Early changes in patient-relevant endpoints in three tralokinumab pivotal Phase 3 trials (ECZTRA 1–3) in adult patients with moderate-to-severe atopic dermatitis

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Introduction

- Atopic dermatitis (AD) is a chronic, inflammatory skin disease, with an estimated prevalence of between 2.1% and 4.9% in adults across North America, Europe, and Japan[1]
- Moderate-to-severe AD is characterized by symptoms including excessive dryness, scaling, red or inflamed skin, blisters or bumps, open sores or oozing, and intense itching.[2] These symptoms can be severely debilitating to patients and their quality of life, resulting in sleep disturbance, pain, and depression[2]
- The pathogenesis of AD is complex and multifactorial, combining skin barrier dysfunction and immune dysregulation, leading to chronic type 2 inflammation[3,4]
- Interleukin (IL)-13, a key type 2 cytokine, has been identified as a key driver of the underlying inflammation of AD, with IL-13 levels within lesional skin correlating with AD severity[5–8]
- Tralokinumab is a fully human monoclonal antibody which specifically neutralizes IL-13[9]
  - Recent Phase 3, placebo-controlled trials have investigated tralokinumab in the treatment of moderate-to-severe AD as a monotherapy (ECZTRA 1, NCT03131648; ECZTRA 2, NCT03160885) and in combination with topical corticosteroids (TCS) [ECZTRA 3, NCT03363854]
  - Efficacy results from these trials were promising, with significantly more patients achieving the primary endpoints of Investigator's Global Assessment (IGA) score of 0 or 1 and Eczema Area and Severity Index (EASI) score of 75 (a 75% reduction in EASI score) at 16 weeks with tralokinumab versus placebo in all three studies
- It is important to assess the efficacy of tralokinumab in terms of patient-reported outcomes (PROs), which are vital for providing insight on the real-life value of treatments for AD[10]

Objective

- The objective of this analysis was to examine early changes in several PRO measures across the ECZTRA 1/2 and ECZTRA 3 trials

Methods

Study design

- ECZTRA 1 and 2 were two identically designed, multinational, double-blind, randomized, placebo-controlled, 52-week trials
- ECZTRA 3 was a multinational, double-blind, randomized, placebo plus TCS-controlled 32-week trial
- All trials were conducted in adults with moderate-to-severe AD who were candidates for systemic therapy

Patients

- Key inclusion criteria common for all trials were: ⩾18 years of age; confirmed diagnosis of AD for ⩾1 year; inadequate response to topical medications <1 year prior to screening; IGA score of ⩾3; and EASI score of ⩾12 at screening and ⩾16 at baseline
- Patients were randomized 3:1 to subcutaneous tralokinumab 300 mg or placebo every 2 weeks (ECZTRA 1/2) or 2:1 to subcutaneous tralokinumab 300 mg plus TCS or placebo every 2 weeks plus TCS (ECZTRA 3) for an initial 16 weeks
- Rescue treatment in the form of topical and systemic medications was permitted in all trials to control intolerable AD symptoms

Patient-reported outcomes

- A series of PRO measures were assessed in the three trials **(Figure 1)**
  - Numeric Rating Scale (NRS) for worst daily pruritus (11-point scale with 0 being "no itch" and 10 being "worst itch imaginable") [Daily via an eDiary]
  - NRS for eczema-related sleep interference (11-point scale with 0 indicating that it "did not interfere" and 10 indicating that it "completely interfered") [Daily via an eDiary]
  - Dermatology Life Quality Index (DLQI): 10 items addressing a patient's perception of the impact of their skin disease on different aspects of their daily life over the last week – patients scored the impact on each activity on a 4-point scale (where 0 is "not at all, not relevant" to 3 for "very much") [bi-weekly to week 8, then at weeks 12 and 16]
  - Patient-Orientated Eczema Measure (POEM): consisting of seven items eac addressing a specific AD symptom over the last week (itching, sleep, bleeding, weeping, cracking, flaking, and dryness) – patients indicated the frequency of each experienced in the previous week to generate a total score (bi-weekly to week 8, then at weeks 12 and 16)
  - DLQI and POEM were answered electronically at the study site and all PRO measures were reported prior to clinician assessments

