Specifically targeting interleukin-13 with tralokinumab improved sleep in two Phase 3, randomised, double-blind, placebo-controlled trials in patients with atopic dermatitis

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Introduction

- Atopic dermatitis is a chronic inflammatory skin disease that is associated with sleep loss and impaired quality of life[1-3]
- Several factors may contribute to sleep loss in atopic dermatitis, including pruritus, scratching, and dysregulated cytokine levels[4-6]
- 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, thus preventing its pro-inflammatory activity[7-9]
- In Phase 3 trials, ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885), investigating tralokinumab monotherapy in adults with moderate-to-severe atopic dermatitis, significantly more patients receiving tralokinumab monotherapy achieved the primary endpoints of Investigator Global Assessment of 0 or 1 (IGA-0/1) [clear or almost clear skin] and 75% improvement in Eczema Area and Severity Index (EASI-75) compared with placebo at week 16 of the initial treatment period[10]

Objective

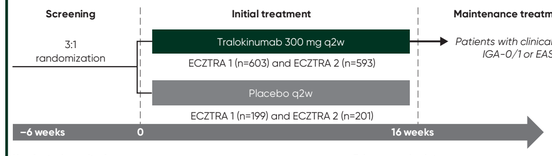
- To assess the effect of tralokinumab monotherapy on sleep loss in patients with moderate-to-severe atopic dermatitis from the ECZTRA 1 and ECZTRA 2 trials during the initial 16-week treatment period

Methods

Study design and patients

- ECZTRA 1 and 2 were identically designed, randomized, double-blind, placebo-controlled, multinational, 52-week trials of tralokinumab monotherapy in patients with moderate-to-severe atopic dermatitis
- Eligible patients were ≥18 years of age with a confirmed diagnosis of atopic dermatitis for ≥1 year and were candidates for systemic therapy due to a recent (within 1 year) history of inadequate response or intolerance to topical treatment. Additional eligibility criteria included an EASI score of ≥16, IGA ≥3, and worst daily pruritus Numeric Rating Scale (NRS) ≥4
- Patients were randomized 3:1 to receive either subcutaneous tralokinumab 300mg or placebo every 2 weeks for an initial treatment period of 16 weeks **(Figure 1)**

Figure 1. ECZTRA 1 and 2 trial design



Key inclusion criteria
- Diagnosis of atopic dermatitis for >1 year
- BSA involvement ⩾10%
- EASI score ⩾12 at screening and 16 at baseline
- IGA score ⩾3 at screening and at baseline
- Worst daily pruritus NRS weekly average score ⩾4 prior to baseline

Primary endpoints
- IGA-0/1 at week 16
- EASI-75 at week 16

Sleep measures assessed up to week 16
- NRS for eczema-related sleep interference
- SCORAD sleep score
- POEM sleep score

[a]Full design of treatment regime after week 16 not shown.
BSA, body surface area; q2w, every 2 weeks.

Measures of sleep

- SCORing Atopic Dermatitis (SCORAD) and Patient-Oriented Eczema Measure (POEM) sleep scores were recently validated for use as single-item, patient-reported assessments of sleep loss in adults with atopic dermatitis[11]
- Several measures of sleep were assessed in ECZTRA 1 and 2 during the initial 16-week treatment period **(Table 1)**:
  - NRS for eczema-related sleep interference
  - SCORAD sleep score
  - POEM sleep score

Statistical analysis

- Changes in eczema-related sleep interference NRS and SCORAD sleep score were assessed by a repeated measurements model, including baseline IGA, region, and treatment-by-week interactions as factors and interaction between week and baseline value as covariates
  - Change = Treatment*Week + baseline*Week + Region + Baseline IGA
- The percentage of patients in each of the five POEM sleep score categories was assessed at baseline and week 16
  - Missing data at week 16 was imputed using last observation carried forward (LOCF), whereby the last observation of POEM sleep score prior to permanent discontinuation of the investigational medicinal product (IMP) or initiation of rescue medication was carried forward
- Data collected after permanent discontinuation of the IMP or initiation of rescue medication were excluded from the analyses

