Tralokinumab improves clinically relevant outcome measures: a post hoc analysis of ECZTRA 3, a randomized clinical trial in patients with moderate-to-severe atopic dermatitis

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Introduction

- Atopic dermatitis (AD) is a chronic inflammatory skin disease,[1] characterized by eczematous lesions and multiple symptoms including pruritus, sleep disturbance, and depression[2,3]
- Tralokinumab is a first-in-class, fully human monoclonal antibody, designed to neutralize interleukin-13, a key driver of the underlying inflammation of AD which is overexpressed in lesional and non-lesional AD skin[4,5]
- The ECZTRA 3 study reflected clinical practice by evaluating the use of tralokinumab 300 mg every 2 weeks in combination with a topical corticosteroid (TCS) used as needed on active lesions compared with placebo plus TCS as needed[6]
- Tralokinumab plus TCS demonstrated superiority versus placebo plus TCS in achieving the primary endpoints of an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) [IGA-0/1] and a 75% improvement in Eczema Area and Severity Index (EASI-75) at week 16[6]
- Use of IGA and EASI as primary outcomes in clinical studies is driven in part by guidance from regulatory authorities such as the U.S. Food and Drug Administration and the European Medicines Agency
- Patient–clinician discussions around the decision to continue, switch, combine, increase dose, or stop therapy should be based on a more comprehensive assessment of treatment and response[7]
- The Harmonising Outcome Measures for Eczema (HOME) initiative suggested that comprehensive assessment of long-term control of AD should include domains of signs, symptoms, quality of life, and a patient global instrument[8]

Objective

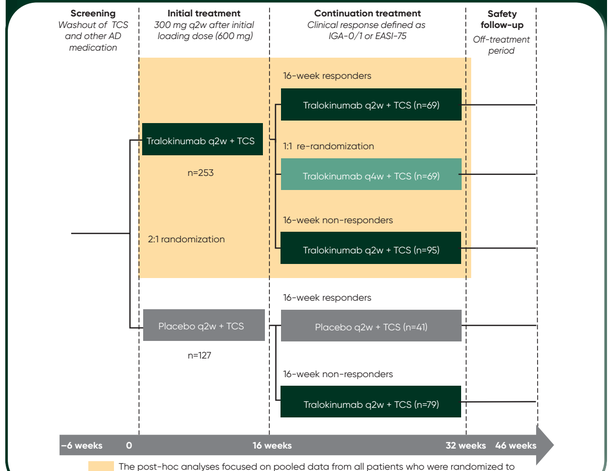
- The objective of this post hoc analysis was to assess response to tralokinumab in combination with TCS as needed, based on outcome domains and time points typically used in clinical practice

Methods

Patients and study design

- ECZTRA 3 enrolled adults with a diagnosis of AD for more than 1 year and a recent history of inadequate response to treatment with topical medications **(Figure 1)**
- Patients were randomly assigned (2:1) to either subcutaneous tralokinumab 300 mg every other week plus TCS or placebo every other week plus TCS for 16 weeks, after which tralokinumab responders (IGA-0/1 and/or EASI-75) were re-randomized 1:1 to continuation treatment with tralokinumab 300 mg every other week or every 4 weeks plus TCS for an additional 16 weeks

Figure 1. ECZTRA 3 trial design (NCT03363854)[6]



- ECZTRA 3 included assessment of:
  - IGA and EASI assessed every 2 weeks
  - Patient Global Impression of Bother (PGI-B) and Numerical Rating Scale (NRS) for worst daily pruritus assessed daily and recorded as the worst weekly and daily score respectively
  - Dermatology Life Quality Index (DLQI) and Patient-Oriented Eczema Measure (POEM) assessed bi-weekly until week 8, every 4 weeks until week 20, and then at week 28 and 32

Post hoc analysis

- Following HOME recommendations,[8] outcomes were selected in the domains o clinician-assessed signs (EASI), patient-reported symptoms (pruritus NRS and POEM) quality of life (DLQI), and a patient global instrument (PGI-B) **(Table 1)**
- Outcomes were assessed at time points typically used in clinical practice for patient follow-up, i.e. after 3 months in the initiation phase and every 6 months in the maintenance phase
- Clinically relevant targets were selected to reflect the achievement of a clinically meaningful change versus baseline during the initial treatment phase (minimal target) and to reflect achievement of mild disease activity (ideal target) during the maintenance phase

