Lebrikizumab Provides Stable Itch Response With No or Minimal Fluctuations Up to One Year in Patients With Atopic Dermatitis

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BACKGROUND

- Lebrikizumab is a novel monoclonal antibody that binds with high affinity and slow off-rate to IL-13, thereby blocking the downstream effects of IL-13 with high potency[1]
- IL-13 is a key mediator in AD[2]
- Itch severely impacts quality of life in patients with AD and may influence sleep quality[3]
- ADvocate1 and ADvocate2 were 2 identically designed Phase 3, randomized, double-blind, placebo-controlled trials in patients with moderate-to-severe AD in which lebrikizumab demonstrated efficacy and an acceptable safety profile[3]
  - 85% of the Week 16 lebrikizumab-treated responders[a] maintained a Pruritus NRS ≥4-point improvement up to Week 52[4]
- Most of the Week 16 lebrikizumab-treated responders[a] maintained a durable and robust EASI 75 response with no or minimal fluctuations up to Week 52[4,5]
  - 71% of patients treated with lebrikizumab Q2W or Q4W achieved EASI 75 for ≥80% of study visits from Weeks 16 to 52[5]

[a] Responders achieved EASI 75 or IGA (0,1) with ≥2-point improvement at Week 16 without rescue medication use
Note: Statistical results of the primary and major secondary endpoints for ADvocate1 and ADvocate2 were confirmed through replicate statistical programming, validation, and quality reviews[3,4]

OBJECTIVE

- To describe the proportion of lebrikizumab-treated patients who maintained a stable itch response with no or minimal fluctuations from Week 16 to Week 52

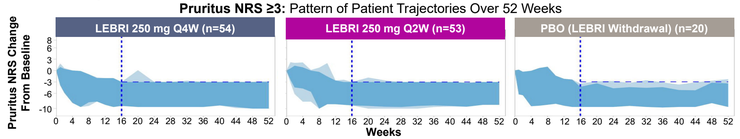
CONCLUSION

- Most patients treated with lebrikizumab monotherapy maintained a stable Pruritus NRS response, with no or minimal fluctuation in efficacy up to Week 52

KEY RESULTS

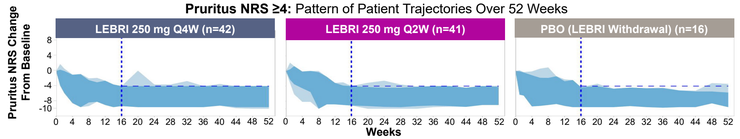
Week 16 Responders[a] Who Continued Treatment With Lebrikizumab Maintained Stable Pruritus NRS ≥3[b] and NRS ≥4[c] Response During the Maintenance Period

Pruritus NRS ≥3: Pattern of Patient Trajectories Over 52 Weeks



- **No or minimal fluctuations[b]:** Patients who maintained Pruritus NRS ≥3-point improvement for ≥80% of visits from Weeks 16 to 52
- **No fluctuation[b]:** Patients who maintained Pruritus NRS ≥3-point improvement for all visits from Weeks 16 to 52

Pruritus NRS ≥4: Pattern of Patient Trajectories Over 52 Weeks

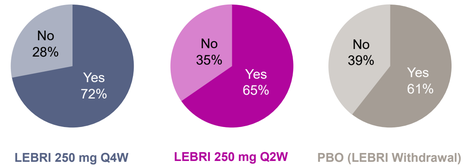


- **No or minimal fluctuations[c]:** Patients who maintained Pruritus NRS ≥4-point improvement for ≥80% of visits from Weeks 16 to 52
- **No fluctuation[c]:** Patients who maintained Pruritus NRS ≥4-point improvement for all visits from Weeks 16 to 52

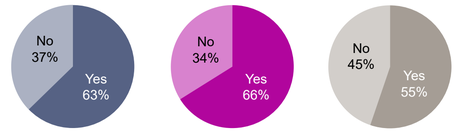
[a] Responders achieved EASI 75 or IGA (0,1) with ≥2-point improvement at Week 16 without rescue medication use; [b] Patients had baseline Pruritus NRS ≥3 and achieved ≥3-point improvement at Week 16; the Pruritus NRS ≥3 stable response was defined as patients who maintained Pruritus NRS ≥3-point improvement for ≥80% of visits from Weeks 16 to 52; [c] Patients had baseline Pruritus NRS ≥4 and achieved ≥4-point improvement at Week 16; the Pruritus NRS ≥4 stable response was defined as patients who maintained Pruritus NRS ≥4-point improvement for ≥80% of visits from Weeks 16 to 52; [d] Patients had baseline Pruritus NRS ≥4 and achieved ≥4-point improvement at Week 16; no fluctuation in Pruritus NRS ≥4 was defined as patients who maintained Pruritus NRS ≥4-point improvement for all visits from Weeks 16 to 52

