Atopic dermatitis (AD) is associated with higher rates of anxiety and depression, likely due to a number of contributing factors such as severe itching, chronic skin changes, widespread healthcare utilization, and a decreased quality of life. Lebrikizumab (LEB) is a novel, high-affinity monoclonal antibody targeting IL-4Rα that selectively prevents formation of the IL-4Rα/IL-13Rα2 heterodimer receptor, thus interfering with endogenous regulation of AD-related cytokine signaling.

**OBJECTIVE**

To evaluate safety, efficacy, and tolerability of LEB vs placebo in patients with moderate-to-severe AD.

**METHODS**

**Study Design**

• Phase 3 study consisting of a 12-week treatment period with a 16-week safety follow-up (Figure 1).

• Patients were randomized 3:0:3 to subcutaneous LEB 100 mg every 4 weeks (Q4W), 250 mg every 4 weeks (Q4W), 250 mg every 11 weeks (Q11W), 250 mg every 11 weeks (Q11W) for Week 1 and Q4W thereafter, or placebo (250 mg Q4W).

• Patients requiring rescue therapy were allowed to use topical corticosteroids for a limited period as necessary and concomitant in the Study. Those requiring systemic rescue therapy were discontinued.

**Efficacy and Patient-Reported Outcomes Assessments**

• The primary endpoint was percent change from Baseline at Week 16.

• Key secondary endpoints included patient-reported outcomes:
  - Physician’s Global Assessment (PGA) improvement from Baseline at Week 16
  - Sleep loss NRS percent change from Baseline at Week 16
  - Patient’s Global Assessment of Disease Improvement (PGADI) percent change from Baseline at Week 16
  - Dermatology Quality of Life Index (DLQI) 0-7 (≥5-point improvement from Baseline at Week 16)
  - Post hoc: evaluable Hospital Anxiety and Depression Scale (HADS) total score change from Baseline at Week 16

• Statistical Analyses:

  - Analysis was performed using an intent-to-treat (ITT) population, all patients who were randomized and received study drug.

  - Missing data from Week 16 were imputed using last observation carried forward (LOCF) or Markov chain Monte Carlo (MCMC) multiple imputation for efficacy data.

  - There was no imputation of missing data for patient-reported outcomes.

**RESULTS**

**Patient-Reported Outcomes**

- LEB-treated patients showed a numerically greater reduction in pruritus NRS by Day 3 vs placebo-treated patients, with further improvement across ADLQI vs placebo to Week 16 as assessed by improvement in percent change from Baseline (Figure 3).

- Improvement in the proportion of patients showing greater improvement in NRS change from Baseline at Day 3, 6, 9, 12, and 15% of LEB 125 mg Q4W, 250 mg Q4W and 4.6% of placebo-treated patients, respectively (Table 1).

**Table 1: Dermatological and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>LEB 125 mg Q4W</th>
<th>LEB 250 mg Q4W</th>
<th>LEB 250 mg Q11W</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>46.5</td>
<td>41.3</td>
<td>42.1</td>
<td>41.3</td>
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<tr>
<td>Sex (%)</td>
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<tr>
<td>Gender (%)</td>
<td>43.7</td>
<td>46.2</td>
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<tr>
<td>Race (%)</td>
<td>59.5</td>
<td>54.2</td>
<td>54.2</td>
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<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
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<tr>
<td><strong>Eczema</strong></td>
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<tr>
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<tr>
<td>EASI, mean</td>
<td>39.9</td>
<td>38.7</td>
<td>38.9</td>
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<tr>
<td>DLQI, median</td>
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<td>16.9</td>
<td>17.2</td>
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<tr>
<td><strong>Symptoms</strong></td>
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<tr>
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<td>Depression</td>
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</tbody>
</table>

**CONCLUSIONS**

- In this phase 3a pilot/proof-of-concept study, 12 LEB groups showed clinical improvement and statistically significant improvements in IGA and DLQI at Week 16 vs placebo.

- Selected biomarkers of 5-5 with LEB improved symptoms and QoL in a weak, clinically meaningful manner, supporting the potential for long-term clinical and cost savings.

- A robust improvement in DLQI by 45.6% at Week 16.

- Post hoc analyses showed a dose-dependent reduction in anxiety and depression (HADS QoL).

- These findings highlight the potential of LEB, with consistent efficacy and safety profiles.

**REFERENCES**

1. **Markov Chain Monte Carlo (MCMC)**: A statistical model that generates random samples from a probability distribution, useful for approximating posterior distributions in Bayesian inference.
2. **Hospital Anxiety and Depression Scale (HADS)**: A self-administered questionnaire used to assess anxiety and depression in medical patients.
3. **Post hoc analyses**:

  - Post hoc analyses are made after the completion of a study to further explore the data and answer questions that were not originally planned.

  - These analyses can provide additional insights but should be interpreted with caution as they may introduce bias or selectivity.

**ADJUANT TREATMENTS**

Treating atopic dermatitis, anxiety, depression, and sleep disorders improves patient outcomes and quality of life.

**FURTHER RESEARCH**

Further studies are needed to explore the full potential of LEB in treating AD and associated comorbidities.