Figure 1. Schedule of PRO measure assessments in initial 16-week period

Schedule of PRO assessments in ECZTRA 1–3		Visit 1[a]		Visit 2[a]		Visit 3[a]		Visit 4[a]		Visit 5[a]		Visit 6[a]		Visit 7[a]		Visit 8[a]
Patient-reported outcome measure	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16
DLQI	X		X		X		X		X				X				X
POEM	X		X		X		X		X				X				X
Eczema-related sleep NRS (weekly average)	Assessed daily with eDiary																
Worst daily pruritus NRS (weekly average)	Assessed daily with eDiary																

Earliest possible time point for assessment

[a]Visit with efficacy assessment after baseline.

Safety

- Adverse events were assessed at baseline and at each subsequent visit

Statistical analysis

- The changes in worst daily pruritus, eczema-related sleep interference, DLQI, and POEM were assessed by a repeated measurements model, including baseline IGA, region, and treatment-by-week interaction as factors and interaction between week and baseline value as covariates
  - Change = Treatment*Week + Baseline*Week + Region + Baseline IGA
  - Data collected after permanent discontinuation or initiation of rescue medication were excluded

Results

Patient characteristics

- 802, 794, and 380 patients were randomized in ECZTRA 1, 2, and 3, respectively.
- Patient demographics were well balanced between randomized groups **(Table 1)**

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

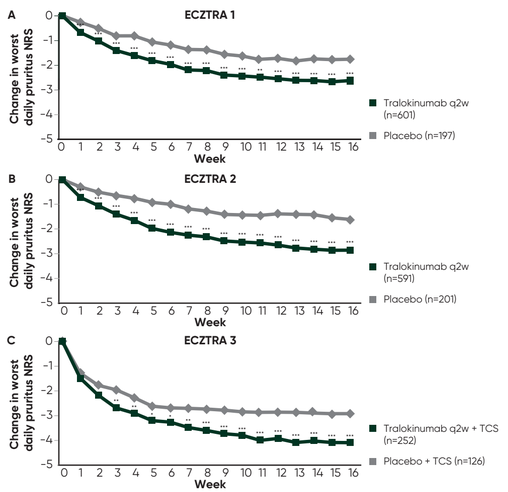
Characteristic	ECZTRA 1		ECZTRA 2		ECZTRA 3	
	Placebo (n=199)	Tralokinumab q2w (n=603)	Placebo (n=201)	Tralokinumab q2w (n=593)	Placebo + TCS (n=127)	Tralokinumab q2w + TCS (n=253)
Mean (SD) age, years	39.4 (15.2)	38.6 (13.7)	35.1 (14.0)	37.2 (14.7)	37.7 (14.8)	39.8 (15.3)
Male, n (%)	123 (61.8)	351 (58.2)	114 (56.7)	359 (60.5)	84 (66.1)	125 (49.4)
Race, n (%)						
White	138 (69.3)	426 (70.6)	123 (61.2)	374 (63.1)	85 (66.9)	203 (80.2)
Black	18 (9.0)	41 (6.8)	17 (8.5)	43 (7.3)	12 (9.4)	23 (9.1)
Asian	40 (20.1)	120 (199)	52 (25.9)	154 (26.0)	24 (18.9)	17 (6.7)
Other[a] or missing data	3 (1.5)	16 (2.6)	9 (4.5)	22 (3.7)	6 (4.7)	10 (4.0)
Mean (SD) disease duration, years	29.6 (15.1)	27.9 (14.5)	27.5 (14.7)	28.3 (15.9)[j]	28.7 (15.0)[o]	28.0 (16.5)
Mean (SD) affected body surface area, %	54.2 (25.6)	52.7 (24.1)	53.0 (25.0)	52.6 (25.6)	49.0 (25.9)	47.6 (23.3)
Mean (SD) EASI	32.9 (13.9)[b]	32.2 (13.7)[k]	32.6 (13.9)	32.1 (14.3)[k]	30.4 (12.8)[o]	28.8 (12.0)[q]
IGA-4 (severe), n (%)	102 (51.3)	305 (50.6)	101 (50.2)	286 (48.2)	60 (47.2)	116 (45.8)
Mean (SD) total SCORAD	71.7 (12.5)[b]	70.3 (13.0)[k]	70.5 (12.2)	70.0 (13.4)[k]	68.9 (13.2)[o]	67.0 (13.3)[q]
Mean (SD) weekly average of worst daily pruritus NRS	7.7 (1.4)[c]	7.7 (1.4)[l]	8.0 (1.4)[l]	7.9 (1.5)[l]	7.9 (1.5)[p]	7.7 (1.5)[r]
Mean (SD) DLQI	17.0 (6.6)[d]	16.8 (7.1)[g]	17.8 (7.3)[l]	17.7 (7.1)[m]	17.2 (7.2)[p]	17.6 (7.1)[s]
Mean (SD) weekly average of eczema-related sleep NRS	6.8 (1.9)[c]	6.9 (2.0)[l]	7.3 (2.1)[l]	7.2 (2.0)[l]	7.1 (2.2)[p]	6.9 (2.1)[s]
Mean (SD) POEM	23.0 (4.6)[d]	22.8 (5.1)[h]	22.9 (5.1)[l]	22.8 (4.9)[m]	22.4 (5.6)[p]	22.3 (5.1)[s]

