Safety of specifically targeting interleukin-13 with tralokinumab in adult patients with moderate-to-severe atopic dermatitis: pooled analysis of five randomized, double-blind, placebo-controlled trials

Eric Simpson,[1] Joseph F Merola,[2] Jonathan I Silverberg,[3] Rebecca Zachariae,[4] Christina Kurre Olsen,[4] Andreas Wollenberg[5]

[1]Oregon Health & Science University, Portland, OR; [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [3]George Washington University School of Medicine and Health Sciences, Washington, DC; [4]LEO Pharma A/S, Ballerup, Denmark; [5]Klinikum der Universität München, Klinik und Poliklinik für Dermatologie und Allergologie, Munich, Germany

Introduction

- Atopic dermatitis (AD) is a chronic inflammatory skin disease[1,2] characterised by eczematous lesions and multiple symptoms, including pruritus, sleep disturbance, and depression[3–5]
- Ocular comorbidities such as various forms of conjunctivitis are commonly present in patients with AD and the incidence of ocular complications is known to increase with AD severity[6]
- Increased rates of conjunctivitis have been reflected in clinical trials of moderate-to- severe patients with AD[7], as well as in real-world data[8]
- The type 2 cytokine interleukin 13 (IL-13) has been identified as a key driver of the underlying inflammation of AD and is overexpressed in lesional and non-lesional AD skin[9,10]
- 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 signalling, thus preventing its pro-inflammatory activity[11]
  - Recent Phase 3 trials have investigated tralokinumab in the treatment of moderate-to-severe AD versus placebo (ECZTRA 1 [NCT03131648] and ECZTRA 2 [NCT03160885]) and in combination with topical corticosteroids (TCS) versus placebo (ECZTRA 3 [NCT03363854])
  - Phase 2 trials have assessed the efficacy and safety of tralokinumab in combination with TCS (Phase 2b [NCT02347176]), as well as of tralokinumab-treated patients' responses to vaccines (ECZTRA 5 [NCT03562377])

Objective

- The objective of this study was to evaluate the conjunctivitis data in adult patients with moderate-to-severe AD pooled from the three Phase 3 ECZTRA trials and the two Phase 2 trials of tralokinumab 300 mg every 2 weeks (q2w) versus placebo

Materials and Methods

Patients

- Eligible patients were ⩾18 years of age with a confirmed diagnosis of AD for ⩾1 year and with an inadequate response to treatment with topical medications. Additional eligibility requirements included an AD body surface area involvement of ⩾10%, Eczema Area and Severity Index (EASI) scores of ⩾12 at screening and ⩾16 at baseline (ECZTRA trials) or ⩾12 at baseline (Phase 2b trial) and an Investigator's Global Assessment (IGA) score of ⩾3

Study designs

- Phase 3 ECZTRA 1 and ECZTRA 2 (tralokinumab monotherapy), Phase 3 ECZTRA 3 (tralokinumab in combination with TCS), Phase 2 ECZTRA 5 (vaccine response in tralokinumab-treated patients with AD) and Phase 2b (efficacy and safety evaluation of tralokinumab) trials **(Figure 1)**

Adverse event (AE) reporting

- Conjunctivitis was classified as an AE of special interest (AESI) and comprised the following preferred terms: 'conjunctivitis', 'conjunctivitis allergic', 'conjunctivitis bacterial' and 'conjunctivitis viral', and was summarized for the initial treatment period (16 weeks for ECZTRA and 12 weeks for Phase 2b)
- Events were captured from the AE form (ECZTRA) or from a Medical Dictionary for Regulatory Activities (MedDRA) search (Phase 2b)

Statistical analysis

- Results presented are based on the safety analysis set, which comprises all randomized patients who were exposed to investigational medicinal product
- Cochran-Mantel-Haenszel weights were applied to calculate adjusted AE incidences to account for different randomization rates between tralokinumab and placebo
- Rates were calculated using the number of patients divided by patient-years of exposure (PYE) multiplied by 100
- Hazard ratio (HR) and 95% confidence interval (CI) are from a Cox regression model with treatment groups as fixed effect, stratified by trial and baseline disease severity (IGA)

Results

- The analyses evaluated all randomized patients (n=2285) who received at least one dose of tralokinumab 300 mg q2w (n=1605) or placebo (n=680), pooled from the five trials
  - Results described below are based on the first conjunctivitis event

Incidence and severity of conjunctivitis

- The overall adjusted incidence and adjusted rate of conjunctivitis AESIs were 7.5%/26.6 for tralokinumab and 3.2%/11.4 for placebo and the HR versus placebo was 2.4 (95% CI 1.5, 3.8) **(Table 1)**
  - The majority of conjunctivitis AESIs were reported as the preferred term 'conjunctivitis'
- Most conjunctivitis AESIs were mild to moderate in severity in both the tralokinumab and placebo arms **(Figure 2)**
- Conjunctivitis events (based on all conjunctivitis events) recovered/resolved (78.6% vs 73.9%) or were considered to be recovering/resolving (2.8% vs 4.3%) in the tralokinumab group and placebo group, respectively **(Table 2)**
  - There were no serious events, although events led to permanent discontinuation of two (1.4%) tralokinumab patients
- Of the 145 conjunctivitis AESIs in the tralokinumab group, 39 (27.1%) were confirmed diagnoses. Of the 21 conjunctivitis AESIs in the placebo group, six (29%) were confirmed diagnoses (data available from the ECZTRA trials only)

