Impact of Lebrikizumab on Patient-Reported Outcomes in Atopic Dermatitis: Prospective and Post Hoc Analyses of a Phase 2b Clinical Trial Demonstrate Clinically Meaningful Improvements

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SYNOPSIS

- Atopic dermatitis (AD) is associated with higher rates of anxiety and depression, likely due to a number of contributing factors such as intense itching, disrupted sleep, stigma, increased healthcare costs, and a decreased quality of life[1]
- 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
- In a randomized, double-blinded, placebo-controlled, dose-ranging, phase 2b study of LEB in patients with moderate-to-severe AD (NCT03443024),[2] LEB demonstrated dose-dependent, statistically significant improvement in the primary endpoint (percent change from Baseline to Week 16 in Eczema Area and Severity Index [EASI]), along with a favorable safety profile

OBJECTIVE

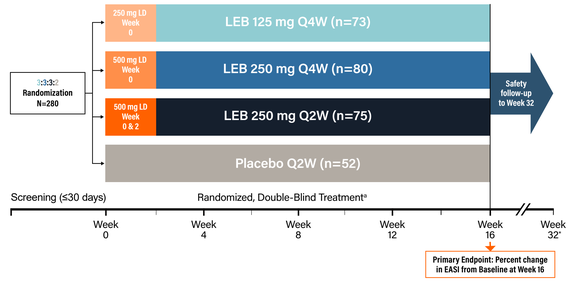
- Because patient-reported outcomes have proven to be valuable measures of treatment effect in AD, the objective here was to evaluate the impact of LEB on patient-reported outcomes, including those for anxiety and depression, using data from the phase 2b study of LEB in adult patients with moderate-to-severe AD

METHODS

Study Design

- This phase 2b study consisted of a 16-week treatment period with a 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 for as brief a period as necessary and could remain in the study; those requiring systemic rescue therapy were discontinued

Figure 1. Study Design



[a]Patients were seen every two weeks and received all study drug injections in the clinic.
*Follow-up safety visit at Week 24 and a follow-up phone call at Week 32; off-treatment results for select efficacy assessments were collected at Week 20 and Week 24
EASI, Eczema Area and Severity Index; LD, loading dose; LEB, lebrikizumab; Q2W, every 2 weeks; Q4W, every 4 weeks; Wk, week

Efficacy and Patient-Reported Outcomes Assessments

- The primary endpoint was percent change in EASI from Baseline at Week 16
- Key secondary endpoints included patient-reported outcomes:
  - Pruritus numeric rating scale (NRS) ≥4-point improvement and percent change from Baseline at Week 16
  - Sleep-loss NRS percent change from Baseline at Week 16
  - Patient-Oriented Eczema Measure (POEM) change from Baseline at Week 16
  - Dermatology Life Quality Index (DLQI) 0 or 1 (no impact of AD on QoL) and change from Baseline at Week 8 and Week 16
- Post hoc analyses evaluated Hospital Anxiety and Depression Scale (HADS) total score change from Baseline at Week 16

Statistical Analyses

- Analyses used the modified intention-to-treat (mITT) population (all patients who were randomized and received study drug)
- Missing data through Week 16 were imputed using Markov chain Monte Carlo (MCMC) multiple imputation for efficacy data
- There was no imputation of missing data for patient-reported outcomes

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 (77.3%-79.5%) and greater than placebo (44.2%)
- Rescue medication use was almost 3-fold higher in LEB-treated patients vs. placebo-treated patients: 12.3%, 12.5%, and 13.3% for LEB 125 mg Q4W, 250 mg Q4W, 250 mg Q2W, respectively, vs. 34.6% for placebo
- Patient demographics and baseline disease characteristics were well matched across groups (**Table 1**)

