Efficacy and safety of tralokinumab plus concomitant topical corticosteroids in adult patients with moderate-to-severe atopic dermatitis: results from the 32-week, Phase 3 ECZTRA 3 trial

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Introduction

- Atopic dermatitis (AD) is a chronic inflammatory skin disease[1,2] characterized by eczematous lesions and multiple symptoms including pruritus, sleep disturbance, and depression.[3-5] The type 2 cytokine, interleukin (IL)-13, is a key driver of the underlying inflammation of AD and is overexpressed in lesional and non-lesional AD skin[6,7]
- Topical corticosteroids (TCS) are the current mainstay of therapy for AD, but TCS alone are often inadequate for the treatment of moderate-to-severe AD. In addition, prolonged use of TCS may cause unwanted adverse effects[8,9]
- Tralokinumab, a first-in-class, fully human monoclonal antibody, is designed to neutralize IL-13, specifically inhibiting downstream IL-13 signaling and thereby preventing pro-inflammatory activity[6,7,10]

Objective

- The objective of the ECZTRA 3 trial (NCT03363854) was to evaluate the efficacy and safety of tralokinumab in combination with TCS, compared with placebo in combination with TCS, in treating patients with moderate-to-severe AD for up to 32 weeks. The ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885) trials, described elsewhere, assessed tralokinumab monotherapy

Methods

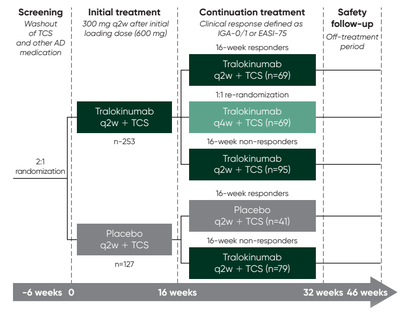
Patients

- Eligible patients were ⩾18 years of age with a confirmed diagnosis of AD for ⩾1 year and with an inadequate response to treatment with topical medications. Additional eligibility requirements included an AD body surface area involvement of ⩾10%, Eczema Area and Severity Index (EASI) of ⩾12 at screening and 16 at baseline, Investigator's Global Assessment (IGA) score of ⩾3, and worst daily pruritus Numeric Racing Scale (NRS) of ⩾4 prior to baseline

Study design

- Patients were randomized 2:1 to receive either subcutaneous tralokinumab 300 mg every 2 weeks (q2w) plus TCS or placebo q2w plus TCS over an initial treatment period of 16 weeks **(Figure 1)**

Figure 1. Study design of the ECZTRA 3 trial



- At 16 weeks, tralokinumab responders (defined as being IGA-0/1 and/or EASI-75 responders at week 16) were re-randomized 1:1 to continuation treatment with tralokinumab q2w or every 4 weeks (q4w) plus TCS for an additional 16 weeks. Placebo responders continued with placebo and al non-responders received tralokinumab q2w plus TCS for an additional 16 weeks

Endpoints

- Primary efficacy endpoints were an IGA score of 0 (clear) or 1 (almost clear) [IGA-0/1] and a 75% improvement in EASI (EASI-75), both at week 16
- Key secondary endpoints were change from baseline to week 16 in SCORing AD (SCORAD) score, reduction of worst daily pruritus NRS (weekly average) ⩾4, and Dermatology Life Quality Index (DLQI) score
- Continuation endpoints included IGA-0/1 at week 32 among patients with IGA-0/1 at week 16 and EASI-75 at week 32 among patients with EASI-75 at week 16, both after initial randomization to tralokinumab

Concomitant TCS use during ECZTRA 3

- TCS (mometasone furoate, 0.1% cream, 180–200 g. Europe: Class 3 [potent]; USA: Class 4 [midstrength]) was supplied proactively from randomization to the end of treatment
- A thin film of the dispensed mometasone was applied by the patient once daily to active lesions as needed and discontinued when control was achieved
- Lower-potency TCS or topical calcineurin inhibitor could be prescribed if needed on areas where the supplied TCS was not advisable or was considered unsafe

Safety

- Adverse events assessments were performed at baseline and at each visit

Statistical analyses

- Primary and key secondary endpoints for the initial 16-week treatment period were assessed using a hierarchical testing procedure and Holm–Bonferroni multiplicity adjustment
- IGA-0/1 and EASI-75 at week 32 were summarized using descriptive statistics

