Efficacy and safety of tralokinumab monotherapy in adult patients with moderate-to-severe atopic dermatitis: results from two 52-week, Phase 3 trials (ECZTRA 1 and ECZTRA 2)

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Introduction

- Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itch and eczematous lesions[1]
- The underlying pathophysiology of AD is a complex and multifaceted combination of skin barrier dysfunction and immune dysregulation, leading to chronic type 2 inflammation[2,3]
- Tralokinumab is a fully human monoclonal antibody designed to specifically neutralize interleukin (IL)-13, a key driver of the underlying inflammation in AD[4–8]
- The ECZTRA 1 and ECZTRA 2 studies were identically designed, multinational, double-blind, randomized, placebo-controlled, 52-week trials of tralokinumab monotherapy in more than 1500 patients with moderate-to-severe AD

Objectives

- The objectives of ECZTRA 1 (NCT03131648) and 2 (NCT03160885) were to evaluate the efficacy and safety of tralokinumab monotherapy compared with placebo in patients with moderate-to-severe AD for up to 1 year, as assessed by severity and extent of AD, itch, and health-related quality of life

Methods

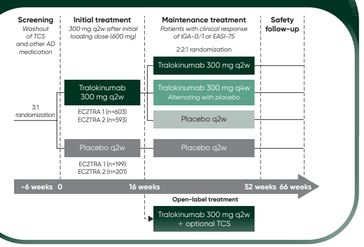
Patients

- Eligible patients were ⩾18 years of age, with a confirmed diagnosis of AD for ⩾1 year, and candidates for systemic therapy due to a recent (within 1 year) history of inadequate response to treatment with topical treatments or for whom topical treatments were medically inadvisable
- Rescue treatment for AD could be provided if medically necessary. However, patients who received rescue treatment were considered non-responders in the primary analyses

Study design

- Patients were randomly assigned 3:1 to receive either subcutaneous tralokinumab 300 mg or placebo every 2 weeks (q2w) for an initial treatment period of 16 weeks **(Figure 1)**

Figure 1. ECZTRA 1 and 2 trial design



- At 16 weeks, tralokinumab responders (Investigator's Global Assessment [IGA]–0/1 and/or Eczema Area and Severity Index [EASI]–75 were re-randomized 2:2:1 to receive tralokinumab 300mg q2w or every 4 weeks (q4w), or placebo, for an additional 36 weeks of maintenance treatment
- Non-responders at week 16 were transferred to open-label tralokinumab 300 mg q2w with optional use of topical corticosteroids (TCS) for an additional 36 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 Numeric Rating Scale (NRS) [weekly average] ⩾4 from baseline to week 16, and change from baseline to week 16 in Dermatology Life Quality Index (DLQI) score
- Maintenance endpoints were IGA–0/1 at week 52 among patients with IGA–0/1 at week 16, achieved without rescue medication, and EASI–75 at week 52 among patients with EASI–75 at week 16, achieved without rescue medication, both after initial randomization to tralokinumab
- Adverse events (AEs) were assessed at baseline and each subsequent visit

Statistical analysis

- To control for the overall type 1 error rate at a 5% significance level, a prespecified testing hierarchy was used for assessment of the primary, key secondary, and maintenance endpoints
- The primary analysis of the binary endpoints considered patients who received rescue medication (including TCS) and patients with missing data to be non-responders. An alternative analysis was also applied where all observed data was used, irrespective of rescue medication use, with missing data imputed as non-responders
  - The difference between response rates among treatment groups was analyzed using the Cochran-Mantel-Haenszel test, stratified by baseline IGA score and region
- For the primary analysis of the continuous endpoints, a repeated measurements model was used, where data collected after permanent discontinuation or initiation of rescue medication were excluded from the analysis
- The primary analysis of the maintenance endpoints considered patients who, prior to week 52, received rescue medication and/or were transferred to open-label treatment as non-responders. The differences in response rates were analyzed using the Cochran-Mantel-Haenszel test, stratified by region

Results

Patient characteristics

- Patients were randomly assigned to recieve either tralokinumab 300 mg every other week or placebo; 603:199 in ECZTRA 1 and 593:201 in ECZTRA 2
- Baseline demographics and disease characteristics were well balanced between randomized groups. Patients had a long duration of AD and over 50% had severe AD (IGA–4) at baseline **(Table 1)**

Table 1. Demographic and clinical characteristics of randomized patients at baseline