Table 1. Demographics and Baseline Characteristics

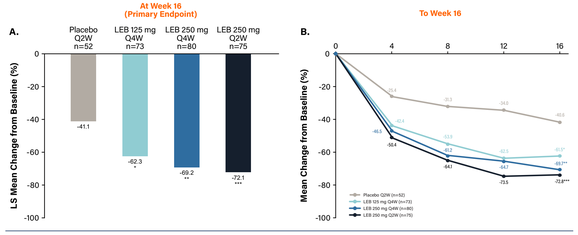
	Placebo Q2W n=52	LEB 125 mg Q4W n=73	LEB 250 mg Q4W n=80	LEB 250 mg Q2W n=75
Baseline Demographics				
Age, mean (SD), years	42.2 (18.2)	36.7 (16.5)	40.2 (17.9)	38.9 (17.4)
Male, no. (%)	28 (53.8)	27 (37.0)	33 (41.3)	26 (34.7)
Race, no. (%)				
White	26 (50.0)	37 (50.7)	42 (52.5)	40 (53.3)
Black or African 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)
Baseline Disease Characteristics				
Disease duration, mean (SD), years	24.4 (17.4)	22.8 (15.4)	23.3 (16.7)[a]	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, mean (SD)[b]	7.4 (2.4)	7.6 (2.0)	7.1 (2.4)	7.6 (1.9)
Sleep-loss NRS score, mean (SD)[c]	1.8 (1.2)	2.1 (1.0)	2.0 (1.2)	2.2 (1.2)
POEM total score, mean (SD)	19.4 (6.8)	21.5 (5.7)[d]	19.9 (6.7)	20.4 (5.7)
DLQI, mean (SD)	14.1 (7.1)	14.5 (7.1)[d]	14.2 (7.7)	14.1 (6.9)
HADS total score, mean (SD)	13.6 (8.0)	12.7 (8.0)	13.5 (8.9)	12.5 (7.8)

[a]Sample size is n=79; [b]Sample sizes are as follows: n=49 for placebo and n=68, n=77, and n=69 for the 3 LEB groups, respectively
[c]Sample sizes are as follows: n=49 for placebo and n=68, n=77, and n=70 for the 3 LEB groups, respectively
[d]Sample size is n=72.
BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; LEB, lebrikizumab; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure.

Primary Endpoint

- All LEB groups showed dose-dependent, statistically significant improvement in the primary endpoint vs. 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%, $P<0.001$] vs. placebo [41.1%]) (**Figure 2A**)
  - Dose-dependent differences in mean percent change in the EASI were seen as early as the first visit (Week 4) (**Figure 2B**)

Figure 2. Percent Change in EASI

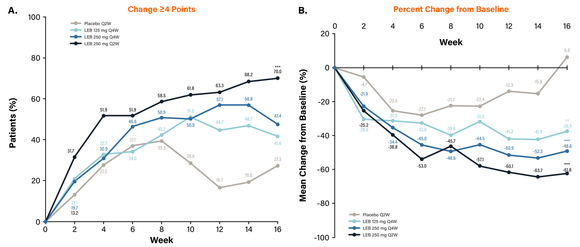


*P<0.05, **P<0.01, and ***P<0.001 vs. placebo from least squares mean values and an analysis of covariance with a factor of treatment group and corresponding Baseline EASI as a covariate; statistical comparison at Week 16 only.
Post-Baseline up through Week 16 visit summary statistics represent average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

Patient-Reported Outcomes

- LEB-treated patients showed a numerically greater reduction in pruritus NRS by Day 2 vs. placebo-treated patients, with further improvement across LEB arms vs. placebo to Week 16 as assessed by ≥4-point improvement or percent change from Baseline (**Figure 3**)
  - Differences in the proportions of patients achieving pruritus NRS change ≥4 points at Day 2: 6.3%, 5.6%, 15.3% of LEB 125 mg Q4W, 250 mg Q4W, 250 mg Q2W vs. 4.5% of placebo-treated patients, respectively

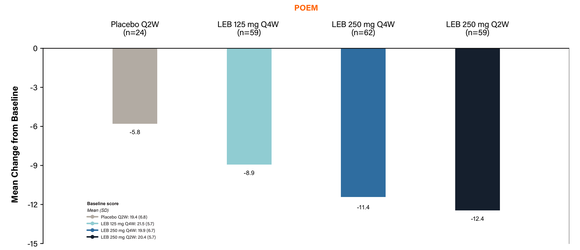
Figure 3. Lebrikizumab Improved Pruritus Through Week 16



**P<0.01 and ***P<0.001 vs. 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; statistical comparison at Week 16 only. Patient numbers fluctuate at each week as these are observed data.
LEB, lebrikizumab; LS, least squares; NRS, numeric rating scale; Q2W, every 2 weeks; Q4W, every 4 weeks.

