Progressive and sustained improvements in the extent and severity of atopic dermatitis in patients with moderate-to-severe disease treated with tralokinumab in combination with topical corticosteroids as needed

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Background

- Atopic dermatitis is a chronic, inflammatory skin disease characterized by recurrent eczematous skin lesions[1]
- Interleukin 13 (IL-13) is a key driver of the underlying type 2 inflammation and skin barrier dysfunction in AD[2,3]
- Tralokinumab is a fully human immunoglobulin G4 monoclonal antibody that specifically binds to the IL-13 cytokine with high affinity, preventing interaction with the IL-13 receptor and subsequent downstream IL-13 signaling[2-4]
- The Phase 3 ECZTRA 3 (NCT03363854) trial evaluated the efficacy and safety of tralokinumab compared with placebo, in combination with topical corticosteroids (TCS) as needed, in patients with moderate-to-severe atopic dermatitis for up to 32 weeks[5]

Objective

- To assess the effects of tralokinumab plus TCS as needed on the extent and severity of atopic dermatitis over the 32-week treatment period

Methods

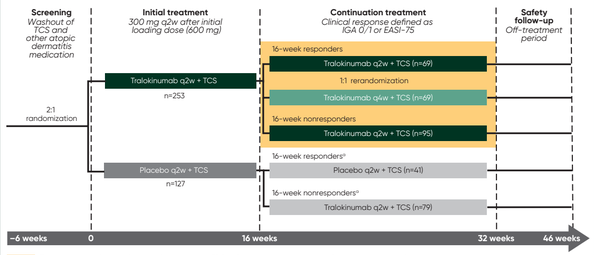
Patients

- Eligible patients were ⩾18 years of age with a confirmed diagnosis of atopic dermatitis for ⩾1 year, atopic dermatitis body surface area involvement of ⩾10%, an Eczema Area and Severity Index (EASI) score of ⩾12 at screening and ⩾16 at baseline, an Investigator's Global Assessment (IGA) score of ⩾3, and worst daily pruritus Numeric Rating 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 as needed or placebo q2w plus TCS as needed for an initial treatment period of 16 weeks **(Figure 1)**

Figure 1. ECZTRA 3 trial design



[a]To maintain blinding of the study, patients who achieved the clinical response criteria with placebo continued to receive placebo (q2w) and patients not achieving the clinical response criteria with placebo were assigned tralokinumab q2w plus TCS as needed. These patients were not included in analyses after Week 16.
EASI–75, at least 75% improvement in the Eczema Area and Severity Index; IGA 0/1, Investigator's Global Assessment score of 0 or 1; q2w, every 2 weeks; q4w, every 4 weeks; TCS, topical corticosteroids.

- TCS (180–200 g mometasone furoate 0.1% cream; Europe, Class 3 [potent]; USA, Class 4 [mid-strength]) was supplied free of charge by the sponsor from randomization to the end of treatment
- Patients were instructed to apply a thin film of the TCS once daily to active lesions as needed and discontinue when control was achieved
- Lower potency TCS or topical calcineurin inhibitors could be prescribed if needed on areas where the supplied TCS was not advisable or considered unsafe
- To allow for measurement of amount of TCS used, patients were instructed to return used and unused TCS tubes at each biweekly trial visit
- At Week 16, patients who achieved clinical response with tralokinumab (IGA score of 0 or 1 and/or 75% improvement in EASI [EASI–75]) were rerandomized 1:1 to tralokinumab q2w plus TCS or every 4 weeks (q4w) plus TCS for an additional 16 weeks
- Patients not achieving the clinical response criteria with tralokinumab received tralokinumab q2w plus TCS from Week 16

Endpoints

- EASI was assessed at baseline and at scheduled biweekly visits throughout the trial and was reported as mean change from baseline and as the proportion of patients achieving reductions in their EASI scores of at least 50% (EASI–50), at least 75% (EASI–75), and at least 90% (EASI–90)
- SCORing Atopic Dermatitis (SCORAD) was assessed at baseline and at scheduled biweekly visits throughout the trial
- Adverse events were assessed at baseline and at each visit

