Safety of tralokinumab for the treatment of atopic dermatitis in patients with up to 4.5 years of treatment: an updated integrated analysis of eight clinical trials

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Background

- Patients with moderate-to-severe AD often require long-term treatment, and more data are needed to assess safety in long-term use of biologics
- Tralokinumab is a fully human monoclonal antibody that specifically neutralizes IL-13, a key driver of inflammation in AD, and is indicated for the treatment of patients with moderate-to-severe AD
- In phase 3 trials, tralokinumab was efficacious and well-tolerated as monotherapy and in combination with TCS in adults and adolescents with moderate-to-severe AD[1-3]

Objective

- To evaluate the long-term safety of tralokinumab in an integrated analysis of seven placebo-controlled phase 3 parent trials of up to 52 weeks' duration, and the ongoing, up to 5-year extension study (ECZTEND)

Results

Overall Summary of TEAEs

- No SAEs at the preferred term level were reported in ≥0.1% of the patients (**Table 1**)
- Discontinuation of treatment due to AEs was low (IR=2.8; ALL-TRALO Safety Set)
  - The most common AEs leading to drug withdrawal were dermatitis atopic (1.1%), injection site reaction (0.5%), conjunctivitis (0.2%), and eosinophilia (0.2%)

Table 1. Overall summary of TEAEs

	PBO-CTRL Safety Set (Week 0-16)[a]				ALL-TRALO Safety Set	
	Tralokinumab (N=1939; PYE=587.2)		Placebo (N=913; PYE=271.3)		Tralokinumab (N=2693; PYE=5320.2)	
	n (adj%)	adj IR	n (adj%)	adj IR	n (%)	IR
Adverse events (AEs)	1325 (67.5)	424.8	616 (68.1)	475.3	2307 (85.7)	202.2
Severity						
Mild	1087 (55.4)	295.2	471 (51.6)	278.5	2051 (76.2)	126.1
Moderate	617 (30.5)	125.5	326 (37.0)	174.7	1472 (54.7)	52.4
Severe	90 (4.3)	14.7	55 (6.4)	22.6	259 (9.6)	5.2
Serious AEs	43 (2.0)	6.7	29 (3.3)	11.1	226 (8.4)	4.5
AEs leading to drug withdrawal	42 (2.0)	6.8	18 (2.0)	7.0	147 (5.5)	2.8
Death[b]	1 (0.1)	0.3	0.0	0.0	1 (<0.1%)	0.0

[a]Study size–adjusted % and IR; [b]The reported death occurred after the patient discontinued treatment in the initial period of the of the vaccine study (ECZTRA 5) trial. The cause of death was noted as due to septic shock and respiratory failure, caused by suppurative pneumonia, as well as pulmonary embolism, caused by underlying emphysema with liver disease and malnutrition as contributing factors. These were assessed by the investigator as not related to IMP (tralokinumab and vaccines). Merola J, Bagel J, Almgren P, *et al. J Am Acad Dermatol.* 2021; 85(1):71–78

Most Frequently Reported TEAEs

- The most frequently reported AEs occurring more frequentlywith the known safety profile of tralokinumab: nasopharyngitis, upper respiratory tract infection, conjunctivitis, injection site reaction, conjunctivitis allergic and injection site pain (**Table 2**)
- Dermatitis atopic and asthma were reported less frequently with tralokinumab vs placebo
- with tralokinumab vs placebo were consistent

Table 2. Most frequently reported TEAES (≥2% in any treatment group of the Placebo-controlled Safety Set)

	PBO-CTRL Safety Set (Week 0-16)[a]				ALL-TRALO Safety Set	
	Tralokinumab (N=1939; PYE=587.2)		Placebo (N=913; PYE=271.3)		Tralokinumab (N=2693; PYE=5320.2)	
Preferred Term unless otherwise noted	N (adj%)	adj IR	N (adj%)	adj IR	N (%)	IR
Dermatitis atopic	299 (13.5)	50.9	194 (23.0)	99.5	757 (28.1)	18.5
Nasopharyngitis	313 (15.9)	58.6	114 (12.6)	46.5	723 (26.8)	18.4
Upper Respiratory Tract Infection	122 (6.2)	21.3	42 (4.6)	16.3	325 (12.1)	6.9
Headache	95 (5.1)	17.7	40 (4.4)	15.0	231 (8.6)	4.7
Conjunctivitis	100 (4.9)	16.9	14 (1.6)	5.4	246 (9.1)	5.0
Injection site reaction	85 (4.4)	14.7	2 (0.3)	0.9	183 (6.8)	3.6
Pruritus	54 (2.6)	8.8	28 (3.2)	11.0	134 (5.0)	2.6
Injection site pain	54 (2.6)	8.9	12 (1.5)	5.1	78 (2.9)	1.5
Asthma	29 (1.5)	5.0	24 (2.6)	8.8	90 (3.3)	1.7
Conjunctivitis allergic	45 (2.3)	7.7	12 (1.3)	4.5	137 (5.1)	2.7
Diarrhoea	33 (1.7)	5.6	19 (2.0)	7.0	133 (4.9)	2.6

[a]Study size–adjusted % and IR.

