Lebrikizumab, a High-Affinity IL-13 Inhibitor, Improves Clinical Manifestations in Moderate-to-Severe Atopic Dermatitis: Primary Results From a Randomized, Double-Blinded, Placebo-Controlled, Dose-Ranging, Phase 2b Study

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INTRODUCTION

- Moderate-to-severe atopic dermatitis (AD) is a prevalent, debilitating condition characterized by a broad range of clinical manifestations, including skin lesions and intense, persistent pruritus that can have a significant, multi-dimensional impact on quality of life[1,2]
- Interleukin (IL)-13 is a central pathogenic mediator driving multiple features of AD pathophysiology underlying the range of clinical manifestations[3-5]
- Lebrikizumab (LEB) is a novel, high-affinity monoclonal antibody targeting IL-13 that selectively prevents formation of the IL-13Rα1/IL-4Rα heterodimer receptor signaling complex while leaving endogenous regulation of IL-13 intact

OBJECTIVE

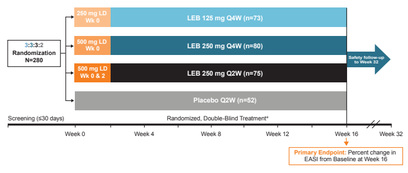
- To report the efficacy and safety of LEB from a randomized, double-blinded, placebo-controlled, dose-ranging, phase 2b study in adults with moderate-to-severe AD (NCT03443024)

METHODS

Study Design

- This phase 2b study consisted of a 16-week treatment period with 16-week safety follow-up (**Figure 1**)
- Patients were randomized 3:3:3:2 to subcutaneous LEB 125 mg every 4 weeks (Q4W; 250 mg loading dose [LD]), 250 mg Q4W (500 mg LD), 250 mg every 2 weeks (Q2W; 500 mg LD at Weeks 0 and 2), or placebo Q2W for 16 weeks
- Patients requiring rescue therapy were allowed to use topical corticosteroids (TCS) for as brief a period as possible and could remain in the study; those requiring systemic rescue therapy were discontinued

Figure 1. Study Design



*Patients were seen every two weeks and received all study drug injections in the clinic
EASI, Eczema Area and Severity Index; LD, loading dose; Q2W, every 2 weeks; Q4W, every 4 weeks; Wk, week

Study Patients

- Eligible patients were ≥18 years, with Eczema Area Severity Index (EASI) ≥16, Investigator's Global Assessment (IGA) score ≥3 (5-point scale), ≥10% body surface area (BSA) affected, and chronic AD for ≥1 year for which topical treatment provided inadequate control or was medically inadvisable
- Patients were excluded for having had treatment with TCS or topical calcineurin inhibitors (TCI) within 1 week prior to Baseline
- Prior biologics were allowed if washout occurred as follows relative to Baseline: dupilumab within 3 months, cell-depleting (eg, rituximab) within 6 months, other biologics within 5 half-lives or 16 weeks, and investigational drug within 8 weeks or 5 half-lives

Efficacy and Safety Assessments

- The primary endpoint was percent change in EASI from Baseline at Week 16
- Secondary endpoints included proportion of patients achieving EASI50, EASI75, EASI90, IGA score of 0 or 1 (IGA 0/1), pruritus numeric rating scale (NRS; 11-point scale [0 to 10]) change ≥4 points, and percent change in pruritus NRS from Baseline at Week 16
- Visits occurred biweekly through Week 16, and at Weeks 20 and 24; a safety follow-up visit occurred at Week 24, with telephone follow-up at Week 32; safety assessments included treatment-emergent adverse events (TEAEs)

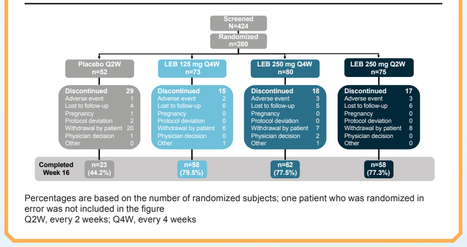
Statistical Analyses

- Efficacy analyses used the modified intent-to-treat (mITT) population (all patients who were randomized and received study drug)
- Safety analyses used the safety population (those randomized who received ≥1 dose of study drug)
- Missing data through Week 16 were imputed using Markov chain Monte Carlo (MCMC) multiple imputation, with no imputation for missing pruritus data (prespecified)
  - Data for patients requiring topical rescue were included if available; data for those requiring systemic rescue were considered missing from the time of withdrawal
  - A post hoc analysis was performed for pruritus, whereby missing data were imputed using MCMC imputation
- Statistical comparisons were performed between LEB and placebo (and not between LEB groups)

