Lebrikizumab Delivers Clinically Meaningful and Continuous Improvement in Itch-Free Days in Atopic Dermatitis Through One Year

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BACKGROUND

- Itch is the most burdensome symptom for patients with AD and impacts quality of life[1]
- 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[2]
- ADvocate1 (NCT04146363) and ADvocate2 (NCT04178967) 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 a safety profile[3,4]
  - 85% of the Week 16 lebrikizumab-treated responders[a] maintained a Pruritus NRS ≥4-point improvement up to Week 52[4]

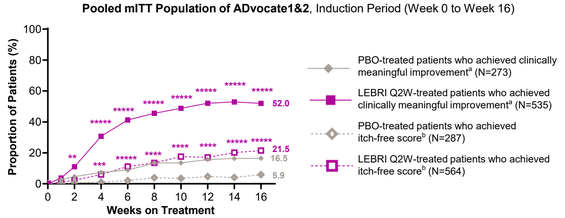
OBJECTIVES

- To evaluate the response rates of patients achieving the clinically meaningful improvement (MCID)[5,b] of Pruritus NRS score ≥3-point improvement and the response rates of patients achieving Pruritus NRS score 0 or 1 during the Induction and Maintenance periods in the pooled ADvocate1&2 population
- To evaluate the mean number of clinically meaningful improvement[b] and itch-free days per week and per month based on the response rate of Pruritus NRS score over 52 weeks in the pooled ADvocate1&2 population

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

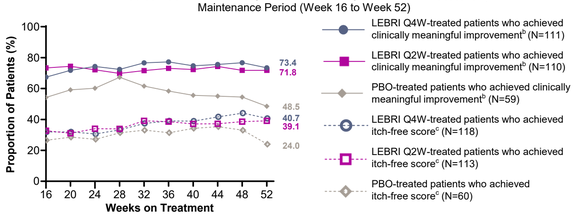
KEY RESULTS

A Higher Proportion of Lebrikizumab-Treated Patients Achieved Clinically Meaningful Improvement[a] and Itch-Free Score[b] Compared With Placebo-Treated Patients



** p<0.01; *** p<0.001; **** p<0.0001; ***** p<0.00001 vs. PBO using the Cochran-Mantel-Haenszel test adjusted by study (ADvocate1 vs. ADvocate2), geographic region (US vs. EU vs. rest of world), age (adolescent patients 12 to <18 years vs. adults ≥18 years), and disease severity (IGA 3 vs. 4)
[a] Pruritus NRS ≥3-point improvement in patients with baseline Pruritus NRS ≥3; [b] Pruritus NRS score of 0 or 1

A Higher Proportion of Week 16 Responders[a] Who Continued Treatment With Lebrikizumab Achieved Clinically Meaningful Improvement[b] and Itch-Free Score[c]



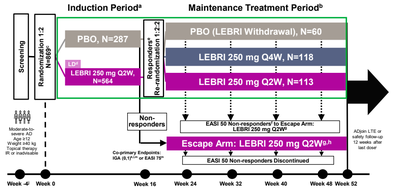
[a] Responders achieved EASI 75 or IGA (0,1) with ≥2-point improvement at Week 16 without rescue medication use; [b] Pruritus NRS ≥3-point improvement in patients with baseline Pruritus NRS ≥3; [c] Pruritus NRS score of 0 or 1

CONCLUSIONS

- Patients with AD treated with lebrikizumab reported an increase in the proportion of itch-free days (Pruritus NRS score of 0 or 1) and clinically meaningful improvement days (Pruritus NRS ≥3-point improvement)
  - Given that itch is a burdensome symptom, rapid itch relief holds great importance for both patients and physicians
- In the ADvocate 1&2 monotherapy trials, lebrikizumab Q4W treatment delivered clinically meaningful and continuous improvement in itch-free days through 52 weeks
- During the Induction Period, more lebrikizumab-treated patients achieved clinically meaningful improvement and an itch-free score compared with placebo-treated patients
- During the Maintenance Period, a higher proportion of patients who continued treatment with lebrikizumab achieved clinically meaningful improvement and an itch-free score

METHODS

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 a 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

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

- Patients used the Pruritus NRS to rate their worst itch severity over the past 24 hours
- Pruritus NRS was recorded daily by the patient using an electronic diary up to Week 52
- The Pruritus NRS is a patient-reported, validated, 11-point scale[6]:
  - 0 indicating "no itch"
  - 10 indicating "worst itch imaginable"
- Itch-free was defined as a Pruritus NRS score of 0 or 1
- Clinically meaningful improvement (also defined as MCID) was defined as Pruritus NRS ≥3-point improvement in patients with baseline Pruritus NRS ≥3

Outcomes

- The following endpoints were analyzed for both Induction and Maintenance periods based on the pooled ADvocate1&2 mITT population and MMP population[a]:
  - The mean number of itch-free[b] days per week or per month was reported
  - The mean number of clinically meaningful improvement[c] days per week or per month was reported
  - The proportion of patients achieving itch-free[b] score was reported
  - The proportion of patients achieving clinically meaningful improvement[c] was reported