Table 1. Disease domains and targets assessed

Disease domain and scoring	Initial treatment phase minimal target (clinically relevant change versus baseline after 3 months)	Maintenance treatment phase ideal target (mild disease activity after 6 months)
EASI (0–72)	50% reduction	Absolute score ⩽7
NRS for worst daily pruritus (0–10)[a]	⩾ 3-point reduction	Absolute score ⩽4
PGI-B (0–4)[b]	⩾ 1- point reduction	Absolute score ⩽2
DLQI (0–30)[c]	⩾ 4-point reduction	Absolute score ⩽5[c]
POEM (0–28)[e]	⩾ 4-point reduction	Absolute score ⩽7[d]

[a]Weekly average of worst daily score, 11-point scale, 0 = "no itch" to 10 = "worst itch imaginable"; [b]Worst score recorded during the week, 5-point scale, 0 = "not at all" to 4 = "very much"; [c]10 items addressing impact of skin disease over the last week, 4-point scale, 0 = "not at all, not relevant" to 3 = "very much"; [d]Measured at week 20; [e]Total frequency of 7 symptoms over the last week (itching, sleep, bleeding, weeping, cracking, flaking, and dryness), 5-point scale, 0 = "no days" to 4 = "every day"

- This post hoc analysis included pooled data from all patients who were randomized to tralokinumab plus TCS at the start of ECZTRA 3 to assess:
  - The proportion of tralokinumab plus TCS-treated patients who achieved the individual disease domain targets at 3 and 6 months
  - The impact of selecting patients by holistic assessment at month 3 on the proportion achieving meaningful improvement in the extent and severity of lesions (EASI-50 or EASI-75) at month 6
    - Subgroup analyses of patients achieving both a perceived improvement in the overall disease burden (PGI-B) AND a meaningful improvement in any one of the other targets at 3 months

Statistical analyses

- Post hoc analysis was based on the full analysis set and included all patients who received tralokinumab plus TCS in the initial treatment period
- In the assessment of the defined binary targets, subjects who received rescue medication were considered non-responders and subjects with missing data were imputed as non-responders

Results

Patient characteristics

- Patients had a long duration of AD prior to being enrolled into the study; almost half of patients had severe AD (IGA-4) at baseline and mean body surface area (BSA) involvement was close to 50% **(Table 2)**
- Overall, 60% of patients had a worst PGI-B score of 4 (very much bothered by their AD) at baseline

Table 2. Patient demographics and disease characteristics at baseline

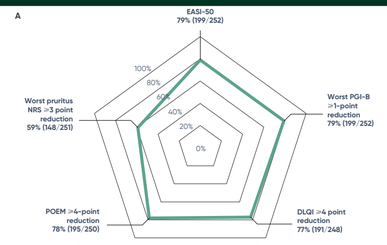
	Tralokinumab q2w + TCS (n=253[a])
Mean (SD) age, years	39.8 (15.3)
Male, n (%)	125 (49)
Mean (SD) duration of AD, years	28.0 (16.5)
Region, %	
North America[a]	41.9
Europe[b]	58.1
Mean (SD) BSA involvement with AD, %	47.6 (23.3)
Severe disease (IGA-4), %	46
Mean (SD) EASI	28.8 (12.0)
Mean (SD) weekly worst daily pruritus NRS score	7.7 (1.5)
Mean (SD) DLQI	17.6 (7.1)
Mean (SD) POEM	22.3 (5.1)
PGI-B, n (%)[c]	
0	0
1	4 (1.6)
2	13 (5.2)
3	84 (33.3)
4	151 (59.9)

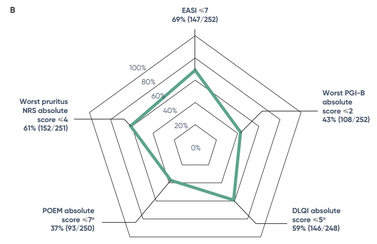
[a]Includes USA and Canada; [b]Includes Belgium, Germany, Netherlands, Poland, Spain, and UK; [c]PGI-B: 0: "not at all", 1: "slightly", 2: "somewhat", 3: "a lot", or 4: "very much"; [d]One patient was not dosed due to use of prohibited medication and was therefore excluded from the full analysis set.