RESULTS

- A total of 73, 80, 75, and 52 patients were randomized to LEB 125 mg Q4W, 250 mg Q4W, 250 mg Q2W, and placebo, respectively
- Week 16 completion rates were similar across all LEB groups and greater than placebo (**Figure 2**)

Figure 2. Patient Disposition



Percentages are based on the number of randomized subjects; one patient who was randomized in error was not included in the figure
Q2W, every 2 weeks; Q4W, every 4 weeks

- Patient demographics and Baseline disease characteristics were well matched across groups (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics (mITT Population)

	Placebo Q2W n=52	LEB 125 mg Q4W n=73	LEB 250 mg Q4W n=80	LEB 250 mg Q2W n=75
Baseline Demographics				
Age, mean (SD), years	42.2 (18.2)	36.7 (16.5)	40.2 (17.9)	38.9 (17.4)
Male, no. (%)	28 (53.8)	27 (37.0)	33 (41.3)	26 (34.7)
Race, no. (%)				
White	26 (50.0)	37 (50.7)	42 (52.5)	40 (53.3)
Black or African American	16 (30.8)	26 (35.6)	28 (35.0)	23 (30.7)
American Indian or Alaska Native	0	1 (1.4)	1 (1.3)	1 (1.3)
Asian	6 (11.5)	8 (11.0)	7 (8.8)	6 (8.0)
Multiple/Other	4 (7.7)	1 (1.4)	2 (2.5)	5 (6.7)
Body mass index, mean (SD), kg/m²	29.7 (8.0)	30.1 (7.7)	29.2 (6.9)	28.1 (6.4)
Baseline Disease Characteristics				
Disease duration, mean (SD), years	24.4 (17.4)	22.8 (15.4)	23.3 (16.7)[b]	22.1 (17.2)
EASI, mean (SD)	28.9 (11.8)	29.9 (13.5)	26.2 (10.1)	25.5 (11.2)
IGA, no. (%)				
3, moderate	32 (61.5)	43 (58.9)	54 (67.5)	53 (70.7)
4, severe	20 (38.5)	30 (41.1)	26 (32.5)	22 (29.3)
BSA involvement, mean (SD), percent	46.5 (22.7)	45.5 (24.5)	41.1 (20.9)	39.4 (21.5)
Pruritus NRS score,[a] mean (SD)	7.4 (2.4)	7.6 (2.0)	7.1 (2.4)	7.6 (1.9)

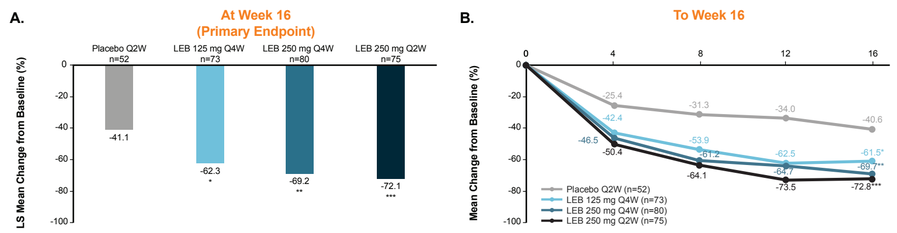
[a]Placebo Q2W, n=49; LEB 125 mg Q4W, n=68; LEB 250 mg Q4W, n=77; LEB 250 mg Q2W, n=69; [b]n=79
Percentages are based on the number of patients in the modified intent-to-treat (mITT) population with a non-missing response
BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment (5-point scale); NRS, numeric rating scale; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation

- Rescue medication was infrequently required in LEB-treated patients (LEB 125 mg Q4W: 12.3%; 250 mg Q4W: 12.5%; 250 mg Q2W: 13.3%; placebo: 34.6%)
- Topical medication was used by 28.8% of placebo- versus 12.3%, 3.8%, and 8.0% of LEB 125 mg Q4W, 250 mg Q4W, and 250 mg Q2W-treated patients, respectively
- Mean duration of topical medication use was 8 days for placebo versus 4.9, 1.0, 2.5 days for LEB 125 mg Q4W, 250 mg Q4W, and 250 mg Q2W, respectively
- These findings suggest that TCS use would not have confounded study results

Primary Endpoint

- All LEB groups showed dose-dependent, statistically significant improvement in the primary endpoint versus placebo at Week 16 (least squares mean percent change in EASI: LEB 125 mg Q4W [-62.3%; *P*<0.05], 250 mg Q4W [-69.2%, *P*<0.01], 250 mg Q2W [-72.1%, *P*<0.001] versus placebo [41.1%]; (**Figure 3**)

Figure 3. Percent Change in EASI (mITT Population)

