Assessing long-term maintenance of efficacy with tralokinumab monotherapy in patients with moderate-to-severe atopic dermatitis: combined results from two phase 3, randomized, double-blind, placebo-controlled trials (ECZTRA 1 and 2)

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Introduction
Atopic dermatitis (AD) is a chronic inflammatory skin disease, characterized by erythematous plaques, pruritus and dry skin, that affects up to 20% of adults and children globally. While AD is usually managed with topical corticosteroids (TCS) with variable response rates, an unmet need persists for a sustained treatment solution that addresses the challenges of intermittent treatment and the potential adverse effects associated with topical corticosteroids. Tralokinumab is a fully human, immunoglobulin G4 monoclonal antibody that specifically binds to IL-31 receptor alpha (IL-31Ra), a key mediator in the pathogenesis of AD, and is approved for the treatment of moderate to severe AD in the US and EU. This study evaluated the long-term efficacy and safety of tralokinumab monotherapy in patients with moderate-to-severe AD who had responded to tralokinumab during an initial treatment period (Week 16).

Objectives
The primary objectives of this study were to: 1) assess the long-term maintenance of efficacy with tralokinumab monotherapy in patients with moderate-to-severe AD who had responded to tralokinumab during an initial treatment period; 2) compare the long-term maintenance efficacy of tralokinumab 300 mg every 2 weeks (q2w) and every 4 weeks (q4w); and 3) evaluate safety in the long-term maintenance period. The secondary objectives included: 1) analyzing time to relapse following treatment discontinuation; 2) examining the long-term efficacy and safety of tralokinumab 300 mg q2w in patients who discontinued tralokinumab treatment after the Week 16 initial treatment period; and 3) assessing the long-term efficacy of tralokinumab treatment in patients who were re-randomized to receive tralokinumab for 52 weeks following an initial treatment period of 16 weeks.

Methods
Study Design and Patients
ECZTRA 1 (ClinicalTrials.gov Identifier: NCT03400658) and ECZTRA 2 (ClinicalTrials.gov Identifier: NCT03400712) were double-blind, randomized, placebo-controlled trials to evaluate the efficacy and safety of tralokinumab in AD. Patients were randomized 2:1 to receive tralokinumab 300 mg q2w or placebo (q2w/Placebo). Tralokinumab was administered subcutaneously at Weeks 0, 2, 4, 8, and every 2 weeks thereafter, with a maximum treatment duration of 52 weeks. Placebo patients who achieved an Investigator’s Global Assessment (IGA) score of 0 or 1 and/or Eczema Area and Severity Index (EASI) 75 at Week 16 (all without rescue medication) were transferred to open-label tralokinumab therapy (Tralokinumab 300 mg q2w). Patients with missing data were imputed as non-responders.

Patients, Demographics, and Clinical Characteristics
At Week 16, 124 patients (8.1%) did not achieve an IGA score of 0 or 1 and/or EASI 75 with tralokinumab q2w and were re-randomized to receive placebo (Placebo q2w). The median time to relapse was not reached for patients re-randomized to tralokinumab q2w or q4w. In patients who achieved EASI-75 with tralokinumab at Week 16 without rescue medication use, the probability of no relapse at 52 weeks was 42% (95% confidence interval [CI]: 30–51%) for the q2w group and 36% (95% CI: 24–48%) for the q4w group. The median time to relapse was 1.0 years (95% CI: 0.4–2.0) for the q2w group and 1.0 years (95% CI: 0.5–2.4) for the q4w group. The majority of patients who achieved IGA score 0 or 1 and/or EASI 75 at Week 16 (all without rescue medication) were women (63%) and white (91%). The mean age was 36 years (range: 18–75 years). The mean body surface area (BSA) was 0.44 square meters (range: 0.03–1.0 square meters).

Conclusions
A large proportion of patients who achieved EASI-75 with tralokinumab q2w during the initial treatment period maintained EASI-75 at Week 52 following 36 weeks of maintenance treatment with tralokinumab q2w with optional TCS. Patients who achieved an IGA score of 0 or 1 and/or EASI 75 at Week 16 and continued on open-label tralokinumab treatment plus optional topical corticosteroids (TCS) experienced the longest times to relapse during maintenance treatment. Patients who achieved an IGA score of 0 or 1 and/or EASI 75 at Week 16 without rescue medication use and continued on open-label tralokinumab treatment plus optional TCS maintained 100% response at Week 52. In patients who achieved EASI-75 with tralokinumab at Week 16 without rescue medication use, the median time to relapse was reached for patients re-randomized to placebo. In patients who discontinued tralokinumab treatment after the initial treatment period of 16 weeks, the median time to relapse was not reached for patients re-randomized to tralokinumab q2w or q4w. Safety was assessed in all patients who received at least one dose of maintenance treatment. The most common (≥10%) treatment-emergent adverse events were dryness, red or inflamed skin, and intense itching (mostly TCS) in patients who discontinued tralokinumab treatment after the initial treatment period (Week 16) and continued on open-label treatment. The safety profile of tralokinumab in the long-term maintenance period was similar to that observed in the initial treatment period. In conclusion, tralokinumab monotherapy was effective and safe for the long-term maintenance of patients with moderate-to-severe AD who had responded to tralokinumab during the initial treatment period. Future studies should evaluate the long-term efficacy of tralokinumab monotherapy in patients with extensive disease or those who are refractory to topical corticosteroids.