Figure 1. Study design

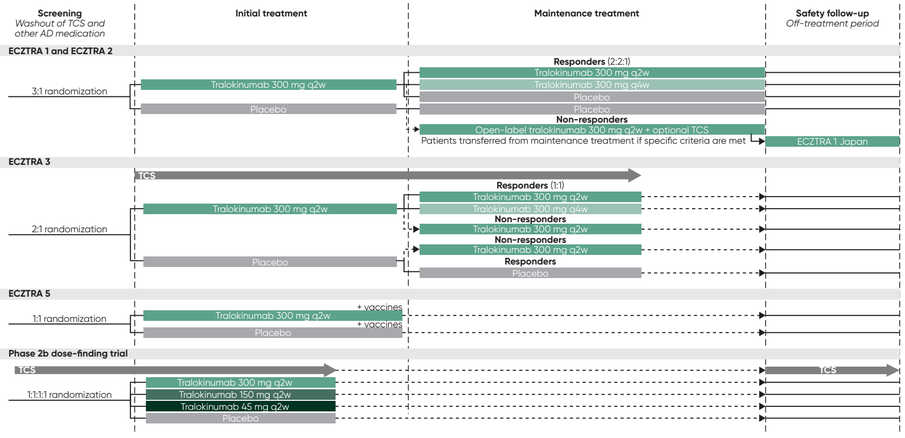
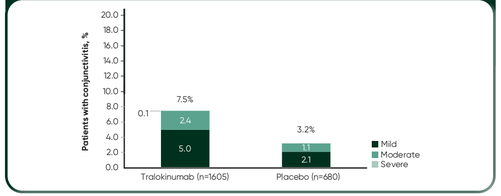


Table 1. Summary of conjunctivitis AESIs by preferred term (first event only, AD pool, initial treatment period)

	Tralokinumab total (n=1605)					Placebo total (n=680)					HR vs placebo (95% CI)
AE	PYE	N (%)	adj. %	R	adj. R	PYE	N (%)	adj. %	R	adj. R	
Conjunctivitis	453.7	126 (7.9)	7.5	27.8	26.6	190.3	21 (3.1)	3.2	11.0	11.4	2.4 (1.5, 3.8)
Conjunctivitis	459.6	90 (5.6)	5.4	19.6	19.0	191.4	13 (1.9)	1.9	6.8	7.0	2.8 (1.6, 5.0)
Conjunctivitis allergic	467.9	34 (2.1)	2.0	7.3	6.7	191.9	7 (1.0)	1.1	3.6	3.8	1.8 (0.8, 4.0)
Conjunctivitis bacterial	472.6	4 (0.2)	0.2	0.8	0.7	192.8	1 (0.1)	0.2	0.5	0.6	1.3 (0.2, 12.0)
Conjunctivitis viral	473.0	1 (0.1)	0.1	0.2	0.2	193.1	1 (0.1)	0.1	0.5	0.5	0.4 (0.0, 6.5)

HR and 95% CI are from a Cox regression model with treatment groups as fixed effect, stratified by trial and baseline disease severity (IGA).
%, percentage of patients with one or more events; adj. %, adjusted percentage calculated using Cochran-Mantel-Haenszel weights; R, adjusted rate calculated using Cochran-Mantel-Haenszel weights; n, number of patients; N, number of patients with one or more events; PYE, patient-years of exposure calculated by preferred term until onset of the first event; R, rate (number of patients divided by PYE multiplied by 100).

Figure 2. Conjunctivitis severity in tralokinumab-treated and placebo-treated patients (first event only, AD pool, initial treatment period)



Adjusted incidences are presented; Percentages above the bars represent the adjusted incidence rate overall.

Table 2. Overall summary of AESIs – conjunctivitis (all events, AD pool, initial treatment period)

	Tralokinumab total E (%)	Placebo total E (%)
Events	145	23
Drug related[a]		
Action taken with drug		
Drug withdrawn	2 (1.4)	–
Outcome		
Fatal	–	–
Not recovered/not resolved	26 (17.9)	5 (21.7)
Recovering/resolving	4 (2.8)	1 (4.3)
Recovered/resolved	114 (78.6)	17 (73.9)
Recovered/resolved with sequelae	1 (0.7)	–
Unknown	–	–

[a]Related AEs comprise AEs considered possibly or probably related by the investigator and AEs with missing causality.
%, percentage calculated based on number of events divided by total number of events; E, number of AEs.