q2w, every 2 weeks; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation. [a]Including American Indian or Alaska native and Native Hawaiian or other Pacific Islander; [b]n=197; [c]n=195; [d]n=194; [e]n=601; [f]n = 598; [g]n=591; [h]n=589; [i]n=200; [j]n=592; [k]n=591; [l]n=584; [m]n=587; [n]n=586; [o]n=126; [p]n=125; [q]n=252; [r]n=251; [s]n=250.

Patient-reported outcomes

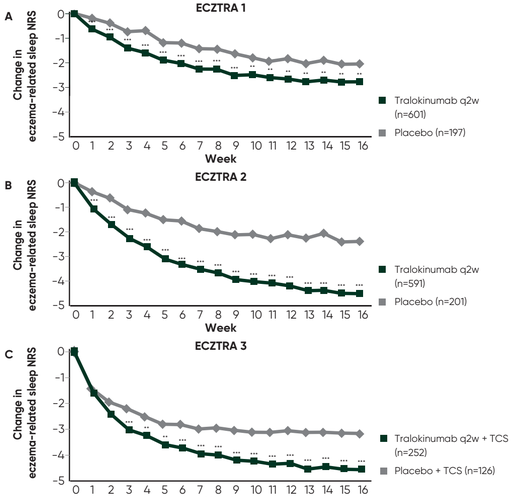
- Tralokinumab improved weekly average NRS worst daily pruritus from baseline compared with placebo by week 1 in ECZTRA 1 (−0.7 vs. −0.2; $P<0.001$) and ECZTRA 2 (−0.7 vs. −0.3; $P<0.001$), and week 3 in ECZTRA 3 (−2.6 vs. −2.0; $P=0.003$) **(Figure 2)**
- Tralokinumab reduced weekly mean eczema-related sleep interference from baseline compared with placebo by week 1 in ECZTRA 1 (−0.6 vs. −0.2; $P<0.001$) and ECZTRA 2 (−0.7 vs. −0.2; $P<0.001$) and week 2 in ECZTRA 3 (−2.3 vs. −1.9; $P=0.037$) **(Figure 3)**

Figure 2. Changes in worst daily pruritus NRS in ECZTRA 1, 2, and 3



*P<0.05; **P<0.01; ***P<0.001. Data collected after permanent discontinuation of investigational medicinal product or initiation of rescue medication not included. In case of no post-baseline assessments before initiation of rescue medication, the week 1 change will be imputed as 0.

