Conjunctivitis in adolescent patients aged 12–17 with moderate-to-severe atopic dermatitis treated with tralokinumab up to week 52: results from the phase 3 ECZTRA 6 trial

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Introduction

- Atopic dermatitis (AD) is a chronic inflammatory skin disease with limited safe and effective treatments suitable for long-term use in adolescents with moderate-to-severe disease[1,2]
- Various forms of conjunctivitis are commonly present in adult patients with AD,[3] and can increase with biological treatments targeting the type 2 inflammatory pathway[4,5]
  - Higher frequency of conjunctivitis was observed with dupilumab (which targets interleukin-4 and -13) vs placebo in an adolescent AD trial[2]
- Tralokinumab is a fully human monoclonal antibody that binds with high affinity to interleukin-13, a key driver of AD pathogenesis[6–8]
- Here, we examine the frequency and rate of conjunctivitis in adolescents treated with tralokinumab vs placebo in the phase 3 ECZTRA 6 trial

Objective

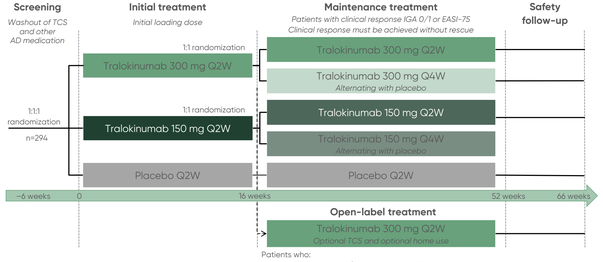
- To examine conjunctivitis frequency and severity in tralokinumab-treated adolescents with moderate-to-severe atopic dermatitis

Materials and Methods

Study design

- Adolescent patients were randomized 1:1:1 to subcutaneous tralokinumab 150 mg or 300 mg every 2 weeks (Q2W), or placebo for an initial treatment period of 16 weeks
- Primary endpoints were Investigator's Global Assessment (IGA) score 0/1 and ≥75% improvement from baseline in Eczema Area and Severity Index (EASI-75) at Week 16
- Patients achieving primary endpoints without rescue treatment were re-randomized to tralokinumab Q2W or every 4 weeks (Q4W), at their same initial tralokinumab dosage for 36 weeks of maintenance treatment as shown in **Figure 1**, while Placebo responders continue in the Placebo Q2W
- Patients not achieving primary endpoints at Week 16, those receiving rescue treatment from Week 2 to Week 16, and those meeting other specific criteria† were transferred to open-label treatment of tralokinumab 300 mg Q2W plus optional mild-to-moderate strength topical corticosteroids (TCS)
- Key secondary endpoints include change in SCORing AD (SCORAD) from baseline to Week 16, reduction of worst daily pruritus numeric rating scale (NRS) (weekly average) of at least 4 from baseline to Week 16, and change in Children's Dermatology Life Quality Index (CDLQI) score from baseline to Week 16

Figure 1. ECZTRA 6 trial design



Rescue treatment during initial and maintenance treatment defined as: TCI, TCS or systemic AD treatment.
AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids. †Patients not achieving EASI-75 over ≥4 weeks with IGA ≥2 after IGA=0 at Week 16, or with IGA ≥3 after IGA=1 at Week 16, or who had IGA >1 at Week 16; patients who receive rescue treatment after Week 16

Statistical analyses and endpoints

- Conjunctivitis frequency and rate were examined in adolescent patients aged 12–17 years with moderate-to-severe AD treated with tralokinumab for up to 52 weeks in the phase 3 ECZTRA 6 trial (NCT03526861)
- Conjunctivitis was classified as an adverse event of special interest (AESI) prior to trial initiation
  - This broad term comprised the following preferred terms: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, and conjunctivitis viral
- Results were based on the safety analysis set comprised of all patients randomized and exposed to investigational medicinal product, excluding 9 patients from two sites with Good Clinical Practice non-compliance (N=289)
- Rates were calculated as:
  - Number of events per patient-years of exposure x 100

Results

Patient characteristics

- Baseline demographic and clinical characteristics were comparable across treatment groups (**Table 1**)

