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 is a chronic, type 2 inflammatory skin disease, characterized by excessive skin dryness, red or inflamed skin, and intense itching[1-3]
- Tralokinumab is a fully human, immunoglobulin G4 monoclonal antibody that specifically binds to and neutralizes interleukin (IL)-13, preventing receptor interaction and subsequent downstream signaling, thus inhibiting the pro-inflammatory activity of IL-13 in atopic dermatitis[4-8]
- Early improvements in disease severity and symptoms in adults with moderate-to-severe atopic dermatitis were observed in two pivotal Phase 3 clinical trials with tralokinumab monotherapy (ECZTRA 1 and 2)[9]
  - Significantly more patients receiving tralokinumab monotherapy achieved Investigator's Global Assessment (IGA) 0/1 and Eczema Area and Severity Index reduction of >75% (EASI-75) compared with placebo at Week 16
- There is a need for additional insight into dosing over time for atopic dermatitis treatments
  - In addition, reducing the dosing frequency of a long-term medication while maintaining efficacy may have positive implications for patient adherence and health care costs

Objectives

- To investigate the long-term efficacy beyond 16 weeks of tralokinumab monotherapy in adult patients with moderate-to-severe atopic dermatitis pooled from two Phase 3 trials, including:
  - The maintained efficacy in patients achieving an IGA score of 0 or 1 and/or EASI-75 at Week 16 and continuing with tralokinumab once every two weeks (q2w), once every 4 weeks (q4w), or placebo
- To monitor the clinical response in patients who did not achieve an IGA score of 0 or 1 (clear or almost clear skin) or EASI-75 at Week 16, who continued on open-label tralokinumab treatment plus optional topical corticosteroids (TCS)

Methods

Study Design and Patients

- ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885) were identically designed, multinational, double-blind, randomized, placebo-controlled, 52-week trials of tralokinumab monotherapy
- Patient eligibility criteria and stratification factors can be found in **Figure 1**
- At Week 16, tralokinumab responders (patients who achieved IGA 0/1 and/or EASI-75 with tralokinumab) were re-randomized 2:2:1 to maintenance treatment with tralokinumab 300 mg q2w or q4w, or placebo (in the primary analysis, patients who used rescue medication, including TCS, were considered to be non-responders)
- Patients who did not achieve IGA 0/1 and/or EASI-75 at week 16 were transferred to open-label treatment with tralokinumab 300 mg q2w, with optional use of TCS up to week 52

Analyses

- Maintenance of response (IGA 0/1, EASI-75, or both) was assessed at Week 52 in a prespecified pooled analysis
  - Difference in response rates was analyzed using the Cochran-Mantel-Haenszel test stratified by region (North America, Europe, Australia, and Asia) and patients who used rescue medication (mostly TCS) were considered non-responders
- Two post hoc analyses using Kaplan-Meier estimates assessed the time to relapse of IGA 0/1 and EASI-75 response during maintenance treatment
  - Relapse was defined as transfer to open-label treatment, rescue medication use, or discontinuation of treatment (due to lack of efficacy or adverse event [AE] or for other reasons, where lack of efficacy could not be excluded)
- Both time to IGA 0/1 or EASI-75 response in the open-label group was assessed using Aalen Johansen estimator of cumulative incidence for each response type

Safety

- AEs were assessed at each visit during both the initial 16-week treatment period and during the maintenance period

Results

Patients, Demographics, and Clinical Characteristics

- 1596 adult patients were randomized to tralokinumab 300 mg q2w (1196) or placebo (400) in the initial treatment period
- Baseline demographics and clinical characteristics were well balanced between treatment groups (**Table 1**)
  - Mean duration of atopic dermatitis was 28.2 years and around one-half of patients (49.7%) had IGA 4 (severe disease) at baseline

Table 1. Demographic and disease characteristics at baseline for all randomized patients in ECZTRA 1 and 2