Table 1. Patient-reported sleep measures assessed during the initial 16-week treatment period

Sleep measure	Scale	Collected
NRS for eczema-related sleep interference (24-hour recall)	11-point numeric scale of the extent to which eczema interfered with sleep the last night 0 = "did not interfere" to 10 = "completely interfered"	Daily via eDiary by patients
SCORAD sleep score (3-day recall)	Visual analog scale of average sleeplessness over the last 3 days/nights 0 = "no sleeplessness" to 10 = "worst imaginable sleeplessness"	At biweekly visits
POEM sleep score (7-day recall)	5-point categorical scale of the frequency of sleep disturbance in the previous week 0 = "no days" to 4 = "every day"	Electronically at biweekly visits up to week 8, then weeks 12 and 16

Results

Patient characteristics

- In total, 802 and 794 patients were randomized in ECZTRA 1 and 2, respectively **(Table 2)**
- Overall, baseline characteristics were similar across both trials **(Table 2)**

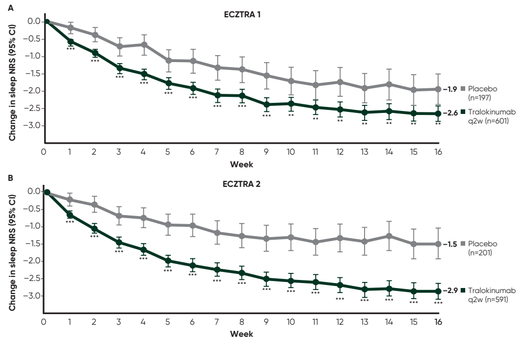
Table 2. Patient demographics and baseline characteristics at baseline

	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 atopic dermatitis, years	29.6	27.9	27.5	28.3
Mean BSA involvement with atopic dermatitis, %	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 average eczema-related sleep NRS	6.8	6.9	7.3	7.2
Mean SCORAD sleep score	6.4	6.5	7.2	7.0
Mean POEM sleep score	3.3	3.3	3.3	3.3

Eczema-related sleep interference NRS

- There was a greater improvement in weekly average eczema-related sleep interference NRS with tralokinumab compared with placebo in both ECZTRA 1 and ECZTRA 2 **(Figure 2)**
  - Change from baseline in eczema-related sleep interference NRS was larger with tralokinumab compared with placebo at each week, with separation observed between the treatment groups ($P<0.001$) from week 1
- The least-square mean (LSM) change from baseline at week 16 was greater with tralokinumab compared with placebo in both trials (ECZTRA 1, −2.6 [95% confidence interval (CI) −2.9, −2.4] vs. −1.9 [95% CI −2.4, −1.5]; $P=0.007$, and ECZTRA 2, −2.9 [95% CI −3.1, −2.7] vs. −1.5 [95% CI −1.9, −1.1]; $P<0.001$) **[Figure 2]**

Figure 2. Change in eczema-related sleep NRS in (A) ECZTRA 1 and (B) ECZTRA 2 by week during the initial treatment period

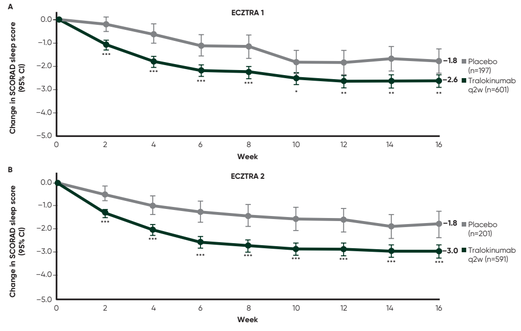


**P<0.01 versus placebo; ***P<0.001 versus placebo. Data collected after permanent discontinuation of the IMP or initiation of rescue medication not included. In case of no post-baseline assessment before initiation of rescue medication, the week 2 change was imputed as 0. Repeated measurements model: change = treatment*week + baseline*week + region + baseline IGA.