Proportion of Responders[a] With Pruritus NRS ≥3[b] or NRS ≥4[c] Stable Response

Patients maintaining Pruritus NRS ≥3-point improvement for ≥80% of visits from Weeks 16 to 52, %



Patients maintaining Pruritus NRS ≥4-point improvement for ≥80% of visits from Weeks 16 to 52, %



SUPPLEMENTAL MATERIALS

- Animated Individual Patient Trajectory for Responders With Pruritus NRS ≥3 Stable Response
- Animated Individual Patient Trajectory for Responders With Pruritus NRS ≥4 Stable Response

METHODS

Key Eligibility Criteria

- Adults or adolescents (≥12 to <18 years; weight ≥40 kg)
- Diagnosis of AD, as defined by the American Academy of Dermatology Consensus Criteria, for ≥1 year before screening
- Moderate-to-severe AD, defined as having all the following at the baseline visit:
  - EASI ≥16
  - IGA ≥3
  - BSA involvement ≥10%
- Candidate for systemic therapy
- Biologic naïve

Assessments

- The Pruritus NRS is a patient-administered, validated, 11-point scale[6]:
  - 0 indicating "no itch"
  - 10 indicating "worst itch imaginable"
- Patients used the Pruritus NRS to rate their worst itch severity over the past 24 hours
- Pruritus NRS was recorded daily by the patient through an electronic diary up to Week 52
- Baseline weekly Pruritus NRS scores were calculated by averaging the daily scores up to 7 days before the first injection with ≥4 non-missing values
- Post-baseline weekly Pruritus NRS scores were calculated by averaging the daily scores from the previous 7 days with ≥1 non-missing values

Outcomes

- **Stability of response**, defined as no or minimal fluctuations in Pruritus NRS, was reported
  - Pruritus NRS ≥3 stable response: Proportion of lebrikizumab responders[a] with baseline Pruritus NRS ≥3 who achieved ≥3-point improvement in Pruritus NRS at Week 16 and maintained Pruritus NRS ≥3-point improvement **for ≥80% of visits from Week 16 to Week 52** (score defined as MCID[7])
  - Pruritus NRS ≥4 stable response: Proportion of lebrikizumab responders[a] with baseline Pruritus NRS ≥4 who achieved ≥4-point improvement in Pruritus NRS at Week 16 and maintained Pruritus NRS ≥4-point improvement for **≥80% of visits from Week 16 to Week 52**
- **No fluctuation** in Pruritus NRS was also reported
  - Pruritus NRS ≥3: Lebrikizumab responders[a] with baseline Pruritus NRS ≥3 who achieved ≥3-point improvement in Pruritus NRS at Week 16 and maintained Pruritus NRS ≥3-point improvement **for all the visits from Week 16 to Week 52**
  - Pruritus NRS ≥4: Lebrikizumab responders[a] with baseline Pruritus NRS ≥4 who achieved ≥4-point improvement in Pruritus NRS at Week 16 and maintained Pruritus NRS ≥4-point improvement **for all the visits from Week 16 to Week 52**

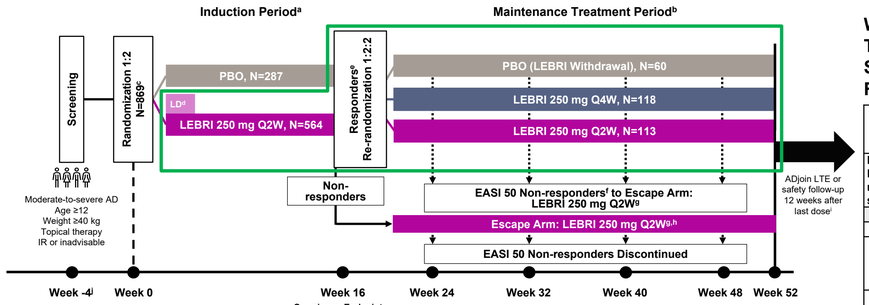
[a] Responders achieved EASI 75 or IGA (0,1) with ≥2-point improvement at Week 16 without rescue medication use