Conclusions

- Long-term use of tralokinumab for up to 4.5 years, was well tolerated in patients (≥12 years)
- The pattern of AEs was consistent with previously reported data[4] and with no new safety signals identified
- Most AEs were non-serious, mild or moderate in severity, and did not lead to treatment discontinuation
- The IRs did not increase with increasing duration of treatment exposure

Overall Summary of Treatment-Emergent AESIs

- In the ALL-TRALO Safety Set most (97%) of the AESI Eye disorder events were mild to moderate and the majority (69%) were recovered or resolved, and 0.4% lead to permanent discontinuation of study drug (**Table 3**)
- AESIs, including eye disorders, skin infections requiring systemic treatment, eczema herpeticum and malignancies were observed in the ALL-TRALO Safety Set at rates similar to or lower than reported in the PBO-CTRL Safety Set

Table 3. Overall summary of treatment-emergent AESIs

	PBO-CTRL Safety Set (Week 0-16)[a]				ALL-TRALO Safety Set	
	Tralokinumab (n=1939; PYE=587.2)		Placebo (n=913; PYE=271.3)		Tralokinumab (n=2693; PYE=5320.2)	
	N (adj%)	adj IR	N (adj%)	adj IR	N (%)	IR
AESI eye disorders	158 (8.0)	27.8	30 (3.4)	11.4	410 (15.2)	8.9
AESI conjunctivitis[b]	149 (7.4)	25.8	27 (3.1)	10.4	386 (14.3)	8.3
AESI keratitis[c]	6 (0.3)	1.0	3 (0.3)	1.0	28 (1.0)	0.5
AESI keratoconjunctivitis[d]	6 (0.4)	1.2	0 (0.0)	0.0	22 (0.8)	0.4
AESI skin infections requiring systemic treatment	48 (2.3)	7.7	45 (5.1)	18.1	142 (5.3)	2.8
AESI eczema herpeticum[e]	9 (0.5)	1.6	12 (1.4)	4.8	34 (1.3)	0.6
AESI malignancies[f]	1 (<0.1)	0.1	1 (0.1)	0.4	20 (0.7)	0.4

[a]Study size–adjusted % and IR; [b]Conjunctivitis category includes several PTs, such as conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, and conjunctivitis viral; [c]Keratitis category includes several PTs, such as keratitis, keratitis viral, and ulcerative keratitis; [d]Keratoconjunctivitis category includes the PTs atopic keratoconjunctivitis and keratitis; [e]Eczema herpeticum category includes preferred terms such as eczema herpeticum and kaposi's varicelliform eruption; [f]Malignancies diagnosed after dosing, excluding basal cell carcinoma, localized squamous cell carcinoma of the skin, and carcinoma in situ of the cervix; the malignancies diagnosed after randomization in the ALL-TRALO safety analysis set include prostate cancer (N=4), invasive breast carcinoma (N=3), breast cancer (N=2), invasive ductal breast carcinoma (N=2), adenoid cystic carcinoma, angiosarcoma, cutaneous T-cell lymphoma, keratoacanthoma, malignant melanoma in situ, malignant melanoma, ovarian cancer, papillary thyroid cancer, tonsil cancer.

Other Safety Areas of Clinical Interest

- Rates of other safety areas of clinical interest were low for the PBO-CTRL and ALL-TRALO Safety Sets (**Table 4**)
- The findings are consistent with the known safety profile of tralokinumab, with no new safety signals detected

Table 4. Other safety areas of clinical interest

	PBO-CTRL Safety Set (Week 0-16)[a]				ALL-TRALO Safety Set	
	Tralokinumab (n=1939; PYE=587.2)		Placebo (n=913; PYE=271.3)		Tralokinumab (n=2693; PYE=5320.2)	
Preferred Term unless otherwise noted	N (adj%)	adj IR	N (adj%)	adj IR	N (%)	IR
ADRs for tralokinumab reported in <2% of patients						
Eosinophilia	15 (0.7)	2.3	2 (0.3)	0.9	29 (1.1)	0.5
Eosinophil count increased	7 (0.4)	1.2	-	-	20 (0.7)	0.4
Special warnings and precautions for use						
Helminth infections NEC (HLT)	-	-	-	-	-	-
Known risks of AD patient population						
Herpes simplex	26 (1.2)	4.1	9 (1.0)	3.2	111 (4.1)	2.2
Oral herpes	18 (1.0)	3.4	14 (1.5)	5.3	96 (3.6)	1.9
Alopecia areata	8 (0.4)	1.2	5 (0.5)	1.7	27 (1.0)	0.5
Safety areas of interest for systemic AD treatments						
Arthralgia	36 (1.7)	5.8	15 (1.6)	5.6	128 (4.8)	2.5
Nausea	22 (1.0)	3.4	15 (1.7)	5.9	78 (2.9)	1.5
Acne	16 (1.0)	3.5	14 (1.4)	4.8	59 (2.2)	1.1
Herpes zoster	10 (0.5)	1.5	5 (0.5)	1.8	60 (2.2)	1.2
Serious Infections[b]	8 (0.4)	1.4	8 (1.0)	3.2	51 (1.9)	1.0
Pulmonary Embolism	1 (<0.1)	0.1	2 (0.1)	-	1 (<0.1)	0.0
Deep vein thrombosis	-	-	2 (0.2)	0.7	1 (<0.1)	0.0

[a]Study size–adjusted % and IR; [b]SOC: Infections and Infestations + Serious AE = Yes.

