Lebrikizumab Monotherapy Reduces Flares in Patients with Moderate-to-Severe Atopic Dermatitis

James Q. Del Rosso[1], Pearl Kwong[2], Iftikhar Hussain[3], Sebastien Barbarot[4], Jose Manuel Carrascosa[5], Maria Jose Rueda[6], Amber Reck Atwater[6], Hany Elmaraghy[6], Luna Sun[6], Sherry Chen[7], Chitra R. Natalie[6], and Stephan Weidinger[8]

[1]JDR Dermatology Research, Las Vegas, NV, USA; [2]Solutions Through Advanced Research, Jacksonville, FL, USA; [3]Vital Prospects Clinical Research Institute, Tulsa, OK, USA; [4]Department of Dermatology, Centre Hospitalier Universitaire de Nantes, Nantes, France; [5]Department of Dermatology, Hospital Universitari Germans Trias I Pujol. IGTP, Barcelona, Spain; [6]Eli Lilly and Company, Indianapolis, IN, USA; [7]Tigermed, Somerset, NJ, USA; [8]Department of Dermatology, University Hospital Schleswig-Holstein, Kiel, Germany

BACKGROUND

- Patients with moderate-to-severe atopic dermatitis (AD) commonly experience worsening of disease severity (flares), often requiring acute treatment with topical corticosteroids (TCS) or other rescue medication.
- Atopic Dermatitis is an IL-13 dominant disease.[1] Lebrikizumab targets and potently neutralizes IL-13 signaling with high binding affinity to a specific epitope with a slow off-rate.[2,3]
- Lebrikizumab achieved primary and all key secondary endpoints at Week 4 and Week 16 in 2 randomized, double-blind, placebo-controlled, phase 3 clinical trials in adults and adolescents with moderate-to-severe AD; ADvocate 1 (NCT04146363) and ADvocate 2 (NCT04178967).[4]
  - Significant improvements vs placebo were seen as early as Week 2 for Eczema Area and Severity Index (EASI)-75 and for ≥4-point improvement in pruritus numeric rating scale (NRS) in ADvocate 1.

FLARE DEFINITIONS

- Flare was defined 3 ways for these analyses:
  - Per protocol rescue flare: initiation or intensification of rescue therapy with topicals (corticosteroids, calcineurin inhibitors, crisaborole); systemics (corticosteroids, immunosuppressants, biologics, Janus Kinase inhibitors); phototherapy; or photochemotherapy
  - High potency TCS/systemic rescue flare: use of topical high potency corticosteroids or systemics (corticosteroids, immunosuppressants, biologics, Janus Kinase inhibitors); phototherapy; or photochemotherapy
  - AE flare: an exacerbation of AD, captured as a treatment-emergent adverse event[a]

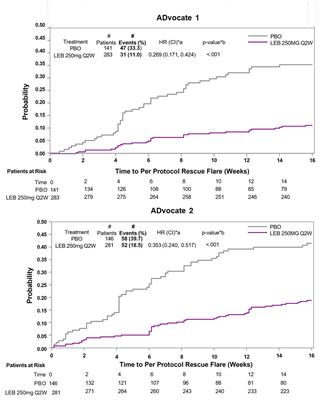
[a] AD exacerbation was defined using specific *Medical Dictionary for Regulatory Activities* preferred terms of dermatitis atopic, rebound atopic dermatitis, or eczema.

OBJECTIVE

- To assess the ability of lebrikizumab to reduce flares in patients with moderate-to-severe AD through the 16-week initial randomized treatment period in the advocate 1 and advocate 2 phase 3 clinical studies.[4]

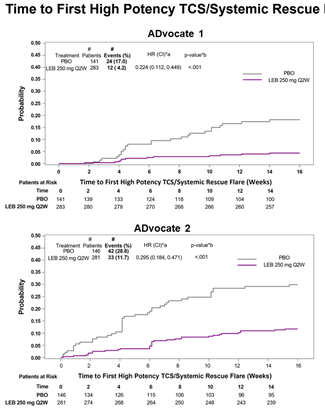
KEY RESULTS

Time to First Flare: Per Protocol Rescue Flare



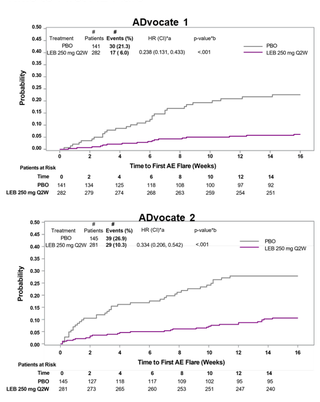
[a] HR: stratified by geographic region (US vs EU vs rest of world), age (adolescents vs adults), and disease severity (IGA 3 vs 4)
[b] Log-rank for comparison with placebo, stratified by geographic region (US vs EU vs rest of world), age (adolescents vs adults), and disease severity (IGA 3 vs 4)
Per protocol rescue flare was defined as initiation or intensification of rescue therapy with topicals (corticosteroids, calcineurin inhibitors, crisaborole); systemics (corticosteroids, immunosuppressants, biologics, Janus Kinase inhibitors); phototherapy; or photochemotherapy. Analysis was based on the ITT population (ADvocate 1) or mITT population (ADvocate 2).