Results

Patient characteristics

- A total of 380 patients were randomized to receive either tralokinumab q2w plus TCS (n=253) or placebo q2w plus TCS (n=127) over the initial 16-week treatment period
- Baseline demographics and disease characteristics were similar across both treatment groups **(Table 1)**. Patients had a long duration of AD prior to being enrolled into the study, with nearly half of patients experiencing severe AD (IGA-4) at baseline

Table 1. Patient demographics and disease characteristics at baseline

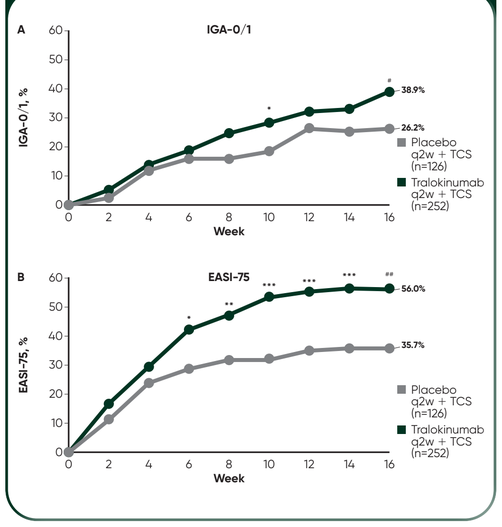
	Placebo q2w + TCS (n=127)	Tralokinumab q2w 1 TCS (n=253)
Mean age, years	**37.7**	**39.8**
Male, n (%)	84 (66)	125 (49)
Mean duration of AD, years	28.7	28.0
Region, %		
North America[a]	42.5	41.9
Europe[b]	57.5	58.1
Mean BSA involvement with AD, %	49.0	47.6
Severe disease (IGA-4), %	47	46
Mean EASI	30.4	28.8
Mean weekly average worst daily pruritus NRS score	7.9	7.7
Mean SCORAD	68.9	67.0
Mean DLQI	17.2	17.6

[a]Includes USA and Canada; [b]Includes Belgium, Germany, Netherlands, Poland, Spain, and UK.

Primary endpoints

- At week 16, more patients achieved an IGA-0/1 and EASI-75 with tralokinumab q2w plus TCS compared with placebo q2w plus TCS ($P<0.05$ and $P<0.001$, respectively) **(Figure 2)**

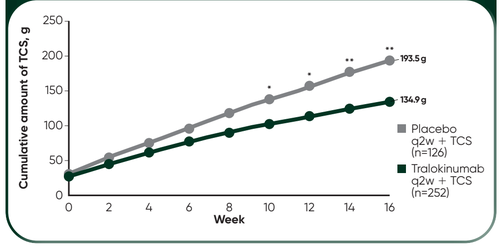
Figure 2. Proportion of patients receiving placebo q2w plus TCS or tralokinumab q2w plus TCS who achieved A an IGA score of 0 (clear) or 1 (almost clear) skin and B) a 75% improvement in EASI score over the 16-week initial treatment period



*$P<0.05$ versus placebo plus TCS; **$P<0.01$ versus placebo plus TCS; ***$P<0.001$ versus placebo plus TCS. Model-based treatment difference: #$P<0.05$ versus placebo plus TCS; ##$P<0.001$ versus placebo plus TCS. Composite estimand (primary analysis): patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.

- The cumulative amount of TCS used through to week 16 was lower with tralokinumab q2w plus TCS (134.9 g) compared with placebo q2w plus TCS (193.5 g; $P<0.01$) **(Figure 3)**
- Use of rescue treatment, which included higher potency TCS or systemic treatment for AD, was reported by 2.8% of patients in the tralokinumab q2w plus TCS group and 10.2% of those in the placebo q2w plus TCS group