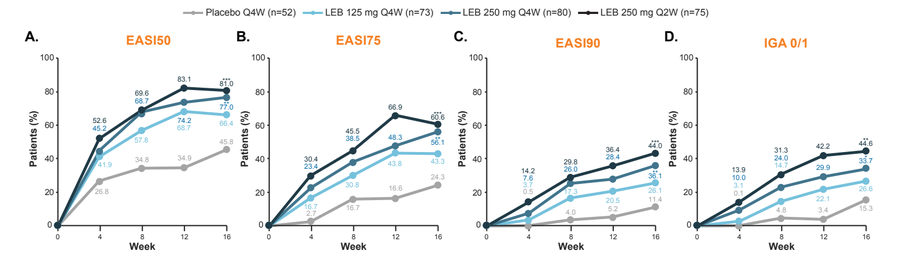


*P<0.05, **P<0.01, and ***P<0.001 versus placebo from least squares mean values and an analysis of covariance with a factor of treatment group and corresponding Baseline EASI score as a covariate; statistical comparison at Week 16 only
Post-Baseline up through Week 16 visit summary statistics represent average values, obtained by averaging the summary statistics generated from each imputed dataset
EASI, Eczema Area and Severity Index; LS, least squares; Q2W, every 2 weeks; Q4W, every 4 weeks

Secondary Endpoints

- A greater proportion of LEB- versus placebo-treated patients achieved EASI50, EASI75, EASI90, and IGA 0/1 at Week 16, with statistically significant improvements seen with LEB 250 mg Q2W and Q4W (**Figure 4**)

Figure 4. Secondary Endpoints To Week 16 (mITT Population)

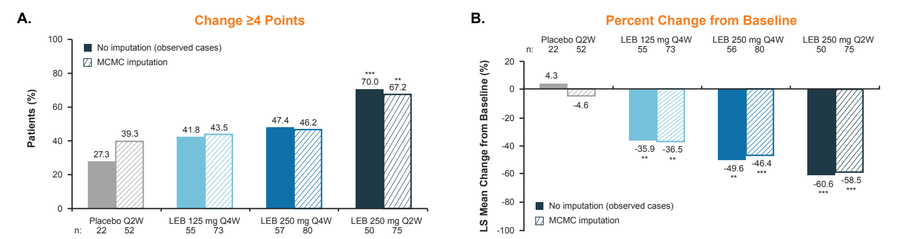


*P<0.05, **P<0.01, and ***P<0.001 versus placebo from pairwise Cochran-Mantel-Haenszel tests
Post-Baseline up through the Week 16 visit summary statistics represent average values, obtained by averaging the summary statistics generated from each imputed dataset
EASI50/75/90, ≥50%/75%/90% improvement from Baseline in Eczema Area and Severity Index; IGA 0/1, score of 0 'clear' or 1 'almost clear' in investigator global assessment (5-point scale) from Baseline; Q2W, every 2 weeks; Q4W, every 4 weeks

Patient-Assessed Pruritus

- A greater proportion of LEB- versus placebo-treated patients achieved pruritus NRS change ≥4 points at Week 16; dose-dependent, statistically significant improvement was also seen in LEB- versus placebo-treated patients for the least squares mean percent change in pruritus NRS from Baseline (**Figure 5**)

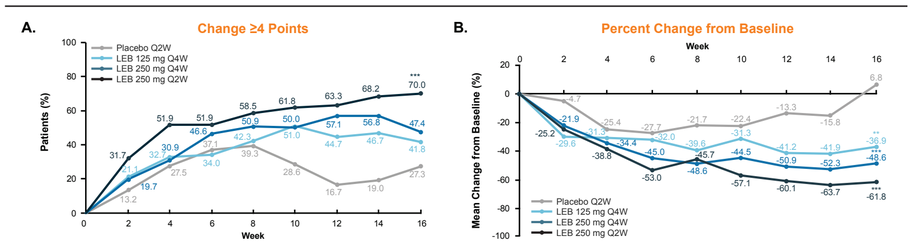
Figure 5. Pruritus NRS At Week 16 (mITT Population)



**P<0.01 and ***P<0.001 versus placebo; panel A: from pairwise Cochran-Mantel-Haenszel tests; panel B: from an analysis of covariance with a factor of treatment group and corresponding Baseline pruritus NRS as the covariate
LS, least squares; MCMC, Markov chain Monte Carlo; NRS, numeric rating scale; Q2W, every 2 weeks; Q4W, every 4 weeks

- Improvements in pruritus NRS were seen to Week 16 (**Figure 6**)

Figure 6. Pruritus NRS To Week 16 (mITT Population; Observed Cases)