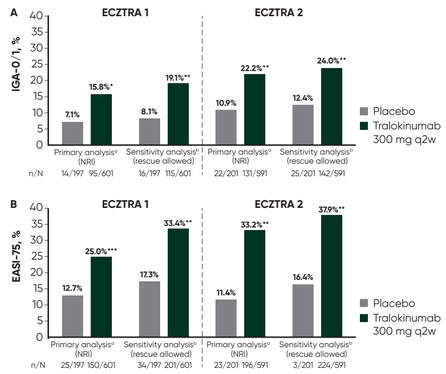
	ECZTRA 1 (n=802)		ECZTRA 2 (n=794)	
	Placebo (n=199)	Tralokinumab q2w (n=603)	Placebo (n=201)	Tralokinumab q2w (n=593)
Mean age, years	39	39	35	37
Male, n (%)	123 (62)	351 (58)	114 (57)	359 (61)
Mean duration of AD, yrs	29.6	27.9	27.5	28.3
Region, %				
USA[a]	24.6	24.7	45.3	45.5
Europe[b]	59.8	59.4	29.4	29.5
Australia	0	0	15.4	15.2
Asia	15.6	15.9	10.0	9.8
Mean BSA with AD, %	54.2	52.7	53.0	52.6
Severe disease (IGA–4), %	51.3	50.6	50.2	48.2
Mean EASI	32.9	32.2	32.6	32.1
Mean weekly worst daily pruritus NRS score	7.7	7.7	8.0	7.9
Mean SCORAD	71.7	70.3	70.5	70.0
Mean DLQI	16.9	16.8	17.8	17.7

[a]USA only in ECZTRA 1; USA and Canada in ECZTRA 2; [b]France, Germany, and Spain in ECZTRA 1; Italy, Poland, Russia, Denmark, and UK in ECZTRA 2; [c]Japan in ECZTRA 1 and Korea in ECZTRA 2.

Primary endpoints

- At week 16, significantly greater IGA–0/1 and EASI–75 response rates were observed with tralokinumab compared with placebo, using both the primary and alternative analysis approaches **(Figure 2)**
- In the primary analysis, IGA–0/1 was achieved by 15.8% versus 7.1% ($P<0.01$) and 22.2% versus 10.9% ($P<0.001$) with tralokinumab versus placebo in ECZTRA 1 and 2 and EASI–75 was achieved by 25.0% versus 12.7% and 33.2% versus 11.4% with tralokinumab versus placebo in ECZTRA 1 and 2 **(Figure 2)**
  - Rescue medication was used by 35.8% and 22.8% of patients receiving tralokinumab and by 46.2% and 44.3% of patients receiving placebo in ECZTRA 1 and 2, respectively

Figure 2. IGA–0/1 and EASI–75 at week 16

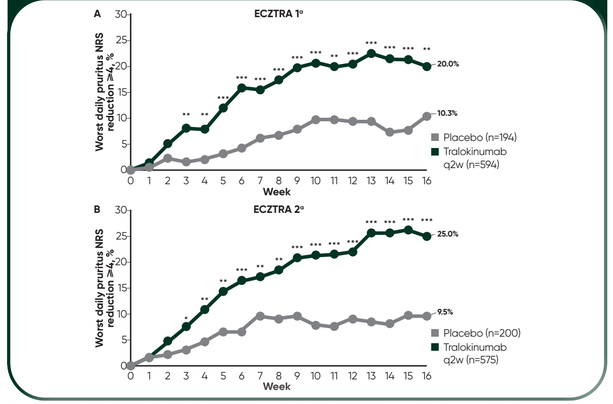


*P<0.01 versus placebo; **P<0.001 versus placebo. [c]Use of rescue medication considered as non-response and missing data imputed as non-response; [d]All data used as observed at week 16, regardless of rescue medication use, and missing data imputed as non-response. NRI, non-responder imputation.

Secondary endpoints

- A reduction in worst daily pruritus NRS (weekly average) ⩾4 was achieved by more patients treated with tralokinumab than with placebo in ECZTRA 1 (20% vs. 10.3%; $P=0.002$) and in ECZTRA 2 (25% vs. 9.5%; $P<0.001$) at week 16 **(Figure 3)**
- Mean change from baseline in SCORAD at week 16 was greater with tralokinumab compared with placebo in ECZTRA 1 (−25.2 vs. −14.7; $P<0.001$) and ECZTRA 2 (−28.1 vs. −14.0; $P<0.001$)
- Mean change from baseline in DLQI at week 16 was greater with tralokinumab than with placebo in ECZTRA 1 (−7.1 vs. −5.0; $P=0.02$) and ECZTRA 2 (−8.8 vs. −4.9; $P<0.001$)
- Greater improvements in SCORAD and DLQI with tralokinumab compared with placebo were observed from the first assessment (week 2) and at each assessment throughout the initial treatment period

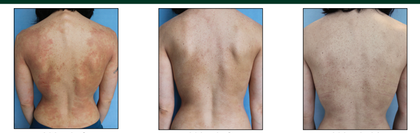
Figure 3. Worst daily pruritus NRS (weekly average) reduction ⩾4



Primary analysis approach: use of rescue medication considered non-response and missing data imputed as non-response. *P<0.05 versus placebo; **P<0.01 versus placebo; ***P<0.001 versus placebo. [a]Based on full analysis set with baseline worst daily pruritus NRS (weekly average) ⩾4.