- By Week 16, LEB-treated patients showed numerically greater improvements in disease severity vs. placebo as assessed by POEM change from Baseline (**Figure 4**)

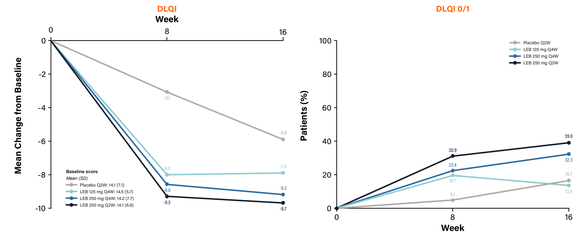
Figure 4. Lebrikizumab Improved Disease Severity at Week 16



mITT population; no imputations were made for missing data; responses of "not done" were not included in summaries; statistical comparisons were not performed.
LEB, lebrikizumab; mITT, modified intent-to-treat; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; Q4W, every 4 weeks.

- Reduction in sleep-loss was numerically greater in all LEB arms vs. placebo by Week 1, with further improvement to Week 16
  - Week 1 mean change from Baseline: LEB 125 mg Q4W (-15.7%), 250 mg Q4W (-9.5%), 250 mg Q2W (-32.0%) vs. placebo (-2.7%)
  - Week 16 mean change from Baseline:: LEB 125 mg Q4W (-48.7%, N.S.), 250 mg Q4W (-53.0%, $P<0.05$), 250 mg Q2W (-64.7%, $P<0.01$) vs. placebo (-20.2%)
- LEB-treated patients showed numerically greater improvements vs. placebo in DLQI change from Baseline and percentage of patients with DLQI 0/1 QoL at Week 8 and Week 16 (**Figure 5**)

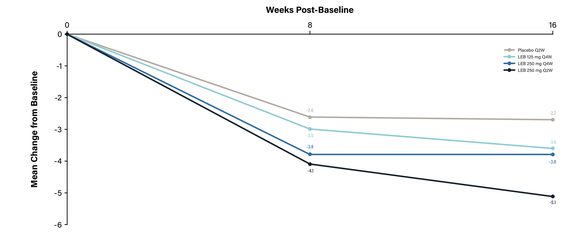
Figure 5. Lebrikizumab Improved Dermatology Health-Related QoL at Week 8 and Week 16



mITT population; no imputations were made for missing data; responses of "not done" were not included in summaries; statistical comparisons were not performed.
DLQI, Dermatology Life Quality Index; LEB, lebrikizumab; mITT, modified intention-to-treat; QoL, quality of life; Q2W, every 2 weeks; Q4W, every 4 weeks.

- Post hoc exploratory analyses showed a numerically greater improvement in HADS total score change from Baseline for LEB arms compared with placebo (**Figure 6**)

Figure 6. Lebrikizumab Improved Patient-Reported Anxiety and Depression (HADS Total Score at Week 8 and Week 16)



mITT population; no imputations were made for missing data; responses of "not done" were not included in summaries.
HADS, Hospital Anxiety and Depression Scale; LEB, lebrikizumab; mITT, modified intent-to-treat; Q2W, every 2 weeks; Q4W, every 4 weeks.

CONCLUSIONS

- In the 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)
- Selective blockade of IL-13 with LEB improved symptoms and QoL in a rapid, clinically-meaningful, dose-dependent manner compared to placebo across a range of AD-specific and other measures
  - Pruritus improved by Day 2 (≥4-pt improvement on pruritus NRS)
  - Disease severity improved at Week 16 (POEM)
  - Sleep improved by Week 1 with further improvement through Week 16 (Sleep-loss NRS)
  - Dermatology-related QoL improved by Week 8 (DLQI and DLQI 0/1)
  - Post hoc analyses showed a dose-dependent reduction in anxiety and depression with LEB compared to placebo as measured by HADS total score
- These data highlight that selective blockade of IL-13 with LEB leads to clinically-relevant improvements in AD symptoms and patient-reported outcomes

REFERENCES

1. Silverberg et al., *Br J Dermatol*., 2019;181:554-565.
2. Guttman-Yassky et al., *JAMA Derm*., 2020;156:411-420.

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