Statistical analysis

- Post hoc analyses of Weeks 16–32 data were conducted by pooling all patients who were randomized to tralokinumab in the initial treatment period, irrespective of tralokinumab dosing regimen beyond Week 16
- Statistical analyses followed prespecifications
- For binary endpoints, the difference in response rates between treatment groups during the initial treatment period were analyzed using the Cochran–Mantel–Haenszel test stratified by region and baseline disease severity
  - Patients with missing data or who received rescue medication prior to the Week 16 visit were imputed as nonresponders
- For continuous endpoints, change from baseline were analyzed using a repeated measurements model with an unstructured (compound symmetric when needed for convergence) covariance matrix and following model: Change from baseline = Treatment * Week + Baseline*Week + Region + Baseline IGA
  - Data collected after initiation of rescue medication or permanent discontinuation of investigational medicinal product were excluded from the analysis

Results

Patient characteristics

- In total, 380 patients were randomized in ECZTRA 3 to receive either tralokinumab q2w plus TCS (n=253) or placebo plus TCS (n=127) in the initial treatment period **(Table 1)**
  - Two patients did not receive a treatment dose and were not included in the analyses
- Overall, baseline demographics and disease characteristics were similar across both treatment groups

Table 1. Patient demographics and disease characteristics at baseline

Characteristic	Tralokinumab q2w + TCS (n=253)	Placebo q2w + TCS (n=127)
Mean age, years (SD)	39.8 (15.3)	37.7 (14.8)
Male, n (%)	125 (49)	84 (66)
Mean duration of atopic dermatitis, years (SD)	28.0 (16.5)	28.7 (15.0)
Mean affected BSA, % (SD)	47.6 (23.3)	49.0 (25.9)
IGA score of 4, %	45.8	47.2
Mean EASI score (SD)	28.8 (12.0)	30.4 (12.8)
Mean total SCORAD score (SD)	67.0 (13.3)	68.9 (13.2)
Mean weekly average worst daily pruritus NRS score (SD)	7.7 (1.5)	7.9 (1.5)

BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, Numeric Rating Scale; q2w, every 2 weeks; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; TCS, topical corticosteroids.

Improvement in the extent and severity of atopic dermatitis at Weeks 16 and 32

- A significantly greater proportion of patients achieved EASI–50, EASI–75, and EASI–90 with tralokinumab q2w plus TCS compared with placebo plus TCS at Week 16 **(Figure 2 and Table 2)**
- EASI–50 was achieved by 79.4% of patients treated with tralokinumab versus 57.9% of patients treated with placebo, equivalent to a treatment difference of 21.3% (95% confidence interval [CI] 11.3, 31.3; $P<0.001$) **(Figure 2A)**
  - EASI–50 response rate was sustained through Week 32, with 81% of patients treated with tralokinumab (204/252) demonstrating EASI–50 response at Week 32
- EASI–75 was achieved by 56% of patients treated with tralokinumab versus 35.7% of patients treated with placebo, equivalent to a treatment difference of 20.2% (95% CI 9.8, 30.6; $P<0.001$) **(Figure 2B)**
  - The EASI–75 response rate progressively increased to 69% (174/252) at Week 24 and was sustained through Week 32 (70.2%; 177/252) with tralokinumab

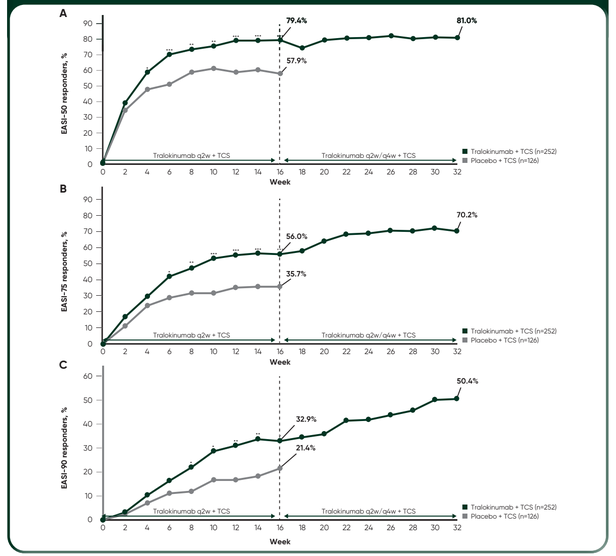
Table 2. The extent and severity outcomes of atopic dermatitis at Weeks 16 and 32