Abbreviations

%, percentage of patients; AD, atopic dermatitis; ADR, adverse drug reaction; AE, adverse event; AESI, AE of special interest; BMI, body mass index; EASI, Eczema Area and Severity Index; HLT, high level term; IL-13, interleukin-13; IGA, Investigator's Global Assessment; IR, Incidence rate (n/100PYE), for IR calculations, patient exposure was censored at the time of first event; JP, Japan; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients with recorded observation, achieving the indicated metric, or with ≥1 event; nP, number of patients with ≥1 event; N, number of patients with recorded observation or in indicated treatment set; NEC (HLT), not elsewhere classified; PBO, placebo; PBO-CTRL, placebo-controlled; PT, preferred term; Q2W, every 2 weeks; PYE, patient-years of exposure; Q4W, every 4 weeks; SD, standard deviation; TCS, topical corticosteroids; TEAE, treatment-emergent AE; TRALO, tralokinumab.

References

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Baseline Demographics and Characteristics

- Baseline demographics and clinical characteristics were similar between the safety sets (**Table 5**)

Table 5. Baseline demographics and characteristics

	PBO-CTRL Safety Set (Week 0-16)		ALL-TRALO Safety Set
	Tralokinumab (N=1939, PYE=587.2)	Placebo (N=913, PYE=271.3)	N=2693, PYE=5320.2
Median age, years (min; max)	33.0 (12.0 ; 92.0)	32.0 (12.0 ; 82.0)	33.0 (12.0 ; 92.0)
Age group, n (%)			
12-17	195 (10.1)	94 (10.3)	280 (10.4)
18-64	1662 (85.7)	784 (85.9)	2304 (85.6)
≥65	82 (4.2)	35 (3.8)	109 (4.0)
Female, n (%)	836 (43.1)	395 (43.3)	1155 (42.9)
Race, n (%)			
White	1307 (67.4)	587 (64.3)	1802 (66.9)
Asian	409 (21.1)	210 (23.0)	588 (21.8)
Black or African American	153 (7.9)	84 (9.2)	211 (7.8)
BMI (kg/m²), N	1934	910	2687
Median (min ; max)	24.8 (14.3 ; 61.3)	25.2 (15.3 ; 61.0)	24.9 (14.3 ; 61.3)
Current medical history, n (%)			
Asthma	769 (39.7)	368 (40.3)	1085 (40.3)
Allergic conjunctivitis	401 (20.7)	207 (22.6)	583 (21.6%)
Atopic keratoconjunctivitis	60 (3.1)	26 (2.8)	84 (3.1)
Median duration of AD, years (min ; max)	24.0 (1.0 ; 77.0)	23.0 (1.0 ; 77.0)	24.0 (1.0 ; 77.0)
Median BSA, % (min ; max)	49.0 (10.0 ; 100.0)	50.0 (10.0 ; 100.0)	50.0 (10.0 ; 100.0)
Median EASI score (min ; max)[a]	27.6 (15.4 ; 72.0)	27.9 (12.5 ; 72.0)	27.8 (12.5 ; 72.0)
IGA, n (%)[a]			
3	1005 (51.8)	475 (52.0)	1391 (51.7)
4	934 (48.2)	438 (48.0)	1302 (48.3)

[a]Full analysis set

Methods

- Two datasets were analyzed:
  - A placebo-controlled (PBO-CTRL) safety analysis set included patients treated with tralokinumab compared with placebo in the initial 16-week period of seven phase 3 trials (**Figure 1**)
    - Study size–adjusted percentages and incidence rates (IRs) were calculated as weighted average using Cochran-Mantel-Haenszel weights
  - An all-tralokinumab (ALL-TRALO) safety analysis set combining the parent trials with the subsequent ECZTEND trial including patients from first dose of tralokinumab until end of tralokinumab exposure or the ECZTEND data cut-off (April 30th, 2022)
    - Only AEs occurring while on active treatment were accounted for and exposure time was defined as the sum of the exposure with active treatment
    - Safety follow up and periods on placebo were disregarded
- AEs were coded using MedDRA version 24.0
- Exposure adjusted IRs were calculated as the number of patients reporting an event per PYE. PYE was defined as the time until the first event or exposure end, whichever came first, and incidence was defined as the first event
- In the ALL-TRALO Safety Set, 2693 patients (≥12 years) received tralokinumab for up to 238.5 weeks (≈4.5 years) with a median exposure time of 76.5 weeks

Figure 1. Integrated safety analysis study design