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 Phase 3 and Phase 2 trials

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Introduction

- Atopic dermatitis (AD) is a chronic, debilitating, inflammatory skin disease[1,2] characterised by eczematous lesions and multiple symptoms, including pruritus, sleep disturbance and depression.[3–5] The type 2 cytokine interleukin 13 (IL-13) is a key driver of the underlying inflammation of AD and is overexpressed in lesional and non-lesional AD skin[6,7]
- 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[6–8]
- Tralokinumab 300 mg every 2 weeks (q2w), as monotherapy and in combination with topical corticosteroids (TCS), was efficacious in the treatment of patients with moderate-to-severe AD in three pivotal Phase 3 ECZTRA trials (ECZTRA 1 [NCT03131648], ECZTRA 2 [NCT03160885] and ECZTRA 3 [NCT03363854]), a Phase 2 trial (ECZTRA 5 [NCT03562377]) and a Phase 2b trial (NCT02347176)[9]
- It is important to understand the safety profile of therapeutics used for the long-term treatment of patients with AD
  - A good safety profile is an important attribute for patients when selecting a treatment for AD[10]

Objective

- To provide an overview of the pooled safety data from three Phase 3 ECZTRA trials and two Phase 2 trials to evaluate the safety of tralokinumab 300 mg q2w in adult patients with moderate-to-severe AD

Methods

Study designs

- Five placebo-controlled trials formed the AD pool: Phase 3 (ECZTRA 1, ECZTRA 2 and ECZTRA 3), Phase 2 (ECZTRA 5) and Phase 2b
- ECZTRA 1 and ECZTRA 2 were identically designed, multinational, double-blind, randomized, placebo-controlled, 52-week clinical trials of tralokinumab monotherapy
- ECZTRA 3 was a multinational, double-blind, randomized, placebo-controlled, 32-week clinical trial of tralokinumab in combination with TCS
- ECZTRA 5 was a multinational, double-blind, randomized, placebo-controlled, 16-week clinical trial to evaluate the effect of tralokinumab monotherapy on vaccine antibody responses
- The Phase 2b trial was a multinational, double-blind, randomized, placebo-controlled, 12-week dosing study of tralokinumab, in combination with TCS

Patients and treatment

- Patients in all five trials were adults ≥18 years of age with a confirmed diagnosis of AD for > 1 year and an Investigator's Global Assessment (IGA) score ≥3 **(Table 1)**
- Patients were randomized to tralokinumab 300 mg q2w or placebo with or without TCS

Safety analysis

- The safety analysis was based on the safety analysis set, which comprised all randomized patients who were exposed to investigational medicinal product
- The safety analysis was performed for the initial 16-week (ECZTRA trials) and 12-week (Phase 2) treatment periods (AD pool), and for the long-term, 36-week maintenance period in the ECZTRA 1 and ECZTRA 2 trials (monotherapy pool) for tralokinumab 300 mg q2w
- An analysis of adverse events (AEs) of special interest (AESIs), including skin infections requiring systemic treatment, eczema herpeticum, eye disorders (conjunctivitis, keratoconjunctivitis and keratitis) and malignancies diagnosed after randomisation, was pre-specified in the study protocol
- All AEs described were treatment emergent, defined as AEs reported after the first dosing of the study drug
- AEs are summarised by the number and proportion of patients with AEs and the number and rate of events by treatment group
- Medical Dictionary for Regulatory Activities (MedDRA) version 2.0 was used
- Event rates are presented as the number of events per 100 patient-years of exposure (PYE)

Statistical analysis

- Cochran-Mantel-Haenszel weights were applied to calculate adjusted AE incidences for the initial treatment period to account for varying randomisation rates between tralokinumab and placebo in the trials
- Risk ratios were estimated from a Poisson regression with treatment as fixed effect, and log values of PYE were used as offset variable