Time to First High Potency TCS/Systemic Rescue Flare



High potency TCS/systemic rescue flare was defined as use of topical high potency corticosteroids; systemics (corticosteroids, immunosuppressants, biologics, Janus Kinase inhibitors); phototherapy or photochemotherapy

Time to First AE Flare



AE flare was defined as an exacerbation of AD, captured as a treatment-emergent adverse event

[a] HR: stratified by geographic region (US vs EU vs rest of world), age (adolescents vs adults), and disease severity (IGA 3 vs 4). [b] Log-rank for comparison with placebo, stratified by geographic region (US vs EU vs rest of world), age (adolescents vs adults), and disease severity (IGA 3 vs 4). Analysis of high potency TCS/systemic rescue flare was based on the ITT population (ADvocate 1) or mITT population (ADvocate 2). Analysis of AE flare was based on the Safety population (ADvocate 1) or modified Safety population (ADvocate 2).

SUMMARY

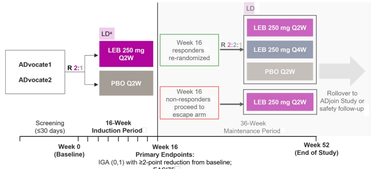
- During the 16-week induction period, a smaller proportion of patients treated with lebrikizumab versus placebo experienced an AD flare as defined by use of at least one per protocol rescue medication (per protocol flare) in ADvocate 1 (11.0% vs 33.3%) and ADvocate 2 (18.5% vs 39.7%)
  - The rate ratio for adjusted per protocol flare rate for lebrikizumab versus placebo was 0.34 in ADvocate 1 and 0.43 in ADvocate 2 (both p<0.001)
- Fewer patients treated with lebrikizumab vs placebo experienced an AD flare as defined by use of a high potency TCS or systemic rescue medication in ADvocate 1 (4.2% vs 17.0%) and ADvocate 2 (11.7% vs 28.8%)
- Fewer patients treated with lebrikizumab versus placebo experienced an AD flare defined as at least one reported TEAE representing AD exacerbation in ADvocate 1 (6.0% vs 21.3%) and ADvocate 2 (10.3% vs 26.9%)

CONCLUSIONS

In patients with AD, treatment with lebrikizumab monotherapy resulted in significantly fewer AD flares than treatment with placebo across multiple definitions of AD flare

METHODS

Study Design



Key Eligibility Criteria

- Adults ≥18 years old and adolescents (≥12 to <18 years old with weight ≥40 kg)
- Moderate-to-severe AD, defined as:
  - EASI score ≥16
  - Investigator's Global Assessment (IGA) score ≥3
  - Body surface area % involvement ≥10%
- Chronic AD for ≥1 year for whom topical treatment was inadequate or inadvisable
- Dupilumab- and tralokinumab-naïve

STATISTICAL METHODS

ANALYSIS POPULATIONS

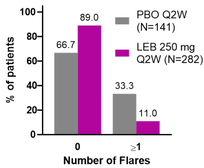
- Intent-to-Treat population (ITT; all randomized patients) for ADvocate 1 and modified ITT (mITT) for ADvocate 2.[a]
- For AE flare and exposure adjusted flare rate, the analysis population was the Safety population for ADvocate 1 and the modified Safety population for ADvocate 2.

STATISTICAL ANALYSES

- The Kaplan-Meier product limit method was used to estimate the survival for time to event analyses (eg, time to first flare).
- The stratified log-rank test was performed with treatment group and covariates (eg, geographic region [US vs EU vs rest of world], age [adolescent patients 12 to <18 vs adults ≥18 years] and baseline disease severity [IGA 3 vs 4]) in the model.
- Flare count (considering multiple flares per patient) based on per protocol rescue flare was summarized and adjusted flare rate was estimated by negative binomial regression.
- Nominal p-values are reported without control for multiplicity.