Characteristic	All randomized (n=1596)	Tralokinumab q2w (n=1196)	Placebo (n=400)
Mean age, y (SD)	37.8 (14.4)	37.9 (14.2)	37.2 (14.8)
Male, n (%)	947 (59.3)	710 (59.4)	237 (59.3)
Region, n (%)			
North America	559 (35.0)	419 (35.0)	140 (35.0)
Europe	711 (44.5)	533 (44.6)	178 (44.5)
Australia	121 (7.6)	90 (7.5)	31 (7.8)
Asia	205 (12.8)	154 (12.9)	51 (12.8)
Mean affected BSA, % (SD)	52.9 (24.9)[a]	52.7 (24.8)	53.6 (25.3)[i]
Mean disease duration, y (SD)	28.2 (15.2)[b]	28.1 (15.2)[j]	28.5 (14.9)[l]
Severe disease (IGA 4), n (%)	794 (49.7)	591 (49.4)	203 (50.8)
Mean EASI (SD)	32.29 (13.97)[c]	32.15 (14.01)[g]	32.72 (13.86)[k]
Mean weekly average worst daily pruritus NRS (SD)	7.81 (1.43)[d]	7.79 (1.45)[h]	7.84 (1.37)[l]
Mean total SCORAD (SD)	70.39 (13.00)[c]	70.16 (13.19)[g]	71.07 (12.38)[k]
Mean DLQI (SD)	17.30 (7.08)[e]	17.25 (7.12)[j]	17.45 (6.98)[m]

[a]n=1595; [b]n=1594; [c]n=1590; [d]n=1577; [e]n=1572; [g]n=1195; [h]n=1192; [i]n=1182; [j]n=1178; [k]n=399; [l]n=398; [m]n=395; [n]n=394

BSA, body surface area; SD, standard deviation; IGA, Investigator's Global Assessment; EASI, Eczema Area Severity Index; NRS, Numeric Rating Scale; SCORAD, Scoring Atopic Dermatitis; DLQI, Disability Life Quality Index; q2w, every 2 weeks

Maintenance of Week 16 Responses at Week 52

- 412 patients achieved IGA 0/1 and/or EASI-75 at Week 16 with tralokinumab q2w and were re-randomized (2:2:1) to continue tralokinumab q2w, tralokinumab q4w, or placebo in the maintenance treatment period
- A large proportion of the patients who continued tralokinumab q2w or q4w maintained IGA 0/1 and/or EASI-75 response at Week 52 (42.4 to 57.3%), without using any rescue medication (including TCS) during the 36-week maintenance period
  - For patients with IGA 0/1 response at Week 16, this response was maintained by 55.9%, 42.4%, and 34.0% of patients re-randomized to tralokinumab q2w, q4w, and placebo, respectively (**Figure 2A**)
  - EASI-75 response was maintained by 57.3%, 50.4%, and 26.4%, respectively (**Figure 2B**)
  - IGA 0/1 or EASI-75 response was maintained by 56.2%, 50.0%, and 27.4% respectively, in patients who had previously achieved either or both responses (**Figure 2C**)

Time to Relapse

- In patients who achieved IGA 0/1 with tralokinumab at Week 16 without rescue medication use, median time to relapse was not reached for patients re-randomized to tralokinumab q2w or q4w
  - Relapse was defined as transfer to open-label treatment, first rescue medication, or discontinuation of investigational medicinal product due to lack of efficacy, AE, or for other reasons, where lack of efficacy could not be excluded
  - The log-rank test *P*-values that resulted from the comparison of each of the tralokinumab treatment groups with placebo were *P*=0.004 for the tralokinumab q2w group and *P*=0.14 for the q4w group (**Figure 3A**)
- In patients who achieved EASI-75 with tralokinumab at Week 16 without rescue medication use, median time to relapse was not reached for patients re-randomized to tralokinumab q2w or q4w
  - The log-rank test *P*-values that resulted from the comparison of each of the tralokinumab treatment groups with placebo were *P*=0.002 for the tralokinumab q2w group and *P*=0.044 for the q4w group (**Figure 3B**)