Table 1. Number of patients by trial, eligibility criteria and treatment

	ECZTRA 1 and ECZTRA 2		ECZTRA 3		ECZTRA 5		Phase 2b trial[a]	
Number of patients in analysis set	Tralokinumab 300 mg q2w ECZTRA 1: 602 ECZTRA 2: 592	Placebo ECZTRA 1: 196 ECZTRA 2: 200	Tralokinumab 300 mg q2w 252	Placebo 126	Tralokinumab 300 mg q2w 107	Placebo 107	Tralokinumab 300 mg q2w 52	Placebo 51
Eligibility criteria	• ≥18 years of age • Confirmed diagnosis of AD for >1 year • AD body surface area involvement >10% • EASI scores ≥12 at screening and ≥16 at baseline • IGA score ≥3 • Pruritus NRS ≥4		• ≥18 years of age • Confirmed diagnosis of AD for >1 year • AD body surface area involvement ≥10% • EASI scores ≥12 at screening and ≥16 at baseline • IGA score ≥3 • Pruritus NRS ≥4		• 18–54 years of age • Confirmed diagnosis of AD for >1 year • AD body surface area involvement ≥10% • EASI scores ≥12 at screening and ≥16 at baseline • IGA score ≥3		• 18–75 years of age • Confirmed diagnosis of AD for .1 year • AD body surface area involvement >10% • EASI score >12 • IGA score >3	
Treatment	• Patients were randomized 3:1 to SC tralokinumab 300mg q2w or placebo q2w for 16 weeks • At 16 weeks, tralokinumab responders[b] were re-randomized 2:2:1 to maintenance treatment with SC tralokinumab q2w or q4w or placebo q2w for an additional 36 weeks • Placebo responders continued with placebo • Non-responders received SC tralokinumab q2w + optional TCS for an additional 36 weeks • Patients who met the predefined criteria during the maintenance treatment period were transfered to open label and received tralokinumab 300 mg q2w with optional use of TCS		• Patients were randomized 2:1 to SC tralokinumab 300 mg SC q2w + TCS or placebo q2w + TCS for 16 weeks • At 16 weeks, tralokinumab responders[b] were re-randomized 1:1 to continuation treatment with SC tralokinumab q2w or q4w + TCS for an additional 16 weeks • Placebo responders continued with placebo • Non-responders received SC tralokinumab q2w + TCS for an additional 16 weeks		• Patients were randomized 1:1 to SC tralokinumab 300 mg q2w or placebo q2w		• Patients were randomized 1:1:1:1 to SC tralokinumab 45 mg, 150 mg or 300 mg q2w[c] + TCS or to placebo q2w + TCS	

[a]50 patients received 45 mg tralokinumab and 51 patients received 150 mg tralokinumab. These two low doses were not included in the AD pool; [b]Defined as being IGA-0/1 and/or EASI-75 responders at week 16; [c]Only the tralokinumab 300 mg q2w group was included in the pooled analysis. EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; SC, subcutaneous.

Results

Patient demographics and clinical characteristics

- For the initial treatment period, the AD pool included 2285 patients: 1605 treated with tralokinumab 300 mg q2w (exposure for the entire treatment period, 1403.9 PYE) and 680 with placebo q2w (exposure for the entire treatment period, 272.6 PYE)
  - Patient demographics and clinical characteristics were similar across treatment arms **(Table 2)**

Table 2. Baseline patient demographics and clinical characteristics (safety analysis set, AD pool)

	Tralokinumab (n=1605)	Placebo (n=680)
Sex, n (%)		
Male	921 (57.4)	375 (55.1)
Female	684 (42.6)	305 (44.9)
Mean age, years (SD)	37.9 (14.3)	37.0 (14.3)
Age group, n (%)		
18–64 years	1528 (95.2)	648 (95.3)
≥65 years	77 (4.8)	32 (4.7)
Median age at onset of AD, years	3.0	3.0
Mean duration of AD, years (SD)	27.7 (15.4)	27.7 (15.2)
Mean body surface area, % (SD)	51.0 (24.4)	50.2 (24.7)
IGA, n (%)		
IGA-3 (moderate)	840 (52.3)	362 (53.2)
IGA-4 (severe)	762 (47.5)	318 (46.8)
IGA-5 (very severe)	3 (0.1)	0
Race, n (%)		
White	1089 (67.9)	430 (63.2)
Black or African American	139 (8.7)	80 (11.8)
Asian	324 (20.2)	143 (21.0)
Other	47 (2.9)	19 (2.8)
Missing	6 (0.4)	8 (1.2)
Ethnicity, n (%)		
Hispanic or Latino	169 (7.4)	56 (8.2)
Not Hispanic or Latino	2111 (92.4)	621 (91.3)
Missing	5 (0.2)	3 (0.4)

SD, standard deviation.