Outcome	Week 16		
	Tralokinumab q2w + TCS	Placebo q2w + TCS	Tralokinumab q2w/q4w + TCS
EASI–50 responders, n (%)	200/252 (79.4)	73/126 (57.9)	204/252 (81.0)
Difference vs placebo (95% CI); *P* value	21.3% (11.3, 31.3); P<0.001		
EASI–75 responders, n (%)	141/252 (56.0)	45/126 (35.7)	177/252 (70.2)
Difference vs placebo (95% CI); *P* value	20.2 (9.8, 30.6); P<0.001		
EASI–90 responders, n (%)	83/252 (32.9)	27/126 (21.4)	127/252 (50.4)
Difference vs placebo (95% CI); *P* value	11.4% (2.1, 20.7); P=0.022		
LS mean change vs baseline EASI score (SE)	-20.8 (0.7)	-15.4 (1.0)	-24.3 (0.4)
Difference vs placebo (95% CI); *P* value	-5.4 (-7.7, -3.0); P<0.001		
LS mean change vs baseline SCORAD score (SE)	-37.6 (1.2)	-26.7 (1.8)	-45.0 (1.0)
Difference vs placebo (95% CI); *P* value	-10.9 (-15.2, -6.6); P<0.001		

CI, confidence interval; EASI, Eczema Area Severity Index; LS, least square; q2w, every 2 weeks; q4w, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; SE, standard error; TCS, topical corticosteroids.

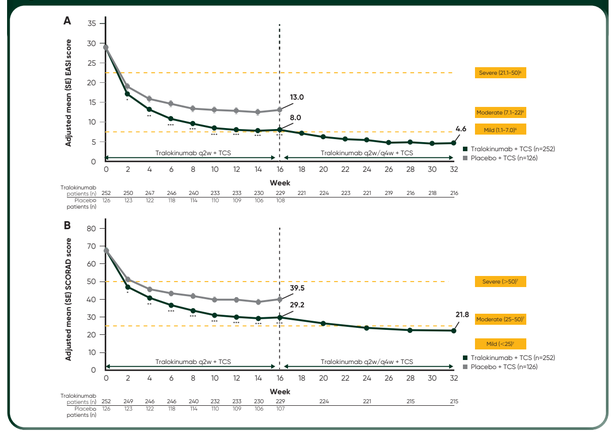
- EASI–90 was achieved by 32.9% of patients treated with tralokinumab versus 21.4% of patients treated with placebo at Week 16, equivalent to a treatment difference of 11.4% (95% CI 2.1, 20.7; P=0.022)
  - The EASI–90 response rate progressively increased to 50.4% (127/252) at Week 32 with tralokinumab **(Figure 2C)**
- Least square (LS) mean (standard error [SE]) EASI scores were reduced from 29.0 (0.5) at baseline to 8.0 (0.5) at Week 16 with tralokinumab q2w plus TCS (72% improvement) versus a LS mean of 13.0 (0.8) with placebo plus TCS at Week 16 **(Figure 3A)**
  - Treatment difference of –5.1 (95% CI –6.9, –3.2; $P<0.001$)
- LS mean (SE) SCORAD was reduced from 67.3 (1.0) at baseline to 29.2 (1.0) at Week 16 with tralokinumab q2w plus TCS (57% improvement) versus a LS mean of 39.5 (1.5) with placebo plus TCS at week 16 **(Figure 3B)**
  - Treatment difference of –10.3 (95% CI –13.8, –6.8; $P<0.001$)
- Continued treatment with tralokinumab plus TCS up to Week 32 further reduced LS mean (SE) EASI score to 4.6 (0.5) and LS mean (SE) SCORAD score to 21.8 (1.0), corresponding to LS mean changes from baseline of 84% and 68% for EASI and SCORAD, respectively, at Week 32 **(Figure 3)**

Figure 2. Proportion of patients achieving (A) EASI–50, (B) EASI–75, and (C) EASI–90 response from baseline to Week 32