Safety

- Safety was assessed in all patients who received at least one dose of maintenance treatment
- The proportion of patients with one or more AE or serious AE was similar between the initial 16-week treatment period and the maintenance period (**Table 2**)
- The majority of AEs were mild or moderate in severity
- Withdrawal from the trial due to an AE only occurred only in a small number of patients

Table 2. Summary of AEs in the initial and maintenance treatment periods of ECZTRA 1 and 2

n (%)	Initial treatment period (baseline to Week 16)		Maintenance period (Weeks 16 to 52) Week 16 tralokinumab responders		
	Tralokinumab 300 mg q2w (n=1194)	Placebo (n=396)	Tralokinumab q2w to tralokinumab q2w (n=159)	Tralokinumab q2w to tralokinumab q4w (n=165)	Tralokinumab q2w to placebo (n=81)
≥1 AE	824 (69.0)	283 (71.5)	116 (73.0)	109 (66.1)	57 (70.4)
≥1 SAE	33 (2.8)	13 (3.3)	1 (0.6)	6 (3.6)	0 (0)
Severity					
Mild	673 (56.4)	204 (51.5)	102 (64.2)	94 (57.0)	44 (54.3)
Moderate	409 (34.3)	182 (46.0)	62 (39.0)	45 (27.3)	27 (33.3)
Severe	65 (5.4)	32 (8.1)	4 (2.5)	5 (3.0)	3 (3.7)
AE leading to withdrawal from trial	28 (2.3)	9 (2.3)	3 (1.9)	2 (1.2)	0 (0)

Further details of the AE profile in these populations have been reported previously.[9]
AE, adverse event; q2w, every 2 weeks; q4w, every 4 weeks; SAE, serious adverse event.

Conclusions

- A large proportion of initial IGA 0/1 or EASI-75 responders at Week 16 maintained response with continued tralokinumab q2w or q4w dosing during the 36-week maintenance period, without the use of rescue medication including TCS
- The time to relapse during the maintenance period was longer for both tralokinumab q2w and q4w patients, compared to patients re-randomized to placebo
  - Patients who achieved the very stringent target of IGA 0/1 had a robust response and experienced the longest times to relapse
  - A step down in tralokinumab dosage to q4w may be an option for some patients achieving clear or almost clear skin with initial q2w dosing
- A substantial proportion of patients not achieving EASI-75 or IGA-0/1 at Week 16 met these outcomes with continued tralokinumab q2w therapy beyond Week 16

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Disclosures

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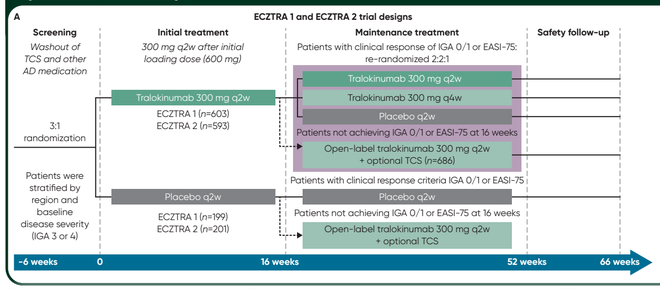
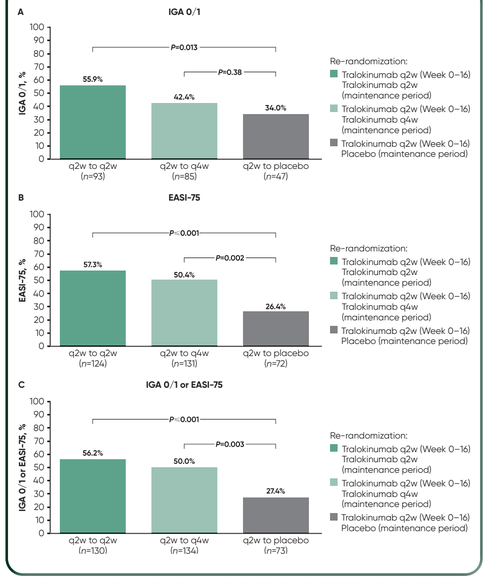
Figure 1. ECZTRA 1 and 2 trial designs