Table 3. Overall safety summary (safety analysis set, initial treatment period)

	AD pool						Monotherapy pool					
	Tralokinumab (n=1605; PYE=473.19)			Placebo (n=680; PYE=193.1)			Tralokinumab (n=1194; PYE=354.46)			Placebo (n=396; PYE=114.47)		
	n (adj. %)	E	adj. R	n (adj. %)	E	adj. R	n (%)	E	adj. R	n (%)	E	adj. R
Events	1080 (65.7)	3148	639.5	449 (67.2)	1276	678.3	824 (69.0)	2479	699.4	283 (71.5)	899	785.3
Serious	37 (2.1)	38	7.4	18 (2.8)	22	11.9	33 (2.8)	34	9.6	13 (3.3)	17	14.9
Severity												
Mild	881 (53.2)	2127	429.8	326 (49.0)	738	391.0	673 (56.4)	1654	466.6	204 (51.5)	500	436.8
Moderate	518 (31.5)	917	189.5	258 (39.0)	478	254.3	409 (34.3)	733	206.8	182 (46.0)	350	305.7
Severe	77 (4.6)	104	20.2	40 (6.3)	60	33.0	65 (5.4)	92	26.0	32 (8.1)	49	42.8
Drug withdrawn (action taken)	38 (2.3)	47	9.9	20 (2.8)	25	13.3	29 (2.4)	34	9.6	11 (2.8)	16	14.0
Outcome												
Fatal	1 (0.1)	1	0.4	0	0	0	0	0	0	0	0	0
Not recovered/not resolved	232 (14.3)	312	65.4	90 (13.5)	126	65.2	167 (14.0)	229	64.6	60 (15.2)	78	68.1
Recovering/resolving	79 (5.0)	87	18.9	36 (5.4)	45	22.7	56 (4.7)	60	16.9	22 (5.6)	25	21.8
Recovered/resolved	997 (60.2)	2699	544.5	416 (62.4)	1096	585.4	769 (64.4)	2152	607.1	264 (66.7)	789	689.2
Recovered/resolved with sequelae	18 (1.0)	18	3.5	2 (0.3)	3	1.7	15 (1.3)	15	4.2	2 (0.5)	3	2.6
Unknown	27 (1.7)	31	7.0	6 (0.9)	6	3.3	21 (1.8)	23	6.5	4 (1.0)	4	3.5

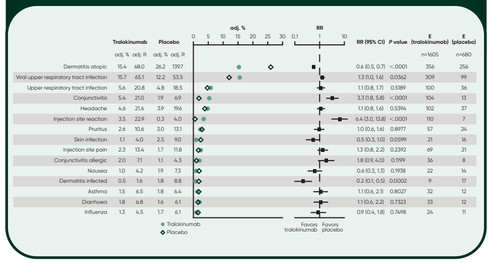
adj., adjusted; E, event; R, rate, PYE, patient-years of exposure

- The monotherapy pool included 1590 patients: 1194 treated with tralokinumab 300 mg and 396 treated with placebo q2w
- As the monotherapy pool constituted the majority of the AD pool, the monotherapy pool resembled the AD pool in baseline demographics and clinical characteristics, with no major differences between patients in the tralokinumab q2w and placebo treatment groups

Safety: AD pool (initial treatment period)

- The overall frequency of AEs was similar for tralokinumab (65.7%) and placebo (67.2%) **(Table 3)**
  - The majority of AEs (>90%) were mild or moderate in severity
- The majority of AEs were recovered/resolved for tralokinumab (60.2%) and placebo (62.4%)
- The most frequently occurring AEs (defined by MedDRA preferred term [MedDRA PT]) in ≥5% of patients for tralokinumab and placebo were atopic dermatitis (15.4% vs 26.2%), viral upper respiratory tract infection (15.7% vs 12.2%), upper respiratory tract infection (5.6% vs 4.8%) and conjunctivitis (5.4% vs 1.9%) **(Figure 1)**
  - Nearly two-thirds of the events related to upper respiratory tract infections (including viral upper respiratory tract infection) were reported as common cold with tralokinumab (64%) and placebo (65%). The majority of the events were classified as mild and none were serious AEs (SAEs), severe AEs nor AEs leading to permanent discontinuation of tralokinumab

Figure 1. The 15 most frequent AEs by preferred term[a] (safety analysis set, AD pool, initial treatment period)



[a]MedDRA PT. CI, confidence interval; RR, risk ratio.