**P<0.01 and ***P<0.001 versus placebo; panel A: from pairwise Cochran-Mantel-Haenszel tests; panel B: from LS mean and an analysis of covariance with a factor of treatment group and corresponding Baseline pruritus NRS as the covariate
Patient numbers fluctuate at each week as these are observed data
LS, least squares; NRS, numeric rating scale; Q2W, every 2 weeks; Q4W, every 4 weeks

- Differences in the proportions of patients achieving pruritus NRS change ≥4 points were seen by Day 2: 6.3%, 5.6%, 15.3% of LEB 125 mg Q4W, 250 mg Q4W, 250 mg Q2W versus 4.5% of placebo-treated patients, respectively

Safety

- TEAEs were reported in 57.5%, 48.8%, 61.3% of LEB 125 mg Q4W, 250 mg Q4W, 250 mg Q2W versus 46.2% of placebo-treated patients, respectively (**Table 2**); most were mild or moderate in severity and did not lead to discontinuation
- Rates of serious TEAEs were low in all treatment groups, and none were related to treatment
- TEAEs reported in ≥5% in any LEB group were upper respiratory tract infection, nasopharyngitis, fatigue, headache, and injection site pain
- Low rates of conjunctivitis were observed across doses: 1.4%, 3.8%, 2.7% of LEB 125 mg Q4W, 250 mg Q4W, 250 mg Q2W versus 0% of placebo-treated patients, respectively
- A similar rate of herpes infections was reported in LEB groups versus placebo: 2.7%, 5.0%, 2.7% of LEB 125 mg Q4W, 250 mg Q4W, 250 mg Q2W versus 3.8% of placebo-treated patients, respectively

Table 2. Summary of Treatment-Emergent Adverse Events (Safety Population)

	Placebo Q2W n=52	LEB 125 mg Q4W n=73	LEB 250 mg Q4W n=80	LEB 250 mg Q2W n=75
Patients reporting ≥1 TEAE, n (%)	24 (46.2)	42 (57.5)	39 (48.8)	46 (61.3)
Patients reporting ≥1 serious TEAE , n (%)	2 (3.8)	2 (2.7)	0	2 (2.7)
Number of serious TEAEs, no.	3	2	0	2
Deaths, n (%)	0	0	0	0
Patients who discontinued study due to TEAE, n (%)	1 (1.9)	2 (2.7)	4 (5.0)	3 (4.0)
Common TEAEs reported in ≥5% in any LEB treatment group,[a] n (%)				
Upper respiratory tract infection	3 (5.8)	6 (8.2)	9 (11.3)	2 (2.7)
Nasopharyngitis	2 (3.8)	4 (5.5)	2 (2.5)	9 (12.0)
Headache	3 (5.8)	3 (4.1)	1 (1.3)	4 (5.3)
Injection site pain	1 (1.9)	0	3 (3.8)	4 (5.3)
Fatigue	0	0	4 (5.0)	0
TEAEs of clinical interest, n (%)				
Injection site reactions[b]	1 (1.9)	2 (2.7)	4 (5.0)	7 (9.3)
Herpes viral infections[c]	2 (3.8)	2 (2.7)	4 (5.0)	2 (2.7)
Conjunctivitis[d]	0	1 (1.4)	3 (3.8)	2 (2.7)

[a]MedDRA Version 20.1 preferred terms; [b]Includes MedDRA preferred terms for injection site-related AEs, including injection site pain, erythema, pruritus, edema, swelling, rash, dermatitis, infection, and reaction; [c]Includes MedDRA preferred terms oral herpes, herpes zoster, genital herpes, herpes simplex, and eczema herpeticum; [d]Includes MedDRA preferred terms conjunctivitis, conjunctivitis bacterial, and conjunctivitis allergic
TEAEs are those with an onset on or after the date of first study drug injection; patients may have reported ≥1 preferred term
Q2W, every 2 weeks; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event

CONCLUSIONS

- In this phase 2b, placebo-controlled study, all LEB groups showed dose-dependent and statistically significant improvement in the primary endpoint (percent change in EASI from Baseline at Week 16)
- LEB demonstrated a dose-dependent response across all endpoints measured, with marked improvement at both 250 mg Q2W and Q4W doses; for skin symptoms, an effect was seen at Week 4
- Effects on itch were observed as early as Day 2 in patients who received a 500 mg loading dose at Day 0
- LEB was well tolerated, and consistent with previous studies, TEAE rates were low; across all LEB AD studies,[6] conjunctivitis has been reported at low rates similar to those in patients receiving placebo
- These data highlight that selective blockade of IL-13 with LEB leads to improvements in key AD clinical severity scores and pruritus while maintaining a favorable safety profile

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