Figure 3. The cumulative amount of TCS used through week 16

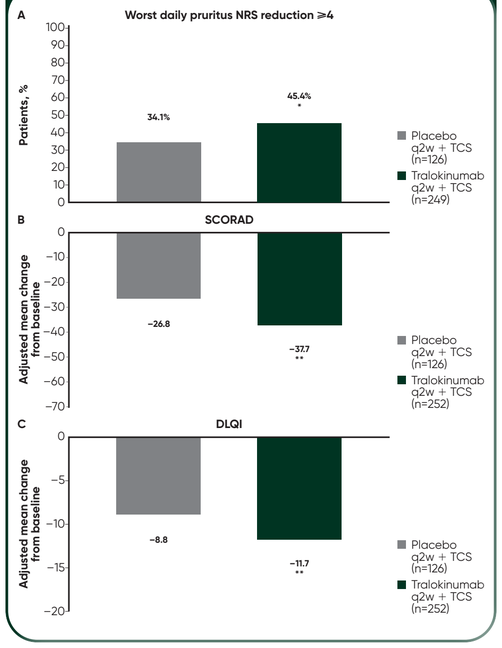


*$P<0.05$ versus placebo plus TCS; **$P<0.01$ versus placebo plus TCS.
Assuming no nonreturned tubes were used. Data collected after permanent discontinuation of investigational medicinal product or initiation of rescue medication not included. Repeated measurements model: TCS (g) = treatment*week + region + baseline IGA.

Secondary endpoints

- Tralokinumab q2w plus TCS significantly improved outcomes for all key secondary endpoints **(Figure 4)**
- A greater percentage of patients treated with tralokinumab q2w plus TCS had a reduction in worst daily pruritus NRS (weekly average) ⩾4 at week 16 compared with placebo q2w plus TCS ($P=0.037$) **(Figure 4a)**
- Patients treated with tralokinumab q2w plus TCS also had a greater mean change from baseline in SCORAD and DLQ compared with those who received placebo q2w plus TCS (both $P<0.001$) **(Figures 4b** and **4c)**

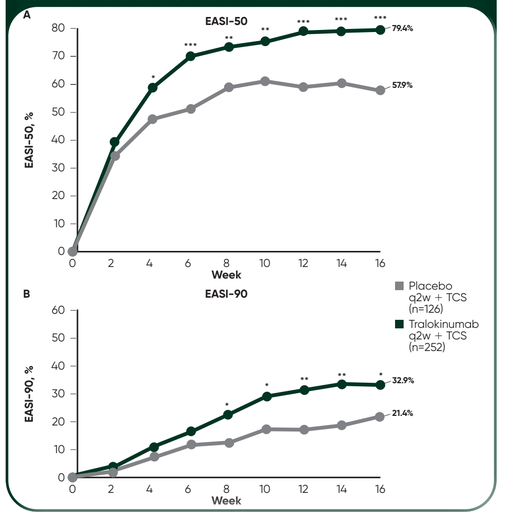
Figure 4. A) Percentage of patients with a reduction in worst daily pruritus NRS (weekly average) ⩾4, B) adjusted mean change from baseline in SCORAD, C) adjusted mean change from baseline in DLQI



*$P=0.037$ versus placebo q2w plus TCS; **$P<0.001$ versus placebo q2w plus TCS. [a]Data collected after permanent discontinuation of investigational medicinal product or initiation of rescue medication not included. Repeated measurements model on postbaseline data: Change = Treatment* Week + Baseline*Week + Region + Baseline IGA. In case of no postbaseline assessments before initiation of rescue medication, the week 2 change is imputed as 0; [b]Mean across multiple imputations where applicable. Patients who received rescue medication considered non-responders. Patients with missing data at week 16 imputed as non-responders. Single imputation analyses: Cochran–Mantel–Haenszel test, stratified by region and baseline IGA. Multiple imputation analyses: combined inference from multiple Mantel–Haenszel risk differences and associated SE. Number of patients (N) based on patients in full analysis set with a baseline pruritus NRS weekly average of at least 4.