Table 1. Baseline characteristics

Patients	Placebo (n=94)	Tralokinumab 150 mg Q2W (n=98)	Tralokinumab 300 mg Q2W (n=97)
Mean age, years	14.3	14.8	14.6
Age group, n (%)			
12–14	49 (52.1)	37 (37.8)	45 (46.4)
15–17	45 (47.9)	61 (62.2)	52 (53.6)
Male sex, n (%)	51 (54.3)	51 (52.0)	47 (48.5)
Mean duration of AD, years (SD)	12.1 (3.5)	12.7 (3.7)	12.1 (3.7)
Severe disease (IGA=4), n (%)	43 (45.7)	44 (44.9)	48 (49.5)
Mean EASI (SD)	31.2 (14.5)	32.1 (12.9)	31.8 (13.9)
Mean SCORAD (SD)	67.4 (14.9)	67.7 (14.4)	68.3 (13.7)
Mean CDLQI (SD)	13.3 (6.0)	12.9 (6.3)	13.4 (7.3)
Mean Weekly Average Peak Pruritus NRS (SD)	7.5 (1.7)	7.5 (1.6)	7.8 (1.5)

AD, Atopic Dermatitis; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; n, Number of subjects in analysis set; NRS, Numeric rating scale; Q2W, Every 2 weeks; SCORAD, Scoring Atopic Dermatitis; SD, standard deviation.

Overall Summary of AEs: Weeks 0–16

- Tralokinumab was well-tolerated and the majority of adverse events (AEs) in the tralokinumab and placebo arms were mild or moderate in severity (**Table 2**)
- No patterns were seen in types of serious AEs and none led to any safety concerns (**Table 2**)
- The majority of AEs had resolved within the initial 16-week period; only one AE led to treatment withdrawal and was not considered related to treatment* (**Table 2**)

Table 2. ECZTRA 6 Safety Summary (Weeks 0–16)

	Placebo (n=94)	Tralokinumab 150 mg Q2W (n=98)	Tralokinumab 300 mg Q2W (n=97)
Adverse events, n (%)	58 (61.7)	66 (67.3)	63 (64.9)
Serious adverse events, n (%)	5 (5.3)	3 (3.1)	1 (1.0)
Severity, n (%)			
Mild	40 (42.6)	48 (49.0)	47 (48.5)
Moderate	31 (33.0)	33 (33.7)	32 (33.0)
Severe	7 (7.4)	5 (5.1)	3 (3.1)
Leading to withdrawal, n (%)	0	1 (1.0)	0
AEs of special interest, n (%)			
Eye disorders	2 (2.1)	4 (4.1)	4 (4.1)
Conjunctivitis†	2 (2.1)	4 (4.1)	3 (3.1)
Eczema herpeticum	1 (1.1)	1 (1.0)	0
Skin infections requiring systemic treatment	2 (2.1)	5 (5.1)	2 (2.1)
Injection site reactions	1 (1.1)	9 (9.2)	7 (7.2)

*Cerebrovascular accident, not considered related to treatment by the investigator or study sponsor; The patient had several risk factors for developing cerebrovascular accident. The event was not considered related to treatment with tralokinumab by either investigator or sponsor/LEO. The outcome was reported as recovered with sequelae.
†Includes the preferred terms conjunctivitis, conjunctivitis bacterial, conjunctivitis allergic and conjunctivitis viral (no cases of conjunctivitis viral were observed)
AE, adverse event; Q2W, Every 2 weeks.

Frequency & Severity of Conjunctivitis: Weeks 0–16

- By Week 16, 2 patients (2.1%; rate 10.7) in the placebo arm had conjunctivitis (AESI) vs 4 patients (4.1%; rate 13.6) in the tralokinumab 150 mg arm and 3 patients (3.1%; rate 10.2) in the 300 mg arm (**Table 3**)
  - Only two conjunctivitis AESIs were reported as the preferred term 'conjunctivitis', both in the tralokinumab 150 mg arm
  - Overall, 2/10 (20%) events were confirmed by an ophthalmologist
- The majority of conjunctivitis AESIs were considered mild in severity; no severe events were reported (**Table 3**)

Table 3. Frequency of Conjunctivitis AESI (Weeks 0–16)