- There was visible improvement in AD lesions within 16 weeks **(Figure 4)**

Figure 4. Example patient case of improvement in EASI from baseline to week 16

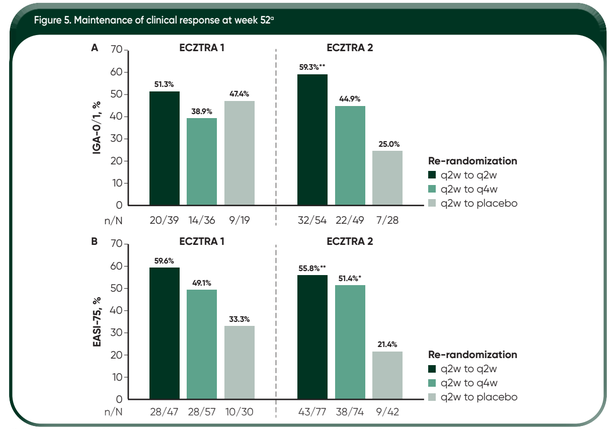


Patient images provided with consent to use; courtesy of Prof. Ketty Peris.

Maintenance/open-label phase

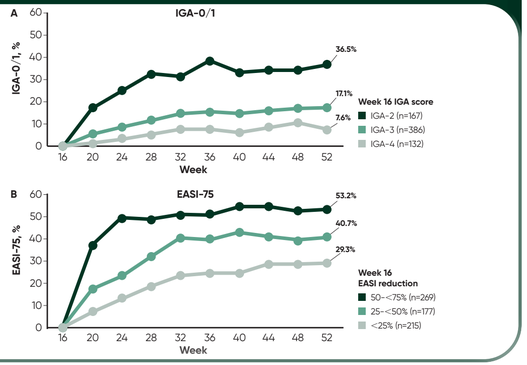
- After the initial 16-week treatment period, eligible patients were transferred to either the maintenance phase or open-label tralokinumab as appropriate **(Figure 1)**
- IGA–0/1 response at week 16, achieved without rescue medication, was maintained at week 52 in 51.3% and 59.3% of patients who continued tralokinumab q2w **(Figure 5A)** and EASI–75 response at week 16, achieved without rescue medication, was maintained at week 52 in 59.6% and 55.8% of patients who continued with tralokinumab q2w **(Figure 5B)**

Figure 5. Maintenance of clinical response at week 52[c]



*P<0.01 versus placebo; **P<0.001 versus placebo. [c]Assessed in patients achieving given primary endpoint (IGA–0/1, EASI–75) at week 16 without use of rescue medication after initial randomization to tralokinumab. Patients who, after week 16, received rescue medication or were transferred to open-label treatment are considered non-responders at week 52. Missing values imputed as non-response.

Figure 6. IGA–0/1 and EASI–75 with open-label tralokinumab 1 optional TCS by AD disease activity at week 16



Data are pooled from ECZTRA 1 and 2; all patients were initially randomized to tralokinumab up to week 16

- Some patients – transferred to open-label tralokinumab q2w plus optional TCS – not achieving IGA–0/1 or EASI–75 at week 16 improved with continued treatment **(Figure 6)**

Safety

- The overall frequency and severity of AEs over 16 weeks was comparable between tralokinumab and placebo **(Table 2)**
- In total, 97% of conjunctivitis cases were mild to moderate, and only one led to treatmentdiscontinuation
- The safety profile at week 52 was comparable with that in the initial treatment period

Table 2. Summary of AEs in the 16 week initial treatment period

n (%) in the initial 16-week period	ECZTRA 1		ECZTRA 2	
	Placebo (n=196)	Tralokinumab q2w (n=602)	Placebo (n=200)	Tralokinumab q2w (n=592)
At least one AE	151 (77.0)	460 (76.4)	132 (66.0)	364 (61.5)
At least one serious AE	8 (4.1)	23 (3.8)	5 (2.5)	10 (1.7)
AE leading to withdrawal from trial	8 (4.1)	19 (3.2)	2 (1.0)	9 (1.5)
Frequent AEs (≥5% in any treatment group)[a]				
Atopic dermatitis	75 (38.3)	156 (25.9)	67 (33.5)	98 (16.6)
Viral upper respiratory tract infection	41 (20.9)	139 (23.1)	17 (8.5)	49 (8.3)
Upper respiratory tract infection	2 (1.0)	9 (1.5)	17 (8.5)	59 (10.0)
Conjunctivitis	4 (2.0)	43 (7.1)	3 (1.5)	18 (3.0)
Skin infection	3 (1.5)	6 (1.0)	11 (5.5)	12 (2.0)
Pruritus	10 (5.1)	32 (5.3)	5 (2.5)	12 (2.0)
Headache	10 (5.1)	28 (4.7)	6 (3.0)	16 (2.7)

[a]AEs reported by system organ class and preferred term according to Medical Dictionary for Regulatory Activities, version 20.0 in the initial treatment period.

Conclusions

- Tralokinumab demonstrated superiority over placebo in all primary and secondary endpoints at week 16
- The majority of patients maintained responses at week 52 with tralokinumab q2w (without the use of TCS)
- After having achieved response, q4w dosing could be appropriate for some patients
- Continued treatment beyond 16 weeks resulted in additional patients achieving treatment success
- The overall frequency of AEs among tralokinumab-treated patients was comparable with that in the placebo group over 52 weeks
- Specifically targeting IL-13 with tralokinumab represents a novel and efficacious approach for the long-term treatment of AD

References

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