- SAEs were lower for tralokinumab (2.1%) than for placebo (2.8%)
- The frequencies of severe (0.6% vs 1.4%) or serious (0.4% vs 1.1%) infections were lower for tralokinumab than for placebo
- The proportion of AEs leading to permanent discontinuation up to 16 weeks of treatment was low and similar for tralokinumab (2.3%) and placebo (2.8%) **(Table 4)**

AD pool (initial treatment period): AESIs

- The incidence of conjunctivitis (AESI term) was higher with tralokinumab (7.5%) versus placebo (3.2%) **(Table 5)** but the majority of events were mild or moderate (98%) and resolved during treatment; two cases of conjunctivitis led to permanent discontinuation
- A lower incidence of skin infection (AESI) requiring systemic treatment was observed for tralokinumab (2.6%) versus placebo (5.5%)
- The frequency of eczema herpeticum (AESI) was lower for tralokinumab (0.3%) than for placebo (1.5%)

Table 4. Most frequent AEs leading to permanent discontinuation of study drug by preferred term[a] (safety analysis set, AD pool, initial treatment period)

	Tralokinumab (n=1605; PYE=473.19)			Placebo (n=680; PYE=193.1)		
Preferred term	n (adj. %)	E	adj. R	n (adj. %)	E	adj. R
Any AEs	38 (2.3)	47	9.9	20 (2.8)	25	13.3
Dermatitis atopic	7 (0.4)	7	1.3	10 (1.5)	10	5.5
Injection site reaction	5 (0.3)	5	1.0	0	0	0
Eosinophilia	3 (0.2)	3	0.5	0	0	0
Conjunctivitis	2 (0.1)	2	0.4	0	0	0

Only events that occurred in >1 patient per preferred term are presented. [a]MedDRA PT. PYE, patient-years of exposure

Table 5. AESIs by SOC and preferred term (safety analysis set, AD pool, initial treatment period)

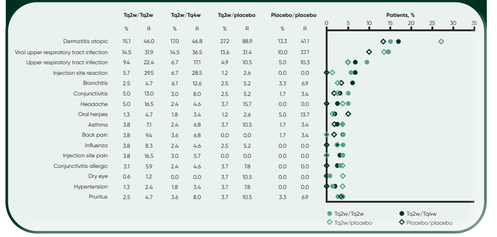
	Tralokinumab (n=1605; PYE=473.19)			Placebo (n=680; PYE=193.1)		
SOC Preferred term	n (adj. %)	E	adj. R	n (adj. %)	E	adj. R
Any eczema herpeticum AESIs	6 (0.3)	6	1.2	10 (1.5)	10	5.2
Infections and infestations	6 (0.3)	6	1.2	10 (1.5)	10	5.2
Eczema herpeticum	6 (0.3)	6	1.2	10 (1.5)	10	5.2
Any malignancies AESIs	1 (0.1)	1	0.2	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.1)	1	0.2	0	0	0
Angiosarcoma	1 (0.1)	1	0.2	0	0	0
Any skin infection AESIs	42 (2.6)	46	9.7	35 (5.5)	42	22.8
Infections and infestations	41 (2.5)	45	9.5	35 (5.5)	42	22.8
Skin infection	13 (0.8)	13	2.6	13 (2.1)	13	7.3
Impetigo	6 (0.4)	6	1.5	4 (0.6)	4	2.2
Dermatitis infected	6 (0.3)	6	1.1	8 (1.2)	10	5.1
Cellulitis	4 (0.3)	4	0.8	2 (0.3)	2	1.0
Staphylococcal skin infection	2 (0.2)	3	0.9	4 (0.6)	5	2.6
Paronychia	2 (0.1)	2	0.4	1 (0.1)	1	0.5
Eczema infected	1 (0.1)	1	0.5	0	0	0
Abscess	2 (0.1)	3	0.5	0	0	0
Infected dermal cyst	1 (0.1)	1	0.2	0	0	0
Skin bacterial infection	1 (0.1)	1	0.2	2 (0.3)	2	1.1
Folliculitis	1 (0.1)	1	0.2	0	0	0
Furuncle	1 (0.1)	1	0.2	0	0	0
Herpes simplex	1 (0.1)	1	0.2	0	0	0
Pyoderma	1 (0.1)	1	0.2	0	0	0
Leishmaniasis	1 (0.1)	1	0.2	0	0	0
Pilonidal cyst	0	0	0	1 (0.2)	2	1.1
Bullous impetigo	0	0	0	1 (0.2)	1	0.6
Carbuncle	0	0	0	1 (0.2)	1	0.6
Eyelid infection	0	0	0	1 (0.2)	1	0.6
General disorders and administration site conditions	1 (0.1)	1	0.2	0	0	0
Injection site reaction	1 (0.1)	1	0.2	0	0	0
Any eye disorder AESIs	132 (7.9)	155	31.1	22 (3.4)	24	12.9
Conjunctivitis (AESI category)	126 (7.5)	145	29.0	21 (3.2)	23	12.3
Infections and infestations	95 (5.7)	109	21.9	15 (2.2)	15	8.0
Conjunctivitis	90 (5.4)	104	21.0	13 (1.9)	13	6.9
Conjunctivitis bacterial	4 (0.2)	4	0.7	1 (0.2)	1	0.6
Conjunctivitis viral	1 (0.1)	1	0.2	1 (0.1)	1	0.5
Eye disorders	34 (2.0)	36	7.1	7 (1.1)	8	4.3
Conjunctivitis allergic	34 (2.0)	36	7.1	7 (1.1)	8	4.3
Keratoconjunctivitis (AESI category)	5 (0.3)	5	1.2	0	0	0
Eye disorders	5 (0.3)	5	1.2	0	0	0
Keratitis	4 (0.3)	4	1.0	0	0	0
Atopic keratoconjunctivitis	1 (0.1)	1	0.2	0	0	0
Keratitis (AESI category)	4 (0.2)	5	0.9	1 (0.2)	1	0.6
Eye disorders	4 (0.2)	5	0.9	0	0	0
Keratitis	4 (0.2)	4	0.7	0	0	0
Ulcerative keratitis	1 (0.1)	1	0.2	0	0	0
Infections and infestations	0	0	0	1 (0.2)	1	0.6
Keratitis viral	0	0	0	1 (0.2)	1	0.6