Treatments were reassigned at Week 16, and the placebo arm was only followed up to Week 16. The tralokinumab arm was followed beyond Week 16 and the different dosing (q2w vs q4w) was ignored. Patients who received rescue medication were considered nonresponders. Patients with missing data were imputed as nonresponders. *P<0.05 vs placebo + TCS; **P<0.01 vs placebo + TCS; ***P<0.001 vs placebo + TCS. EASI, Eczema Area and Severity Index; EASI–50, at least 50% improvement in EASI; EASI–75, at least 75% improvement in EASI; EASI–90, at least 90% improvement in EASI; q2w, every 2 weeks; q4w, every 4 weeks; TCS, topical corticosteroids.

Figure 3. Mean (A) EASI and (B) SCORAD scores from baseline to Week 32



Treatments were reassigned at Week 16, and the placebo arm was only followed up to Week 16. The tralokinumab arm was followed beyond Week 16 and the different dosing (q2w vs q4w) was ignored. Data collected after discontinuation of IMP or initiation of rescue medication were not included. In case of no poststudyline assessment before initiation of rescue medication, the Week 2 change was imputed as 0. Repeated measurements model: Endpoint = Treatment*Week + Baseline*Week + Region + Baseline IGA. Compound symmetry was assumed for the covariance matrix.*P<0.05 vs placebo + TCS; **P<0.01 vs placebo + TCS; ***P<0.001 vs placebo + TCS. EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IMP, investigational medicinal product; q2w, every 2 weeks; q4w, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; SE, standard error; TCS, topical corticosteroids.

TCS use

- Cumulative TCS use at the end of the 16-week treatment period was lower in the tralokinumab group (mean [SE], 134.9 g [11.7]) compared with placebo (mean [SE], 193.5g [16.7]; P=0.004)
- Patients treated with tralokinumab used less TCS (mean [SE], 11.6g [1.57]) compared with patients treated with placebo (mean [SE], 20.2g [2.27]; P=0.002) at Weeks 15–16. Mean TCS (SE) use during Weeks 16–32 ranged from 9.2–13.6 g (1.2–2.0) every 2 weeks

Safety

- Tralokinumab plus TCS was well tolerated, with an overall safety profile comparable to that of placebo plus TCS in the initial 16-week treatment period **(Table 3)**
- 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
- The safety profile at Week 32 was comparable to that of the initial 16-week treatment period

Table 3. Summary of AEs in the initial 16-week treatment period

Week 16, n (%)	Tralokinumab q2w + TCS (n=252)	Placebo q2w + TCS (n=126)
At least one AE	180 (71.4)	84 (66.7)
At least one serious AE	2 (0.8)	4 (3.2)
AE leading to withdrawal from the trial	5 (2.0)	1 (0.8)
Frequent AEs (⩾5% in any treatment group)[a]		
Viral upper respiratory tract infection	49 (19.4)	14 (11.1)
Conjunctivitis	28 (11.1)	4 (3.2)
Upper respiratory tract infection	19 (7.5)	6 (4.8)
Injection site reaction	17 (6.7)	0
Atopic dermatitis	6 (2.4)	10 (7.9)
Headache	22 (8.7)	6 (4.8)

[a]Preferred terms according to Medical Dictionary for Regulatory Activities, version 20.0. AE, adverse event; q2w, every 2 weeks; TCS, topical corticosteroids.

Conclusions

- At Week 16, tralokinumab plus TCS provided significant improvements in the extent and severity of atopic dermatitis, and patients used approximately 50% less of the supplied TCS compared to placebo
- Approximately 80% of patients initiated on tralokinumab plus TCS as needed achieved a clinically meaningful response (EASI–50)[6] from Week 12 onward
- EASI–90 response rates continued to progressively improve over time, with 50% of patients treated with tralokinumab plus TCS achieving EASI–90 at Week 32
- At Week 32, mean EASI and SCORAD scores were reduced by 84% and 68%, respectively, equivalent to an improvement from severe disease at baseline to mild disease[6,7]
- Tralokinumab plus TCS as needed provided progressive and sustained improvements in the extent and severity of atopic dermatitis and was well tolerated in patients with moderate-to-severe atopic dermatitis over 32 weeks

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