Efficacy and Safety of Tralokinumab, an anti-IL-13 monoclonal antibody in a phase 2b study of uncontrolled severe asthma

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INTRODUCTION: Tralokinumab (CAT-354) is a human IgG4 monoclonal antibody that potently and specifically neutralizes interleukin-13 (IL-13). We tested the hypothesis that tralokinumab may show enhanced clinical activity in subjects with uncontrolled severe asthma and elevated IL-13 pathway activation.

METHODS: This double-blind phase 2b study (NCT01402986) enrolled adults with severe asthma, post-bronchodilator forced expiratory volume in 1 second (FEV₁) reversibility ≥12% and ≥200 mL within 3 years/at screening and ≥2 asthma exacerbations in the previous year. Subjects received fluticasone/salmeterol 500 µg/50 µg bid (or equivalent) and continued pre-study controller medications. Following 5-week run-in, subjects with FEV₁ 40–80% predicted or Asthma Control Questionnaire 6 (ACQ-6) score ≥1.5 were randomized to tralokinumab 300 mg/placebo (2:1) every 2 weeks (Q2W) or tralokinumab 300 mg/placebo (2:1) Q2W for 12 weeks followed by every 4 weeks (Q4W). The primary endpoint was asthma exacerbation rate (AER) over 52 weeks. Secondary endpoints included FEV₁, ACQ-6, Asthma Quality of Life Questionnaire (AQLQ), and safety. The trial was powered to detect a 40% reduction in AER for each tralokinumab group (Q2W or Q4W) vs. combined placebo groups with 80% power and significance level 0.15. Subjects with baseline FEV₁ reversibility ≥12% defined a “reversible” subgroup. Baseline levels of serum DPP4 and periostin, genes whose expression is highly induced by IL-13, were assessed as potential surrogate biomarkers with subgroups defined by median levels.

RESULTS: Analyses were based on intent-to-treat population (ITT, N=452). Baseline characteristics, mean (SD): age: 50.2 (12.3); ACQ-6: 2.55 (0.97); FEV₁ % predicted: 68.6 (18.1). AER at week 53 was similar in both tralokinumab groups vs. placebo. Trends towards AER reduction in Q2W were observed in reversible, periostin-high, and DPP4-high subgroups (Table). At week 53, a statistically significant increase in pre-bronchodilator FEV₁ was observed for Q2W and increases were evident in all subgroups. ACQ-6 and AQLQ were significantly different from placebo in the reversible and DPP4-high subgroups for Q2W. No significant differences vs. placebo were observed for secondary endpoints in Q4W group or subgroups. Frequencies of treatment emergent serious adverse events/adverse events were similar within the safety population (tralokinumab Q2W: 12.0/89.3%; Q4W: 16.6/84.8%; placebo: 13.9/84.8%).

CONCLUSIONS: AER reduction and improvement in markers of asthma control in subjects responsive to bronchodilators supports further development of tralokinumab 300 mg Q2W. Elevated levels of surrogate biomarkers may further optimize clinical benefits of tralokinumab.

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Table. Primary and secondary efficacy endpoints for tralokinumab 300 mg Q2W ITT and subgroups

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>ITT (N=150)</th>
<th>FEV₁ reversibility ≥12% (N=43)</th>
<th>Periostin Median (N=80)</th>
<th>DPP4 ≥ Median (N=77)</th>
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<tbody>
<tr>
<td>Asthma exacerbation rate</td>
<td>7% (-30%, 33%)</td>
<td>34% (-32%, 67%)</td>
<td>25% (-19%, 53%)</td>
<td>34% (-6%, 59%)</td>
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P=0.083
| reduction (95% CI) | $P = 0.669$ | $P = 0.245$ | $P = 0.219$ |