Statistical Analyses

- Post hoc analyses were performed on Week 16 responders[a] for the modified pooled population of ADvocate1&2
  - ADvocate2 analyses were performed on a modified population, excluding 14 patients from the pooled maintenance primary population
- If patients used rescue medication, discontinued treatment, or were transferred to the Escape Arm, data collected at or after the event were set as missing[b]
  - For the calculation of proportions of patients who achieved no or minimal fluctuations, NRI was used to impute missing values
- Ribbon plots were generated to show the pattern of patient trajectories with no or minimal fluctuations, which captured the range with maximum and minimum values of individual patients' data at each time point from baseline through Week 52
- Tsunami animations in the supplemental material animated the individual patient trajectory for Pruritus NRS change from baseline through Week 52

[a] Responders achieved EASI 75 or IGA (0,1) with ≥2-point improvement at Week 16 without rescue medication use; [b] Intermittent TCS use was permitted in the Maintenance Period

Study Design: ADvocate1 and ADvocate2



[a] Use of topical/systemic treatments for AD prohibited; [b] Use of intermittent topical rescue medications for AD permitted. Responders who received PBO during induction who were re-randomized to LEBRI received an LD of either 500 mg given at W16 or 500 mg given at W16 and W18; [c] 424 patients (ADvocate1) and 445 patients (ADvocate2) with moderate-to-severe AD; [d] 500 mg LD at W0 and W2; [e] Responders achieved EASI 75 or IGA (0,1) with ≥2-point improvement at W16 without rescue medication use; [f] Patients who did not maintain ≥EASI 50 were assigned to the Escape Arm; [g] Maintenance of response assessed by EASI 50 at W24, W32, W40, and W48, respectively. Patients who received systemic rescue medication were required to washout for 5 half-lives prior to initiating treatment in the Escape Arm; [h] Participants who were eligible for the Escape Arm at W16 received blinded LD at W16 and W18, based on their prior treatment assignment; [i] Patients completing ADvocate1/2 were offered open-label treatment in ADjoin, otherwise patients participated in a safety follow-up 12 weeks after their last dose; [j] ≤30-day screening period; [k] IGA (0,1) with ≥2-point improvement from baseline; [l] FDA primary endpoint; [m] EMA co-primary endpoint

RESULTS

Week 16 Responders[a] Who Continued Treatment With Lebrikizumab Maintained Stable Pruritus NRS ≥3[b] and ≥4[c] Responses During the Maintenance Period

From Weeks 16 to 52, Proportion of Responders[a]:	LEBRI 250 mg Q4W (N=75)	LEBRI 250 mg Q2W (N=81)	PBO (LEBRI Withdrawal) (N=33)
Maintaining Pruritus NRS ≥3 stable response[b] for ≥80% of study visits			
Yes	54 (72.0)	53 (65.4)	20 (60.6)
No	21 (28.0)	28 (34.6)	13 (39.4)
	LEBRI 250 mg Q4W (N=67)	**LEBRI 250 mg Q2W (N=62)**	**PBO (LEBRI Withdrawal) (N=29)**
Maintaining Pruritus NRS ≥4 stable response[c] for ≥80% of study visits			
Yes	42 (62.7)	41 (66.1)	16 (55.2)
No	25 (37.3)	21 (33.9)	13 (44.8)

[a] Responders achieved EASI 75 or IGA (0,1) with ≥2-point improvement at Week 16 without rescue medication use; [b] Patients had baseline Pruritus NRS ≥3 and achieved ≥3-point improvement at Week 16; the Pruritus NRS ≥3 stable response was defined as patients who maintained Pruritus NRS ≥3-point improvement for ≥80% of visits from Weeks 16 to 52; [c] Patients had baseline Pruritus NRS ≥4 and achieved ≥4-point improvement at Week 16; the Pruritus NRS ≥4 stable response was defined as patients who maintained Pruritus NRS ≥4-point improvement for ≥80% of visits from Weeks 16 to 52.
Note: Data are n (%)

Baseline Demographics and Disease Characteristics in Week 16 Lebrikizumab Responders[a]