SOC, System Organ Class, PYE, patient-years of exposure

Safety: monotherapy pool (initial and maintenance treatment period)

- The overall frequency of AEs during the initial treatment period was similar for tralokinumab (69.0%) and placebo (71.5%) and similar to the AD pool
  - The majority of AEs were mild or moderate in severity
- The safety profile during prolonged tralokinumab treatment from 16–52 weeks in the monotherapy pool was consistent with the initial 16-week treatment period, based on overall frequencies of AEs, SAEs, severe AEs and AEs leading to permanent discontinuation **(Figure 2)**
- The overall rate of AEs for tralokinumab q2w during the maintenance treatment period was lower than in the initial treatment period (49.3 vs 69.94 events per 100 PYE) and higher than patients re-randomized to tralokinumab every 4 weeks (q4w) or placebo (414.2 and 442.1 events per 100 PYE, respectively)
- The most frequently occurring AEs (in >5% of patients [MedDRA PT]) for all treatment groups during the maintenance period were generally in line with the most frequently occurring AEs during the initial treatment period in the AD pool and were atopic dermatitis, viral upper respiratory tract infection, upper respiratory tract infection and injection site reaction
- Lower rates of SAEs, severe AEs and AEs leading to permanent discontinuation were also seen for tralokinumab in the maintenance versus initial treatment period

Figure 2. The 15 most frequent AEs by preferred term[a] (safety analysis set, monotherapy pool, maintenance treatment period)



[a]MedDRA PT. %, percentage of patients with one or more events; Placebo/placebo, week 16 placebo responder who continued on placebo; T, tralokinumab; Tq2w/Tq2w, week 16 tralokinumab responder who continued on tralokinumab every 2 weeks; Tq2w/Tq4w, week 16 tralokinumab responder re-randomized to tralokinumab every 4 weeks; Tq2w/placebo, week 16 tralokinumab responder re-randomized to placebo.

Conclusions

- In this analysis of five clinical trials (three Phase 3 and two Phase 2), which included 2285 patients, tralokinumab 300 mg q2w was well tolerated when used as monotherapy and as combination therapy with TCS for treatment of moderate-to-severe AD in the AD pool during the initial 16-week period
- The overall frequencies of AEs were similar for tralokinumab and placebo; skin infections requiring systemic treatment, eczema herpeticum, opportunistic infections and severe or serious infections were lower with tralokinumab than with placebo
- The safety profile during prolonged tralokinumab treatment was consistent with the initial 16-week treatment period and some events decreased in frequency

References

1. Nutten S. Ann Nutr Metab 2015; 66(Suppl 1): 8–16. **2.** Weidinger S, Novak N. Lancet 2016; 387: 1109–1122. **3.** Eckert L et al. J Am Acad Dermatol 2017; 77: 274–279e273. **4.** Silverberg JI et al. Ann Allergy Asthma Immunol 2018; 121: 340–347. **5.** Dalgard FJ et al. J Invest Dermatol 2015; 135: 984–991. **6.** Bieber T. Allergy 2020; 75: 54–62. **7.** Tsoi LC et al. J Invest Dermatol 2019; 139: 1480–1489. **8.** Popovic B et al. J Mol Biol 2017; 429: 208–219. **9.** Wollenberg A et al. J Allergy Clin Immunol 2019; 143: 135–141. **10.** Augustin M et al. J Eur Acad Dermatol Venereol 2020; 34: 142–152.

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