[a] In lebrikizumab responders defined as achieving EASI 75 or IGA (0,1) with ≥2-point improvement at Week 16 without rescue medication use; [b] Pruritus NRS score of 0 or 1; [c] Pruritus NRS ≥3-point improvement in patients with baseline Pruritus NRS ≥3

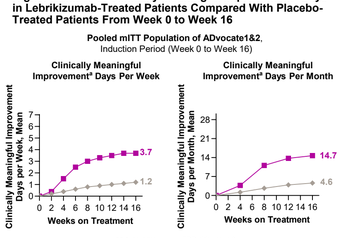
Statistical Analyses

- Analysis populations
  - Pooled ADvocate1&2 mITT population from Week 0 to Week 16 (Induction Period)
  - Pooled ADvocate1&2 MMP population[a] who entered the Maintenance[b] Period through Week 52
- Response rate of clinically meaningful improvement[c] and response rate of itch-free[d] calculation algorithm
  - Analyzed with Cochran-Mantel-Haenszel test with adjustment for stratification factors
    - For the Induction Period analyses, factors included the study, geographic region, age group, and severity of disease
    - For the Maintenance Period analyses, factors included the study and geographic region
- Clinically meaningful improvement[c] and itch-free[d] days' calculation
  - To evaluate the cumulative benefit of lebrikizumab on clinically meaningful improvement[c] and itch-free[d] days over time, the mean of clinically meaningful improvement[c]/itch-free[d] days cumulated per month were calculated using measurements of AUC based on response rates of patients who achieved a Pruritus NRS ≥3-point improvement or a Pruritus NRS score of 0 or 1 at visit intervals, respectively
- Imputation method
  - For the Induction Period, data collected after rescue medication or treatment discontinuation due to lack of efficacy were imputed with NRI
  - For the Maintenance Period, data collected after systemic rescue medication, treatment discontinuation due to lack of efficacy, or transition to Escape Arm were imputed with NRI
  - Data collected after treatment discontinuation due to other reasons were set as missing; missing data were imputed with MI

[a] Lebrikizumab responders defined as achieving 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; [c] Pruritus NRS ≥3-point improvement in patients with baseline Pruritus NRS ≥3; [d] Pruritus NRS score of 0 or 1

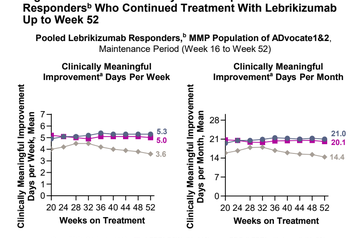
RESULTS

Higher Number of Clinically Meaningful Improvement[a] Days in Lebrikizumab-Treated Patients Compared With Placebo-Treated Patients From Week 0 to Week 16



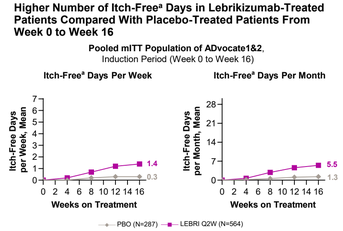
[a] Pruritus NRS ≥3-point improvement in patients with baseline Pruritus NRS ≥3

Higher Number of MCID[a] Days Were Reported in Week 16 Responders[b] Who Continued Treatment With Lebrikizumab Up to Week 52



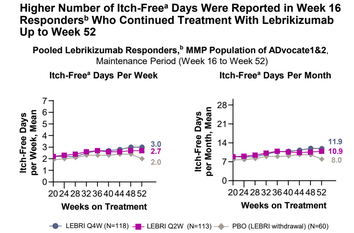
[a] Pruritus NRS ≥3-point improvement in patients with baseline Pruritus NRS; [b] Responders achieved EASI 75 or IGA (0,1) with ≥2-point improvement at Week 16 without rescue medication use

Higher Number of Itch-Free[a] Days in Lebrikizumab-Treated Patients Compared With Placebo-Treated Patients From Week 0 to Week 16



[a] Pruritus NRS score of 0 or 1

Higher Number of Itch-Free[a] Days Were Reported in Week 16 Responders[b] Who Continued Treatment With Lebrikizumab Up to Week 52