- In ADvocate1&2, 291 lebrikizumab-treated patients met the criteria for response at Week 16[a] and were re-randomized to receive lebrikizumab Q4W, lebrikizumab Q2W, or placebo (lebrikizumab withdrawal) from Weeks 16 to 52

	LEBRI 250 mg Q4W (N=118)	LEBRI 250 mg Q2W (N=113)	PBO (LEBRI Withdrawal) (N=60)
Age, years	35.8 (17.3)	36.1 (17.0)	33.8 (16.6)
Adolescent (≥12 to <18 years), n (%)	17 (14.4)	13 (11.5)	8 (13.3)
Adult (≥18 years), n (%)	101 (85.6)	100 (88.5)	52 (86.7)
Female, n (%)	69 (58.5)	53 (46.9)	36 (60.0)
Region, n (%)			
USA	51 (43.2)	44 (38.9)	22 (36.7)
Europe	38 (32.2)	40 (35.4)	18 (30.0)
Rest of the world	29 (24.6)	29 (25.7)	20 (33.3)
Race, n (%)			
White	86 (72.9)	80 (70.8)	33 (55.0)
Asian	17 (14.4)	19 (16.8)	15 (25.0)
Black	12 (10.2)	9 (8.0)	8 (13.3)
BMI, kg/m²	26.2 (5.9)	26.3 (6.9)	25.3 (4.8)
Prior systemic treatment, n (%)	66 (55.9)	51 (45.1)	30 (50.0)
Disease duration since AD onset, years	22.6 (14.8)	21.7 (14.2)	20.4 (14.9)
IGA, n (%)			
3 (Moderate)	78 (66.1)	70 (61.9)	37 (61.7)
4 (Severe)	40 (33.9)	43 (38.1)	23 (38.3)
EASI	28.8 (12.6)	29.5 (10.8)	28.9 (11.2)
BSA % involvement	43.9 (23.2)	45.3 (20.6)	42.9 (22.4)
SCORAD	64.7 (13.0)	66.9 (11.5)	65.5 (12.0)
Pruritus NRS	7.0 (2.1)	7.2 (1.7)	7.5 (1.8)
<4, n (%)	9 (7.8)	3 (2.7)	2 (3.4)
≥4, n (%)	107 (92.2)	108 (97.3)	57 (96.6)

[a] Responders achieved EASI 75 or IGA (0,1) with ≥2-point improvement at Week 16 without rescue medication use
Note: Data are mean (SD) unless stated otherwise