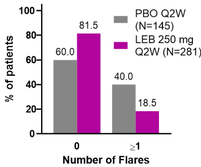
RESULTS
(Through Week 16)

Proportion of Patients With Per Protocol Flare



ADvocate 1

# of flares	N (%) of patients: PBO Q2W (N=141)	LEB 250 mg Q2W (N=283)
0	94 (66.7)	251 (89.0)
1	41 (29.1)	26 (9.2)
2	5 (3.5)	4 (1.4)
≥3	1 (0.7)	1 (0.4)



ADvocate 2

# of flares	N (%) of patients: PBO Q2W (N=145)	LEB 250 mg Q2W (N=281)
0	87 (60.0)	229 (81.5)
1	52 (35.9)	47 (16.7)
2	5 (3.4)	5 (1.8)
≥3	1 (0.7)	0

Adjusted Per Protocol Flare Rates

ADvocate 1

	PBO Q2W (N=141)	LEB 250 mg Q2W (N=282)
Adjusted flare rate	0.380	0.128
Rate ratio (95% CI) vs PBO		0.34 (0.21, 0.55)
P-value vs PBO		<0.001

ADvocate 2

	PBO Q2W (N=145)	LEB 250 mg Q2W (N=281)
Adjusted flare rate	0.438	0.188
Rate ratio (95% CI) vs PBO		0.43 (0.30, 0.61)
P-value vs PBO		<0.001

Baseline Demographics

Result, n (%) unless otherwise noted	ADvocate 1: PBO Q2W (N=141)	ADvocate 1: LEB 250 mg Q2W (N=283)	ADvocate 2: PBO Q2W (N=146)	ADvocate 2: LEB 250 mg Q2W (N=281)
Age, years, mean (SD)	34.2 (16.4)	36.1 (17.8)	35.3 (17.2)	36.6 (16.8)
Adolescent (12 to <18 years)	18 (12.8)	37 (13.1)	17 (11.6)	30 (10.7)
Adult (≥18 years)	123 (87.2)	246 (86.9)	129 (88.4)	251 (89.3)
Female	73 (51.8)	141 (49.8)	75 (51.4)	136 (48.4)
Region				
US	62 (44.0)	128 (45.2)	60 (41.1)	107 (38.1)
Europe	46 (32.6)	92 (32.5)	38 (26.0)	76 (27.0)
Rest of world	33 (23.4)	63 (22.3)	48 (32.9)	98 (34.9)
Race				
White	93 (66.0)	196 (69.3)	85 (58.2)	168 (59.8)
Asian	31 (22.0)	39 (13.8)	44 (30.1)	78 (27.8)
Black/African American	16 (11.3)	33 (11.7)	10 (6.8)	25 (8.9)
BMI, kg/m²	27.8 (7.2)	26.6 (5.8)	26.3 (6.3)	26.7 (6.6)
Prior systemic treatment	85 (60.3)	144 (50.9)	81 (55.5)	156 (55.5)

Baseline Disease Characteristics

Result, mean (SD) unless otherwise noted	ADvocate 1: PBO Q2W (N=141)	ADvocate 1: LEB 250 mg Q2W (N=283)	ADvocate 2: PBO Q2W (N=146)	ADvocate 2: LEB 250 mg Q2W (N=281)
Disease duration since AD onset, years	23.8 (15.4)	22.0 (14.9)	20.1 (14.1)	20.8 (15.2)
IGA, n (%)				
3 (moderate)	83 (58.9)	170 (60.1)	95 (65.1)	175 (62.3)
4 (severe)	58 (41.1)	113 (39.9)	51 (34.9)	106 (37.7)
EASI	31.0 (12.9)	28.8 (11.3)	29.6 (10.8)	29.7 (12.0)
BSA, % involvement	47.8 (23.9)	45.3 (22.5)	46.0 (21.1)	46.1 (22.6)
Pruritis NRS	7.3 (1.7)	7.2 (1.9)	7.2 (1.9)	7.1 (1.9)
Sleep-Loss Scale score	2.3 (1.0)	2.3 (1.0)	2.2 (0.9)	2.2 (0.9)
DLQI	15.7 (7.2)	15.3 (7.4)	15.9 (7.6)	15.4 (7.0)

Use of Rescue Medication Through 16 Weeks

Result, n (%)	ADvocate 1: PBO Q2W (N=141)	ADvocate 1: LEB 250 mg Q2W (N=283)	ADvocate 2: PBO Q2W (N=146)	ADvocate 2: LEB 250 mg Q2W (N=281)
Any rescue medication	47 (33.3)	31 (11.0)	58 (39.7)	52 (18.5)
Topical rescue medication	44 (31.2)	27 (9.5)	54 (37.0)	48 (17.1)
Low-/mid- potency TCS	38 (27.0)	20 (7.1)	24 (16.4)	27 (9.6)
High-potency TCS	15 (10.6)	6 (2.1)	36 (24.7)	25 (8.9)
Calcineurin inhibitor	9 (6.4)	4 (1.4)	6 (4.1)	8 (2.8)
Systemic rescue medication	11 (7.8)	7 (2.5)	9 (6.2)	8 (2.8)

Note: Only data from the 16-week Induction Period are presented. [a] LEB-treated patients received a 500-mg LD at Weeks 0 and 2.

