A Phase 2b Dose-Ranging Efficacy and Safety Study of Tralokinumab in Adult Patients with Severe Atopic Dermatitis (AD)

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Introduction

• Novel, well-tolerated treatments that target the molecular pathways underlying atopic dermatitis (AD), rather than symptomatic relief, are needed
• Interleukin (IL)-13, a type 2 T helper cytokine, has been implicated in the pathophysiology of AD 10 and is reported to be upregulated in acute and chronic lesions. 11 Tralokinumab is an immunoglobulin G monoclonal antibody that potently and specifically neutralizes IL-13. 12,13 We report the findings from a Phase 2b study of tralokinumab in patients with moderate to severe AD
• Serum dipeptidyl peptidase 4 (DPP-4) has been reported as a predictive biomarker for tralokinumab efficacy in patients with severe AD

Methods

Study design
• This was a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study (NCT02347176) with a 12-week treatment period (Figure 1)
• Patients were randomized to receive tralokinumab (45, 150, or 300 mg) following a 2-week run-in period with Class 3 (mid-strength) topical corticosteroids (TCS; administered throughout the study) (Figure 1)

Assessments

Co-primary efficacy analyses (ITT [intention-to-treat] population)
• Change from baseline in total Eczema Area and Severity Index (EASI) at Week 12
• Percentage of Investigator’s Global Assessment (IGA) responders (patients achieving an IGA score of 0 or 1, and at least 2 grades reduction from baseline at Week 12)

Secondary analyses (ITT population)
• Change from baseline in Scoring of Atopic Dermatitis (SCORAD)
• Change from baseline in Pruritus numerical rating scale (NRS) (7-day mean score)
• Change from baseline in Dermatology Life Quality Index (DLQI)
• Percentage of patients achieving ≥50% reduction from baseline in EASI (EASI 50)
• Percentage of patients achieving ≥50% reduction from baseline in SCORAD (SCORAD 50)
• Staphylococcus aureus (S. aureus) colonization and infection were measured on lesional and non-lesional skin

Exploratory analysis (DPP-4 subpopulations)
• Primary endpoints were assessed in a subpopulation of patients with concentrations of DPP-4 equal to or above (DPP-4-high) or below (DPP-4-low) the total population median at baseline (Safety [as-treated population])
• Most frequent treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs)

Statistical analysis
• Continuous endpoints (change from baseline in EASI, SCORAD, pruritus NRS, and DLQI) were analyzed using repeated measures analysis, adjusting for baseline
• Binary endpoints (IGA 50, SCORAD 50, and SCORAD responders, and S. aureus status) were analyzed using logistic regression, adjusting for each baseline endpoint value
• Other endpoints were summarized descriptively

Results

• 204 patients were randomized to treatment and 172 (84.3%) completed the study (Figure 2)
• Demographics and baseline disease characteristics were similar between treatment groups (Table 1)

Figure 2. Patient disposition

Table 1. Demographics and baseline disease characteristics (ITT population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (N=33)</th>
<th>Placebo (N=33)</th>
<th>Placebo (N=33)</th>
<th>Placebo (N=33)</th>
<th>Placebo (N=33)</th>
<th>Placebo (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>25.4 (14.5)</td>
<td>25.3 (14.4)</td>
<td>25.4 (14.5)</td>
<td>25.3 (14.4)</td>
<td>25.4 (14.5)</td>
<td>25.3 (14.4)</td>
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<tr>
<td>Male, n (%)</td>
<td>20 (60.6)</td>
<td>19 (57.6)</td>
<td>20 (60.6)</td>
<td>19 (57.6)</td>
<td>20 (60.6)</td>
<td>19 (57.6)</td>
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<tr>
<td>Race, n (%)</td>
<td>Caucasian</td>
<td>30 (90.9)</td>
<td>30 (90.9)</td>
<td>30 (90.9)</td>
<td>30 (90.9)</td>
<td>30 (90.9)</td>
</tr>
<tr>
<td>Baseline EASI, mean (SD)</td>
<td>32.1 (23.1)</td>
<td>32.1 (23.1)</td>
<td>32.1 (23.1)</td>
<td>32.1 (23.1)</td>
<td>32.1 (23.1)</td>
<td>32.1 (23.1)</td>
</tr>
<tr>
<td>Baseline DLQI, mean (SD)</td>
<td>27.3 (10.9)</td>
<td>27.3 (10.9)</td>
<td>27.3 (10.9)</td>
<td>27.3 (10.9)</td>
<td>27.3 (10.9)</td>
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Efficacy

Primary analyses
• At Week 12, tralokinumab 150 mg and 300 mg significantly reduced total EASI from baseline (adjusted mean change [standard error]; SE) = -4.3 [1.1] and -4.9 [1.1] vs placebo (SE), respectively, compared with placebo (Figure 3A)

Figure 3. Adjusted mean change from baseline in EASI (A) and the percentage of patients with an IGA response at Week 12 (B) (ITT population)

Secondary analyses
• A significant decrease in SCORAD from baseline to Week 12 was demonstrated for tralokinumab 150 mg (p=0.003) and 300 mg (p=0.002), compared with placebo (Figure 4A)

Figure 4. Adjusted mean change from baseline in SCORAD (A), pruritus NRS (B), and DLQI (C) (ITT population)

Safety

• TEAEs and TESAEs are shown in Table 2

Table 2. TEAEs and TESAEs (As-treated population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (N=33)</th>
<th>Placebo (N=33)</th>
<th>Placebo (N=33)</th>
<th>Placebo (N=33)</th>
<th>Placebo (N=33)</th>
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<tbody>
<tr>
<td>Headache</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
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<tr>
<td>Nausea</td>
<td>2 (6.0)</td>
<td>2 (6.0)</td>
<td>2 (6.0)</td>
<td>2 (6.0)</td>
<td>2 (6.0)</td>
<td>2 (6.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
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</tbody>
</table>

Conclusions

• In this Phase 2b study of patients with moderate to severe AD symptoms (despite daily treatment with Class 3 or 4) tralokinumab demonstrated efficacy in the primary and key secondary endpoints, and an acceptable safety and tolerability profile, compared with placebo
• Furthermore, tralokinumab demonstrated significant improvements in quality of life (as shown by reduction in DLQI) and pruritus, compared with placebo
• Patients treated with tralokinumab 300 mg in the DPP-4-high subgroup demonstrated significant efficacy in both primary endpoints compared with placebo; the observed effect sizes were greater than in the ITT population, suggesting that DPP-4 may serve as a predictive biomarker for patients who may benefit from tralokinumab treatment
• However, treatment with Class 3 TCS may have impacted on efficacy effect sizes observed, providing a limitation to the study design
• These data suggest that targeting IL-13 is a promising approach for AD treatment. Clinical efficacy and dose response across a range of relevant endpoints supports the further evaluation of tralokinumab in this disease