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DISCLOSURES

J. del Rosso has served as a research investigator, consultant, and/or speaker for: AbbVie, Allergan, Almirall, Amgen, Arcutis, Bayer, Bausch Health (Ortho Dermatologics), Beiersdorf, Biofrontera, Biorasi, Bristol Myers Squibb, Cara Therapeutics, Cassiopea, Cutera, Dermavant, Dr. Reddy, Eli Lilly and Company, EPI Health, Evommune, Ferndale Pharma Group, Galderma, Incyte Corporation, JEM Health, Journey Medical Corporation, Johnson & Johnson, La Roche Posay, LEO Pharma, L'Oreal, Mayne Pharma, MC2 Therapeutics, Novan (EPI Health), Pfizer, Regeneron, Sanofi, Sebacia, Sol-Gel, Sun Pharma, UCB Pharma, and Vyne (Foamix); **G. Yosipovitch** has conducted clinical trials for or received research funds and/or honoraria for serving on the scientific advisory boards of: AbbVie, Arcutis, Eli Lilly and Company, Escient Pharmaceuticals, Galderma, Kiniksa Pharmaceuticals, LEO Pharma, Novartis, Pfizer, Regeneron, and Sanofi; **S. Ständer** has conducted clinical trials for or received research funds and/or honoraria for serving as a speaker and/or being on the scientific advisory boards of: AbbVie, Almirall, Analysis Group, Beiersdorf, BELLUS Health, BenevolentAI, Bioxcrica, Bristol Myers Squibb, Cara Therapeutics, Celgene, Cello Health, Clexio Biosciences, DS Biopharma, Eli Lilly and Company, Escient Pharmaceuticals, European Academy of Dermatology and Venereology, Forum für medizinische Fortbildung, Galderma, German Federal Ministry of Education and Research, German Research Foundation (DFG), Grünenthal, Integrity CE, Interdisciplinary Centre for Clinical Research (IZKF) Münster, Kiniksa Pharmaceuticals, Klinge Pharma, LEO Pharma, L'Oréal, Maruho, MEDahead, Menlo Therapeutics, Merz Pharma, moroscience, Novartis, Omniceuticals, Perrigo, Pfizer, Pierre Fabre, Sanofi, Sienna Biologics, Symbio Research, touchIME, Trevi Therapeutics, UCB Pharma, Unna Academy, Vanda Pharmaceuticals, Vitor Pharma, and WebMD; **J. I. Silverberg** has received grants and/or personal fees from: AbbVie, AFYX Therapeutics, Arena Pharmaceuticals, Asana BioSciences, Blue Fin Group, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly and Company, Galderma, GlaxoSmithKline, Incyte Corporation, Kiniksa Pharmaceuticals, LEO Pharma, Luna Pharma, Menlo Therapeutics, Novartis, Pfizer, RAPT Therapeutics, Regeneron, and Sanofi; **A. Wollenberg** has served as an advisor and/or paid speaker for and/or participated in clinical trials sponsored by: AbbVie, Aileens Pharma, Almirall, Amgen, Beiersdorf, Bioderma, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Chugai Pharmaceutical, Eli Lilly and Company, Galapagos NV, Galderma, GlaxoSmithKline, Janssen, LEO Pharma, L'Oréal, Novartis, Pfizer, Pierre Fabre, Regeneron, and Sanofi; **P. Lio** reports research grants and/or funding from: AbbVie, AOBiome, and Eczema Foundation; has been on speaker's bureaus for: AbbVie, Eli Lilly and Company, Galderma, Hyphens Pharma, Incyte Corporation, La Roche-Posay/L'Oréal, MyOR Diagnostics, ParentMD, Pfizer, Pierre Fabre, and Regeneron/Sanofi Genzyme; has received consulting fees from and/or been on advisory boards for: AbbVie, Almirall, Amyris, Arbonne, Arcutis, ASLAN Pharmaceuticals, Bodewell, Boston Skin Science, Bristol Myers Squibb, Burt's Bees, Castle Biosciences, Codex Labs, Concerto Biosciences, Dermavant, Dermira, Dermveda, Eli Lilly and Company, Galderma, IntraDerm, Janssen, Johnson & Johnson, Kaleido Biosciences, Kimberly-Clark, L'Oréal, LEO Pharma, Lipidor, Menlo Therapeutics, Merck, Micreos, MyOR Diagnostics, Regeneron/Sanofi Genzyme, Sibel Health, SkinFix, Sonica, Theraplex, UCB Pharma, Unilever, Verrica Pharmaceuticals, and Yobee Care; has stock options with: LearnSkin/Learn Health, Medable, Micreos, Modernizing Medicine, and Yobee Care; has a patent pending for: Theraplex product with royalties paid; and is a board member and scientific advisory committee member of: the National Eczema Association; **J. M. Carrascosa** has been an advisory board member, speaker, or consultant and/or has participated in clinical studies for: AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Janssen, LEO Pharma, Novartis, Pfizer, Sandoz, Sanofi Regeneron, and UCB Pharma; **G. Gallo**, **M. Casillas**, **E. Pierce**, and **Y. Ding** are employees and shareholders of: Eli Lilly and Company; **Z. Xu** is an employee of: CIMS Global LLC; **H. Agell** is an employee of: Almirall; **L. Stein Gold** is an investigator and/or consultant and/or speaker for: AbbVie, Amgen, Arcutis, Bristol Myers Squibb, Dermavant, Eli Lilly and Company, Galderma, Incyte Corporation, Janssen, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, and UCB Pharma.

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ABBREVIATIONS

AD=atopic dermatitis; BMI=body mass index; BSA=body surface area; EASI=Eczema Area and Severity Index; EASI 50/75=at least 50/75% improvement from baseline in EASI; EMA=European Medicines Agency; FDA=US Food and Drug Administration; IGA=Investigator's Global Assessment; IGA (0,1)=IGA response of clear or almost clear; IL=interleukin; IR=inadequate responder; LD=loading dose; LEBRI=lebrikizumab; LTE=long-term extension; MCID=minimum clinically important difference; NRI=non-responder imputation; NRS=Numeric Rating Scale; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SCORAD=SCORing Atopic Dermatitis; SD=standard deviation; TCS=topical corticosteroids; W=Week

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