Target achievement at months 3 and 6

- Overall, 91% of patients receiving tralokinumab every 2 weeks plus TCS achieved at least one of the defined minimum targets (clinically relevant change) for EASI, pruritus, POEM, DLQI, and PGI-B at 3 months **(Figure 2A)**
  - 77–79% achieved a clinically relevant change as judged by EASI, PGI-B DLQI, and POEM, respectively
  - 59% achieved a clinically relevant change as judged by worst daily pruritus NRS

Figure 2. Proportion of patients achieving the individual disease domain targets for (A) clinically relevant change at 3 months and (B) mild AD activity at 6 months[a]

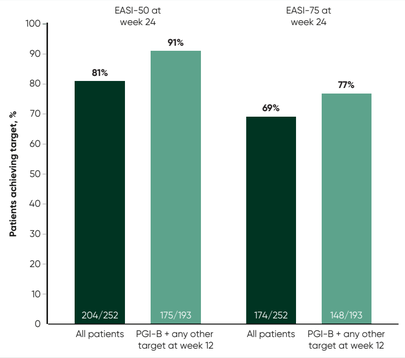




[a]Measured at week 20. Pruritus NRS assessed in patients with worst daily pruritus NRS ⩾3 at baseline; DLQI and POEM assessed in patients with DLQI/POEM total score ⩾4 at baseline; PGI-B assessed in patients with PGI-B >1 at baseline.

- Overall, 82% of patients receiving tralokinumab every 2 weeks or every 4 weeks plus TCS achieved at least one of the defined optimal targets (equivalent to mild disease) at month 6 in the maintenance treatment phase **(Figure 2B)**
  - 59–69% achieved mild AD as judged by EASI, DLQI, and worst daily pruritus NRS
  - 37% and 43% of patients achieved mild AD as judged by POEM or worst weekly PGI-B, respectively
- Overall, 78% (193/247 patients with data at baseline and month 3) achieved both a >1-point reduction in PGI-B and at least one of the other disease domain endpoints at month 3
- Response rates for EASI-50 and EASI-75 at month 6 were higher in the subgroup of patients who achieved both a >1-point reduction in PGI-B and at least one of the other disease domain endpoints at month 3, compared with the whole cohort **(Figure 3)**

Figure 3. Impact of holistic assessment of response at month 3 on achievement of EASI improvement with tralokinumab q2w or q4w plus TCS at month 6



Safety

- Tralokinumab in combination with TCS was well tolerated with the overall safety being comparable to that of placebo in the initial treatment period up to 16 weeks **(Table 3)**. Overall, the safety profile at week 32 was comparable with the initial treatment period
- Tralokinumab in combination with TCS was associated with lower rates of severe and serious infections and eczema herpeticum versus placebo plus TCS
- All conjunctivitis cases were mild to moderate and only one led to treatment discontinuation

Table 3. Adverse events in the initial treatment period up to week 16

Week 16, n (%)	Placebo q2w + TCS (n=126)	Tralokinumab q2w + 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 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 (7.9)	6 (2.4)
Headache	6 (4.8)	22 (8.7)

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

Conclusions

- Tralokinumab 300 mg every other week in combination with TCS as needed was associated with a high proportion of patients (91%) achieving a clinically meaningful improvement (minimal target) in at least one of the pre-defined disease domains (AD signs and symptoms and AD-related quality of life) 3 months after initiating treatment
- A high proportion of patients (82%) achieved an outcome equivalent to mild disease activity (ideal target) in at least one of the pre-defined disease domains (AD signs and symptoms and AD-related quality of life) during the maintenance treatment phase
- Using a holistic approach combining the achievement of the patients' impression of burden target (PGI-B) in combination with one other initiation period target increased the proportion of patients who achieved EASI-50 and EASI-75 in the maintenance period
- This post hoc assessment is in line with previous data showing that IGA and EASI scores do not correlate perfectly with symptom outcome measures and suggest that jointly agreed treatment targets between patients and the clinician are important, as are holistic assessments

References

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Disclosures

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