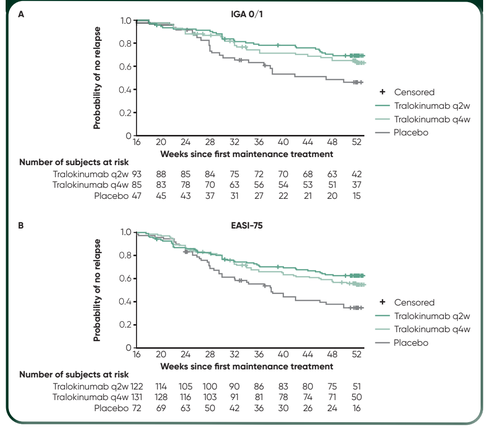
AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; q2w, every 2 weeks; q4w, every 4 weeks; TCS, topical corticosteroids.

Figure 2. Maintenance of Week 16 IGA 0/1 and EASI-75 responses at Week 52 without rescue medication



Analysis of patients who achieved a clinical response of (A) IGA 0/1 at Week 16, (B) EASI-75 at Week 16, (C) IGA 0/1 or EASI-75 at Week 16 (all without rescue medication), with tralokinumab q2w and were re-randomized to receive either tralokinumab q2w, tralokinumab q4w, or placebo until Week 52. Patients who received rescue medication or were transferred to open-label treatment considered non-responders. Patients with missing data were imputed as non-responders. Differences in response rates were analyzed using the Cochran-Mantel-Haenszel test stratified by region and study ID. EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; q2w, every 2 weeks; q4w, every 4 weeks.

Figure 3. Time to relapse during maintenance treatment in patients achieving (A) IGA 0/1 and (B) EASI-75 at Week 16

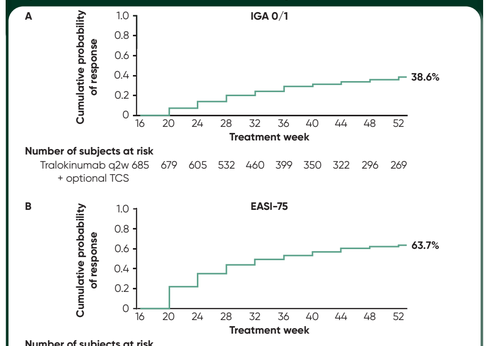


Analysis includes patients who achieved (A) IGA 0/1 or (B) EASI-75 at Week 16 without rescue medication use.
EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; q2w, every 2 weeks, q4w, every 4 weeks.

Time to Response (Open-Label Arm)

- At Week 16, 686 patients who did not achieve IGA 0/1 or EASI-75 with tralokinumab were transferred to open-label treatment with tralokinumab 300 mg q2w with optional TCS
- The probability of achieving IGA-0/1 and EASI-75 increased throughout the open-label treatment period (**Figure 4**)
  - Cumulative response rate based on time to first IGA 0/1 in 685 patients was 38.6% by Week 52
  - Cumulative response rate based on time to first EASI-75 response in 661 patients was 63.7%, by Week 52
  - The probability of achieving clinical response criteria was greater earlier in the open-label period

Figure 4. Time to IGA 0/1 (A) or EASI-75 (B) response during the open-label treatment period



Analysis includes patients who completed Week 16 on tralokinumab 300 mg q2w and transferred to open-label treatment with tralokinumab q2w plus optional TCS.
EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; q2w, every 2 weeks; q4w, every 4 weeks; TCS, topical corticosteroids.

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