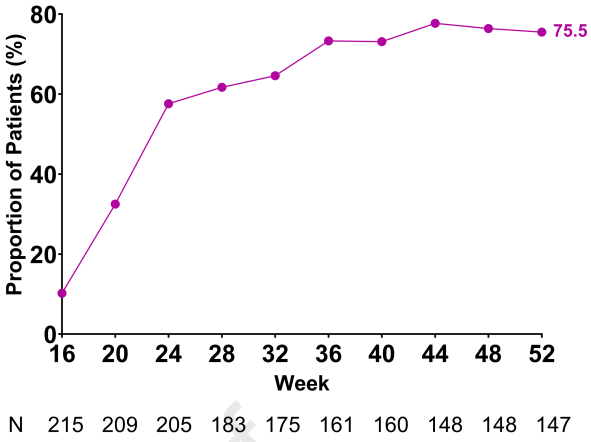


a) IGA 0/1 and ≥2-point improvement



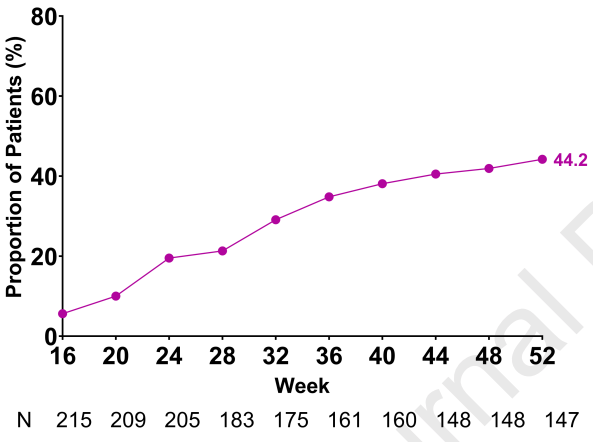
N	215	209	205	183	175	161	160	148	148	147

b) EASI 75



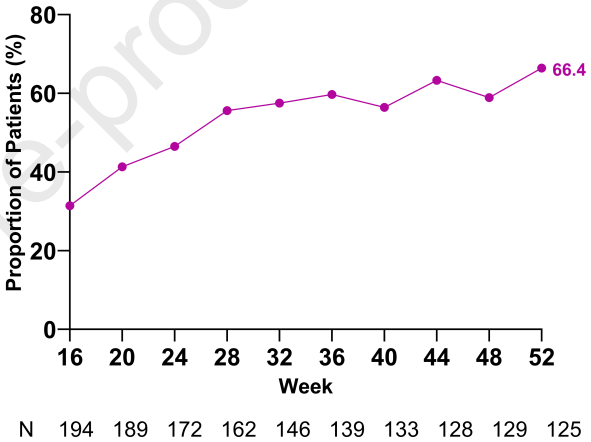
N	215	209	205	183	175	161	160	148	148	147

c) EASI 90



N	215	209	205	183	175	161	160	148	148	147

d) Pruritus NRS ≥4-point improvement



N	194	189	172	162	146	139	133	128	129	125