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

Baseline Demographics and Disease Characteristics

	Pooled mITT Population of ADvocate1&2		Pooled MMP Population of ADvocate1&2[a]		
	PBO (N=287)	LEBRI Q2W (N=564)	LEBRI Q4W (N=118)	LEBRI Q2W (N=113)	PBO (LEBRI Withdrawal) (N=60)
Age, years	34.8 (16.8)	36.4 (17.3)	35.8 (17.3)	36.1 (17.0)	33.8 (16.6)
Adolescent (≥12 to <18 years), n (%)	35 (12.2)	67 (11.9)	17 (14.4)	13 (11.5)	8 (13.3)
Adult (≥18 years), n (%)	252 (87.8)	497 (88.1)	101 (85.6)	100 (88.5)	52 (86.7)
Female, n (%)	148 (51.6)	277 (49.1)	69 (58.5)	53 (46.9)	36 (60.0)
Region, n (%)					
USA	122 (42.5)	235 (41.7)	51 (43.2)	44 (38.9)	22 (36.7)
Europe	84 (29.3)	168 (29.8)	38 (32.2)	40 (35.4)	18 (30.0)
Rest of the world	81 (28.2)	161 (28.5)	29 (24.6)	29 (25.7)	20 (33.3)
BMI, kg/m²	27.1 (6.8)	26.6 (6.2)	26.2 (5.9)	26.3 (6.9)	25.3 (4.8)
Disease duration[b], years	21.9 (14.9)	21.4 (15.0)	22.6 (14.8)	21.7 (14.2)	20.4 (14.9)
IGA, n (%)					
3 (Moderate)	178 (62.0)	345 (61.2)	78 (66.1)	70 (61.9)	37 (61.7)
4 (Severe)	109 (38.0)	219 (38.8)	40 (33.9)	43 (38.1)	23 (38.3)
EASI	30.3 (11.9)	29.3 (11.6)	28.8 (12.6)	29.5 (10.8)	28.9 (11.2)
Pruritus NRS, median (range)	7.4 (1.4-10.0)	7.4 (0.0-10.0)	7.2 (1.0-10.0)	7.3 (2.1-10.0)	7.6 (3.0-10.0)

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

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4. Blauvelt A, et al. *Br J Dermatol*. 2023;188:740-748. 5. Yosipovitch G, et al. *Br J Dermatol*. 2022;186:135-185. 6. Yosipovitch G, et al. *Br J Dermatol*. 2019;181:761-769.

ABBREVIATIONS

AD=atopic dermatitis; AUC=area under the curve; 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=minimal clinically important difference; MI=multiple imputation; mITT=modified Intent-to-Treat; MMP=modified maintenance primary; NRI=non-responder imputation; NRS=Numeric Rating Scale; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation; TCS=topical corticosteroids; W=week

DISCLOSURES

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; **C. Zeidler** has conducted clinical trials for or received research funds and/or honoraria for lectures and/or authorships of: AbbVie, Almirall, Beiersdorf, Boehringer Ingelheim, DERMASENCE, Eli Lilly and Company, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi, UCB Pharma, Uma Academy; **C. J. Apfelbacher** has received institutional funding from: the Dr Wolff Group and Bionorica, and consultancy fees from: the Dr Wolff Group, LEO Pharma, RHEACELL, and Sanofi; **V. Laquer** is a consultant with honorarium for: Cara Therapeutics, Eli Lilly and Company, and Galderma; and is an investigator for: AbbVie, Amgen, AnaptysBio, Arcutis, argenx, ASLAN Pharmaceuticals, Biofrontera, Bristol Myers Squibb, Castle Biosciences, Dermavant, Eli Lilly and Company, Galderma, Incyte Corporation, Janssen, Kiniksa Pharmaceuticals, LEO Pharma, MoonLake Immunotherapeutics, Novartis, Pfizer, RAPT Therapeutics, Sun Pharma, and UCB Pharma; **B. S. Kim** is founder of Klima Biotech; he has served as a consultant for 23andMe, ABRAX Japan, AbbVie, Almirall, Amagma Therapeutics, Amgen, Arcutis, Arena Pharmaceuticals, argenx, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Clexio Biosciences, Eli Lilly and Company, Escient Pharmaceuticals, Evommune, Galderma, Genentech, GlaxoSmithKline, Granular Therapeutics, Incyte Corporation, Innovaderm Research, Janssen, Kiniksa Pharmaceuticals, LEO Pharma, Maruho, Novartis, Pfizer, Recens Medical, Regeneron Pharmaceuticals, Sanofi, Septerna, Vial, and WebMD; he has stock in: ABRAX Japan, KliRNA Biotech, Locus Biosciences, and Recens Medical; he holds a patent for the use of JAK1 inhibitors for chronic pruritus; he has a patent pending for the use of JAK1 inhibitors for interstitial cystitis; he has research grants from: AbbVie, Cara Therapeutics, LEO Pharma, and Veradermics; **M. Casillas** and **E. Pierce** are employees and shareholders of: Eli Lilly and Company; **S. Chen** and **M. Qiao** are employees of: Tigermed; **H. Agell** is an employee of: Almirall; **J. Del Rosso** has served as a research investigator, consultant, and/or speaker for: AbbVie, Allergan, Almirall, Amgen, Arcutis, Bayer Pharmaceuticals, Bausch Health (Ortho Dermatologics), Beiersdorf, Biofrontera, Biorasi, Bristol Myers Squibb, Cara Therapeutics, Cassiopea Pharmaceuticals, Cutera, Dermavant, Dr. Reddy, Eli Lilly and Company, EPI Health, Evommune, Ferndale Laboratories, Galderma, Incyte Corporation, JEM Health, Journey Medical Corporation, Johnson & Johnson, LaRoche Posay, LEO Pharma, L'Oreal, Mayne Pharma, MC2 Therapeutics, Novan (EPI Health), Pfizer, Regeneron, Sanofi, Sebacia, Sol-Gel, Sun Pharma, UCB Pharma, and Vyne Therapeutics (Foamix)

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