SCORAD sleep score

- There was a greater improvement in SCORAD sleep score with tralokinumab compared with placebo in both ECZTRA 1 and ECZTRA 2 **(Figure 3)**
  - Change from baseline in SCORAD sleep score was greater with tralokinumab compared with placebo, with separation observed between the treatment groups from week 2 ($P<0.001$) and at each week onwards ($P<0.05$)
- The LSM change from baseline at week 16 was greater with tralokinumab compared with placebo (ECZTRA 1, −2.6 [95% CI −2.9, −2.3] vs. −1.8 [95% CI −2.3, −1.3]; $P=0.004$, and ECZTRA 2, −3.0 [95% CI −3.2, −2.7] vs. −1.8 [95% CI −2.3, −1.2]; $P<0.001$) **[Figure 3]**

Figure 3. Change in SCORAD sleep score in (A) ECZTRA 1 and (B) ECZTRA 2 by week during the initial treatment period

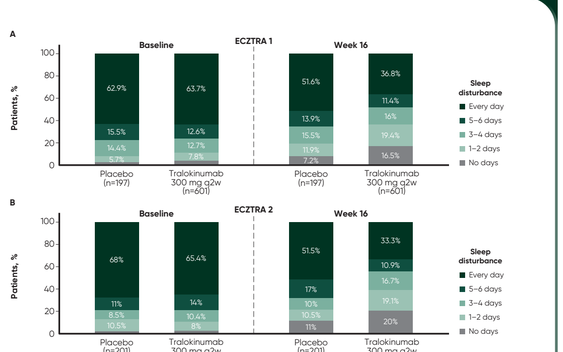


*P<0.05 versus placebo; **P<0.01 versus placebo; ***P<0.001 versus placebo.
Data collected after permanent discontinuation of the IMP or initiation of rescue medication not included. In case of no post-baseline assessment before initiation of rescue medication, the week 2 change was imputed as 0.
Repeated measurements model: change = treatment*week + baseline*week + region + baseline IGA.

POEM sleep score

- There was a greater shift towards lower POEM sleep scores with tralokinumab compared with placebo in both ECZTRA 1 and ECZTRA 2 **(Figure 4)**
  - The majority of patients (87.5–92.8%) across treatment groups reported ≥3 nights of sleep disturbance at baseline in both trials
  - At week 16, 64.2% and 60.9% of tralokinumab-treated patients reported ≥3 nights of sleep disturbance compared to 81% and 78.5% of patients with placebo
- A greater proportion of tralokinumab-treated patients (35.9–39.1%) reported "No days" or "1–2 days" of sleep disturbance at week 16 versus placebo (19.1–21.5%) **[Figure 4]**

Figure 4. POEM sleep scores at baseline and week 16 in (A) ECZTRA 1 and (B) ECZTRA 2



Data collected after permanent discontinuation of IMP or initiation of rescue medication not included. Missing data at week 16 imputed using the LOCF, i.e. last observation of POEM sleep score prior to permanent discontinuation of the IMP or initiation of rescue medication was carried forward.

Conclusions

- Tralokinumab monotherapy 300 mg every 2 weeks demonstrated improvements compared with placebo in three sleep measures (NRS for eczema-related sleep interference, SCORAD sleep score, and POEM sleep score) during the initial 16-week treatment period
- Improvement in sleep measures was consistent across two large Phase 3 trials, ECZTRA 1 and ECZTRA 2
- A greater proportion of tralokinumab-treated patients reported either "no days" or "1–2 days" of sleep disturbance
- Early improvement in sleep measures as early as week 1 with tralokinumab is consistent with its effects on the signs and troublesome symptoms of atopic dermatitis, including pruritus

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Disclosures

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