[a] In Advocate 2, 18 patients were excluded from the ITT as they did not meet eligibility criteria of having moderate-to-severe AD. Thus the analyses in Advocate 2 used the modified ITT.

Data for adjusted flare rate were from negative binomial regression analysis with treatment group, age group, baseline IGA, and region as explanatory variables. The natural logarithm of the flare exposure time in weeks was used as an offset variable in the model to adjust for subjects having different exposure times.
Per protocol rescue flare was defined as initiation or intensification of rescue therapy with topicals (corticosteroids, calcineurin inhibitors, crisaborole); systemics (corticosteroids, immunosuppressants, biologics, Janus Kinase inhibitors); phototherapy; or photochemotherapy

Systemic rescue medications included corticosteroids, immunosuppressants, biologics, and Janus Kinase inhibitors. No patients used crisaborole, phototherapy or photochemotherapy.

REFERENCES

1. Tsoi LC et al. *J Invest Dermatol.* 2019; 139:1480-9.
2. Ultsch M et al. *J Mol Biol. 2013*; 425:1330-9.
3. Okragly A, et al. Presented at the Inflammatory Skin Disease Summit, New York, 2021
4. Silverberg J et al. Presented at American Academy of Dermatology (AAD), Virtual Meeting Experience, 2022

ABBREVIATIONS

AD=atopic dermatitis; AE=adverse event; BSA=body surface area; CI=95% confidence interval; DLQI= Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; EASI-75=75% reduction from baseline in EASI score; EU=European Union; FDA=US Food and Drug Administration; HR=hazard ratio; IGA=Investigator's Global Assessment, ITT=intent-to-treat; LD=loading dose; LEB=lebrikizumab; mITT=modified intent-to-treat; NRS=numeric rating scale; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; R=randomization; TCS=topical corticosteroid; US=United States

DISCLOSURES

- JQ Del Rosso is on the board of directors and president-elect of the American Acne and Rosacea Society. He is a research investigator, consultant, advisor, and/or speaker for AbbVie, Aclaris, Almirall, Amgen (Celgene), Anaptys Bio, Arcutis, Asian, Asthenex, Bausch (Ortho Dermatology), Beiersdorf, Biofrontera, BioPharmX, Biorasi, Blue Creek, Boehringer Ingelheim, Botanix, Brickell, Cara Therapeutics, Cassiopea, Dermata, Dermavant, Dermira, Eli Lilly and Company, Encore, EPI Health, Evommune, Ferndale, Galderma, Genentech, Incyte, Janssen, Jem Health, La Roche Posay, LEO Pharma, MC2, Mendera, Novan, Pfizer, Ralexar, Regeneron, Sanofi-Genzyme, Sente, Solgel, Sonoma (Intraderm), Sun Pharma, UCB, Verrica, and Vyne (Foamix/Menlo). P Kwong is an investigator for Eli Lilly and Company and has received consulting and/or speaker fees from AbbVie, Arcutis, Bristol Myers Squibb, Dermavant, Eli Lilly and Company, EPI Health, Galderma, Incyte, L'Oreal, Novan, Novartis, Ortho, Pfizer, Regeron/Sanofi Genzyme, Sun Pharm, and Verrica. I Hussain is a speaker for Grifols and Optinose, and an investigator for AbbVie, Eli Lilly and Company, Kymab, LEO Pharma, Novartis, Pfizer, Regeneron, and Sanofi. S Barbarot is an investigator or speaker for AbbVie, Almirall, AstraZeneca, Chiesi, Eli Lilly and Company, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi-Genzyme, and UCB Pharma. JM Carrascosa is an investigator and/or has received consulting fees and/or speaker fees and/or has participated in steering committee from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Galderma, Janssen, LEO Pharma, Novartis, and Regeron/Sanofi Genzyme. MJ Rueda, AR Atwater, H Elmaraghy, L Sun, and CR Natalie are employees of Eli Lilly and Company. S Chen is an employee of Tigermed working on behalf of Eli Lilly and Company. S Weidinger is a speaker, advisory board member, and/or investigator for AbbVie, Almirall, Eli Lilly and Company, Kymab, LEO Pharma, Novartis, Pfizer, Regeneron, and Sanofi. He has received research grants from La Roche Posay, Pfizer, and Sanofi.
- This study was previously presented at the International Symposium on Atopic Dermatitis - 12th Georg Rajka International Symposium, 2022

This study was funded by Dermira, a wholly owned subsidiary of Eli Lilly and Company. Almirall, S.A. has licensed the rights to develop and commercialize lebrikizumab for the treatment of dermatology indications, including atopic dermatitis, in Europe. Lilly has exclusive rights for development and commercialization of lebrikizumab in the United States and the rest of the world outside of Europe.