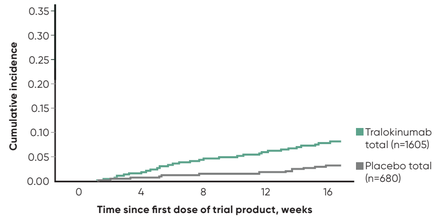
Disease characteristics with and without conjunctivitis

- Patients with conjunctivitis AEs had slight but consistently increased severity in EASI and IGA scores at baseline **(Table 3)**
  - In patients who reported conjunctivitis during the initial treatment period, median EASI score at baseline was 32.0 and 61.2% had severe disease (IGA=4), compared to a median EASI score of 26.7 and 46.3% with IGA=4 at baseline in patients who did not report conjunctivitis, regardless of treatment group
- Patients with a history of allergic conjunctivitis were observed to have an increased incidence of conjunctivitis, as reported in the trial. In total, 56.6% of patients who reported conjunctivitis in the pooled data set, compared to 30.1% of patients who did not report conjunctivitis, had a history of allergic conjunctivitis

Onset and duration of conjunctivitis

- The events of conjunctivitis reported during the initial treatment period had onset throughout the initial treatment period in both treatment groups. The difference in mean number of conjunctivitis events between the treatment groups became apparent from week 4 and increased over time **(Figure 3)**
- The median time to first event was similar for both treatment groups (50.0 days vs 54.0 days)
- However, the duration of the first conjunctivitis event was longer in the tralokinumab group compared to the placebo group (21.0 days vs 14 days) **(Table 4)**

Figure 3. Time to onset of first conjunctivitis event (safety analysis set, AD pool, initial treatment period)



AESIs from the ECZTRA trials are presented based on AESI criteria being met, as evaluated by the investigator. AESIs from the dose-finding trial are based on a specified MedDRA search.

Table 3. Summary of EASI and IGA scores at baseline and atopic comorbidities in patients with and without conjunctivitis AESIs (safety analysis set, AD pool, initial treatment period)

	With conjunctivitis AESIs			Without conjunctivitis AESIs		
Characteristic, n (%)	All treated (n=147)	Tralokinumab (n=126)	Placebo (n=21)	All treated (n=2138)	Tralokinumab (n=1479)	Placebo (n=659)
Median baseline EASI (IQR)	32.0 (21.8–42.6)	30.8 (21.8–41.5)	33.5 (25.6–43.0)	26.7 (19.8–38.9)	26.8 (19.8–38.6)	26.6 (19.7–39.7)
Baseline IGA, N (%)						
IGA–3, moderate	57 (38.8)	51 (40.5)	6 (28.6)	1145 (53.6)	789 (53.3)	356 (54.0)
IGA–4, severe	90 (61.2)	75 (59.4)	15 (71.4)	990 (46.3)	687 (46.5)	303 (46.0)
IGA–5, very severe	–	–	–	3 (0.1)	3 (0.2)	–
Allergic conjunctivitis, n (%)[a]						
Never	62/145 (42.8)	57/126 (45.2)	5/19 (26.3)	1363/2037 (66.9)	969/1427 (67.9)	394/610 (64.6)
Current	60/145 (41.4)	48/126 (38.1)	12/19 (63.2)	387/2037 (19.0)	261/1427 (18.3)	126/610 (20.7)
Past	22/145 (15.2)	20/126 (15.9)	2/19 (10.5)	227/2037 (11.1)	151/1427 (10.6)	76/610 (12.5)

[a]Pooled data only include the ECZTRA trials. IQR, interquartile range

Table 4. Duration of the first event of conjunctivitis AESIs[a] (safety analysis set, AD pool, initial treatment period)

Duration of first event, days	Tralokinumab (n=1605)	Placebo (n=680)
N	100	17
Median (IQR)	21.0 (11.0–88.0)	14.0 (5.0–29.0)

[a]Including only events that have an end date. IQR, interquartile range.

Common treatments

- The majority of patients in both treatment groups received treatment for their conjunctivitis (85.7% of tralokinumab patients vs 71.4% of placebo patients)
- Common treatments in tralokinumab-treated and placebo-treated patients included ophthalmic anti-allergics (31.0% vs 38.1%), anti-infectives (30.2% vs 19.0%), corticosteroids (23.0% vs 9.5%) and combined corticosteroids and anti-infectives (13.5% vs 14.3%)

Conclusions

- The overall incidence of conjunctivitis, identified as an AESI in the initial treatment period for the pooled data set of 2285 patients from the five Phase 2/Phase 3 clinical trials, was higher for tralokinumab 300 mg q2w than for placebo
- The majority of the first events of conjunctivitis were mild to moderate in severity
- Most of the patients who experienced a conjunctivitis event received treatment and their conjunctivitis resolved or was resolving during the trial period
- Patients with conjunctivitis were found to have more severe AD at baseline and had a history of allergic conjunctivitis, which may be predisposing factors to conjunctivitis in AD patients

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