- More patients treated with tralokinumab q2w plus TCS achieved the additional secondary endpoints of EASI-50 and EASI-90 at week 16 compared with those who received placebo q2w plus TCS **(Figure 5)**

Figure 5. The proportion of patients achieving the additional secondary endpoints at week 16: A) at least a 50% reduction in EASI score and B) at least a 90% reduction in EASI score

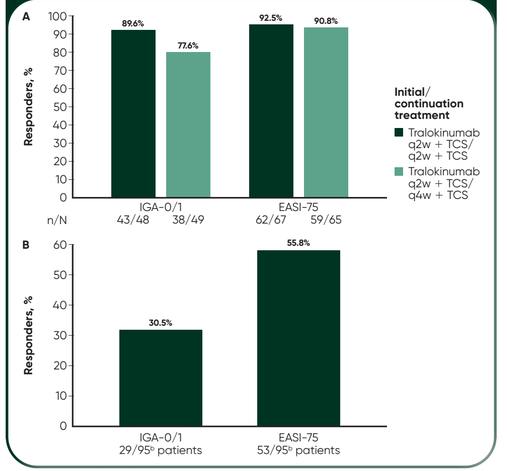


*$P<0.05$ versus placebo plus TCS; **$P<0.01$ versus placebo plus TCS; ***$P<0.001$ versus placebo plus TCS. Patients with missing data imputed as non-responders.

Continuation endpoints

- A clinical response with tralokinumab q2w plus TCS was maintained at week 32 in patients who achieved a response at week 16 **(Figure 6a)**
- Some patients who did not achieve IGA-0/1 or EASI-75 at week 16 were found to improve their IGA-0/1 or EASI-75 scores with continued tralokinumab q2w plus TCS treatment up to week 32 **(Figure 6b)**

Figure 6. Treatment response after continuation of treatment for a further 16 weeks: A) proportion of tralokinumab q2w plus TCS responders (IGA-0/1 and EASI-75) at week 16[a] who maintained their clinical response at week 32 when receiving tralokinumab q2w plus TCS or q4w plus TCS and B) proportion of patients who became IGA-0/1 or EASI-75 responders at week 32 after continued treatment with tralokinumab q2w plus TCS



[a]Analysis of patients who achieved a clinical response with tralokinumab q2w plus TCS at week 16 and were re-randomized to receive either tralokinumab q2w plus TCS or tralokinumab q4w plus TCS until week 32; [b]Of the 95 patients who received tralokinumab q2w plus TCS as initial treatment and were assigned to the tralokinumab non-responder group, seven were mis-assigned: one achieved EASI-75 and IGA-0/1, and six achieved EASI-75.

Safety

- Tralokinumab in combination with TCS was well tolerated in patients with moderate-to-severe AD **(Table 2)**
- The safety profile at week 32 was comparable with the initial 16-week treatment period
- Tralokinumab plus TCS was associated with lower rates of severe and serious infections and eczema herpeticum compared with placebo plus TCS
- All conjunctivitis cases in patients treated with tralokinumab plus TCS were mild or moderate, with only one case leading to treatment discontinuation

Table 2. Summary of adverse events in the initial 16-week treatment period

n (%), week 16	Placebo q2w 1 TCS (n=126)	Tralokinumab q2w 1 TCS (n=252)
At least one AE	84 (66.7)	180 (71.4)
At least one serious AE	4 (3.2)	2 (0.8)
AE leading to withdrawal from the trial	1 (0.8)	5 (2.0)
Frequent AEs (>5% in any treatment group)[a]		
Viral upper respiratory tract infection	14 (11.1)	49 (19.4)
Conjunctivitis	4 (3.2)	28 (11.1)
Upper respiratory tract infection	6 (4.8)	19 (7.5)
Injection site reaction	0	17 (6.7)
Atopic dermatitis	10 (79)	6 (2.4)
Headache	6 (4.8)	22 (8.7)

[a]Preferred terms according to Medical Dictionary for Regulatory Activities, version 20.0.

Conclusions

- All primary and secondary endpoints at week 16 demonstrated superiority of tralokinumab 300 mg q2w plus TCS compared with placebo q2w plus TCS
- Approximately 90% of patients treated with tralokinumab q2w plus TCS who responded at week 16 maintained their response at week 32 with tralokinumab q2w plus TCS
- Less frequent (q4w) dosing of tralokinumab could be appropriate in some patients
- Less TCS was used by tralokinumab-treated patients compared with those who received placebo through the initial 16-week treatment period
- Continued treatment with tralokinumab q2w plus TCS improved the initial response in many patients beyond 16 weeks
- The overall frequency of adverse events was comparable across treatment groups and did not increase with prolonged treatment

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Disclosures

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