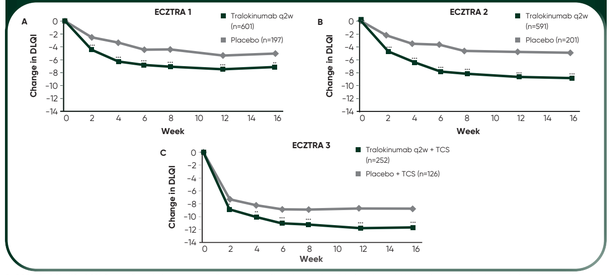
Figure 3. Changes in daily eczema-related sleep NRS in ECZTRA 1, 2, and 3 in ECZTRA 1, 2, and 3



*P<0.05; **P<0.01; ***P<0.001. Data collected after permanent discontinuation of investigational medicinal product or initiation of rescue medication not included. In case of no post-baseline assessments before initiation of rescue medication, the week 1 change will be imputed as 0.

- Tralokinumab reduced mean DLQI compared with placebo in ECZTRA 1 (−4.4 vs. −2.5; $P<0.001$), ECZTRA 2 (−4.7 vs. −2.2; $P<0.001$), and ECZTRA 3 (−8.9 vs. −7.3; $P=0.011$) by week 2 **(Figure 4)**

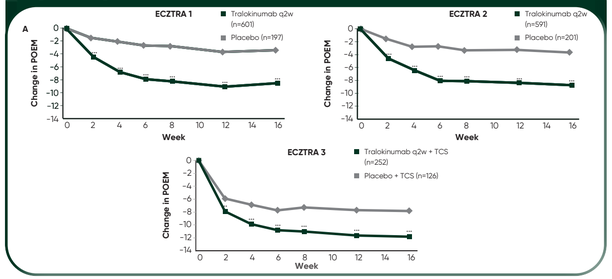
Figure 4. Changes in DLQI in ECZTRA 1, 2, and 3



*P<0.05; **P<0.01; ***P<0.001. Data collected after permanent discontinuation of investigational medicinal product or initiation of rescue medication not included. In case of no post-baseline assessments before initiation of rescue medication, the week 2 change will be imputed as 0.

- Tralokinumab reduced mean POEM compared with placebo in ECZTRA 1 (−4.0 vs. −1.3; $P<0.001$), ECZTRA 2 (−4.6 vs. −1.6; $P<0.001$), and ECZTRA 3 (−7.9 vs. −5.9; $P=0.006$) by week 2 **(Figure 5)**
- Mean improvements from baseline for DLQI and POEM reached minimally clinical important difference of ⩾4 at week 2 for tralokinumab

Figure 5. Changes in POEM score in ECZTRA 1, 2, and 3



*P<0.05; **P<0.01; ***P<0.001. Data collected after permanent discontinuation of investigational medicinal product or initiation of rescue medication not included. In case of no post-baseline assessments before initiation of rescue medication, the week 2 change will be imputed as 0.

Safety

- In the 16-week period, the overall safety of tralokinumab was comparable to placebo
- The incidence of ⩾1 adverse event was similar between tralokinumab and placebo patients in all three trials (76.4% vs. 77.0% in ECZTRA 1, 61.5% vs. 66.0% in ECZTRA 2, and 71.4% vs. 66.7% in ECZTRA 3)
- The majority of adverse events were mild or moderate in severity

Conclusions

- Tralokinumab, with or without concomitant TCS, led to early (within 1–3 weeks) improvements in patient-relevant endpoints compared to placebo across the three trials
- AD severely impacts a patient's quality of life; interventions with the potential to provide such early improvements are highly desirable
- Concomitant use of TCS in ECZTRA 3 may explain why differences between tralokinumab and placebo were observed earlier in ECZTRA 1/2
- The long-term resilience of PRO measure improvements is being assessed in the ongoing ECZTEND trial for tralokinumab (NCT03587805)
- These findings support the previously demonstrated superiority of tralokinumab 300 mg every two weeks when compared to placebo, over 16 weeks of treatment across multiple outcome measures, reflecting the signs and symptoms of AD

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