	Placebo (n=94) PYE 27.9			Tralokinumab 150 mg Q2W (n=98) PYE 29.3			Tralokinumab 300 mg Q2W (n=97) PYE 29.5		
AESI category Preferred term	N (%)	Events	Rate	N (%)	Events	Rate	N (%)	Events	Rate
Conjunctivitis	2 (2.1)	3	10.7	4 (4.1)	4	13.6	3 (3.1)	3	10.2
Conjunctivitis	–	–	–	2 (2.0)	2	6.8	–	–	–
Conjunctivitis bacterial	–	–	–	–	–	–	1 (1.0)	1	3.4
Conjunctivitis allergic	2 (2.1)	3	10.7	2 (2.0)	2	6.8	2 (2.1)	2	6.8
Conjunctivitis viral	–	–	–	–	–	–	–	–	–
Severity									
Mild	2 (2.1)	3	10.7	3 (3.1)	3	10.2	2 (2.1)	2	6.8
Moderate	–	–	–	1 (1.0)	1	3.4	1 (1.0)	1	3.4
Severe	–	–	–	–	–	–	–	–	–

AESI, adverse event of special interest; PYE, patient years of exposure; Q2W, once every 2 weeks.

Outcomes of Conjunctivitis: Weeks 0–16

- Most outcomes (8/9) were recovered or resolved during Weeks 0–16, and none led to permanent tralokinumab discontinuation (**Table 4**)

Table 4. Outcome of Conjunctivitis AESI (Weeks 0–16)

	Placebo (n=94)		Tralokinumab 150 mg Q2W (n=98)		Tralokinumab 300 mg Q2W (n=97)	
	N (%)	Rate	N (%)	Rate	N (%)	Rate
Conjunctivitis AESI	2 (2.1)	10.7	4 (4.1)	13.6	3 (3.1)	10.2
Drug related	1 (1.1)	7.2	1 (1.0)	3.4	1 (1.0)	3.4
Action taken with drug						
Dose not changed	2 (2.1)	10.7	3 (3.1)	10.2	3 (3.1)	10.2
Drug interrupted	–	–	1 (1.0)	3.4	–	–
Outcome						
Fatal	–	–	–	–	–	–
Not recovered/not resolved	–	–	–	–	–	–
Recovering/resolving	–	–	–	–	1 (1.0)	3.4
Recovered/resolved	2 (2.1)	10.7	4 (4.1)	13.6	2 (2.1)	6.8

AESI, adverse event of special interest; Q2W, once every 2 weeks.

Incidence of Conjunctivitis: Weeks 16–52

- During Weeks 16–52, 3 patients (6%; rate 11.9) had conjunctivitis (AESI) in the maintenance treatment phase (pooled tralokinumab arms) as did 11 patients (4.7%; rate 9.3) in the open-label treatment phase (**Table 5**)
  - Of these patients, five had events that were reported as the preferred term 'conjunctivitis'
- All conjunctivitis AESIs during Weeks 16–52 (maintenance and open-label phases) were mild or moderate in severity, with no severe events recorded (**Table 5**)

Table 5. Incidence of Conjunctivitis (Weeks 16–52)

	Maintenance treatment: Tralokinumab pooled total 150/300 mg Q2/4W (n=50) PYE 25.3			Open-label treatment: Tralokinumab 300 mg Q2W plus optional TCS (n=234) PYE 151.1		
AESI category Preferred term	N (%)	Events	Rate	N (%)	Events	Rate
Conjunctivitis	3 (6.0)	3	11.9	11 (4.7)	14	9.3
Conjunctivitis	1 (2.0)	1	4.0	4 (1.7)	6	4.0
Conjunctivitis bacterial	–	–	–	3 (1.3)	4	2.7
Conjunctivitis allergic	2 (4.0)	2	7.9	4 (1.7)	4	2.7
Conjunctivitis viral	–	–	–	–	–	–
Severity						
Mild	1 (2.0)	1	3.95	9 (3.8)	10	6.6
Moderate	2 (4.0)	2	7.90	3 (1.3)	4	2.7
Severe	–	–	–	–	–	–

AESI, adverse event of special interest; PYE, patient years of exposure; Q2W, once every 2 weeks; TCS, topical corticosteroid

Conclusions

- Conjunctivitis frequency in adolescents was low and similar between the tralokinumab and placebo arms of the phase 3 ECZTRA 6 trial
- Conjunctivitis rates were numerically lower in adolescents compared with reported adult rates[4], through Week 16 of the trial
- The majority of conjunctivitis events were mild, and most resolved during Weeks 0–16; none led to permanent discontinuation of tralokinumab
- The frequency and severity of conjunctivitis did not increase with longer-term tralokinumab treatment up to Week 52

References

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