Tralokinumab demonstrated a consistent safety profile with up to 42 months of treatment in moderate-to-severe atopic dermatitis: including adverse events of special interest

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Introduction

- Atopic dermatitis (AD) is a chronic and debilitating inflammatory skin disease requiring long-term treatment options with a favorable safety profile[1,2]
- Tralokinumab, a first-in-class, fully human monoclonal antibody, specifically neutralizes IL-13 with high affinity[3]
- Phase 3 studies with tralokinumab have demonstrated favorable safety and sustained efficacy in adult patients with AD for up to 1 year[4,5]
- An ongoing extension trial, ECZTEND (NCT03587805), is assessing the safety and efficacy of treatment with subcutaneous tralokinumab 300 mg every 2 weeks (Q2W) following participation in a parent trial (PT)
- With one additional year added to the previously published data[6] this analysis further describes the safety profile of tralokinumab during long-term treatment

Objective

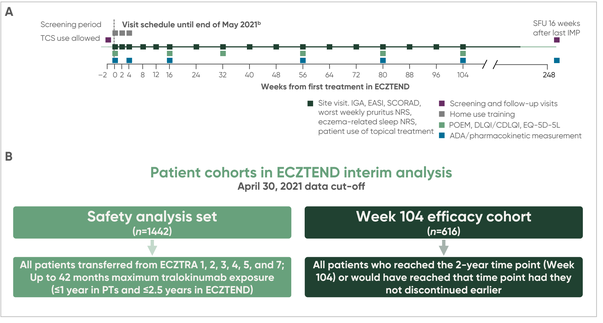
To report an interim safety analysis of patients treated with tralokinumab for up to 42 months, including adverse events of special interest (AESI)

Materials and Methods

Study design and patient cohorts

- ECZTEND is an open-label, 5-year extension trial including adult and adolescent patients with AD in 11 countries who previously participated in the tralokinumab PTs ECZTRA 1-8 or the TraSki investigator-initiated study
- In ECZTEND, patients received open-label tralokinumab 300 mg Q2W (home use) plus optional topical corticosteroids (TCS), with visits every 8 weeks (**Figure 1A**)
- Interim safety analyses presented here include all patients transferred from ECZTRA 1-5 and 7; with patients having received up to 42 months maximum tralokinumab exposure (≤1 year in PTs and ≤2.5 years in ECZTEND; safety analysis set, n=1442) (**Figure 1B**)
  - ECZTRA 1/2: double-blinded, randomized, placebo-controlled, 52-week monotherapy trials
  - ECZTRA 3: double-blinded, randomized, placebo-controlled, 32-week TCS combination trial
  - ECZTRA 4: open-label, 14-week, drug-drug interaction (DDI) trial
  - ECZTRA 5: double-blinded, randomized, placebo-controlled, 16-week, vaccine antibody-response trial
  - ECZTRA 7: randomized, double-blinded, placebo-controlled, 26-week TCS combination trial in Cyclosporin A (CsA) refractory patients
- Interim efficacy analyses are also presented from the ECZTEND Week 104 cohort (n=616), which includes all patients who reached the 2-year time point or would have reached that time point had they not discontinued earlier (**Figure 1B**)

Figure 1. ECZTEND study design (A) and patient cohorts in interim analyses (B)



Endpoints and analyses

- Primary endpoint: Number of AEs during the treatment period from baseline of ECZTEND up to Week 268
- Secondary endpoints: Proportions of patients achieving an Investigator's Global Assessment (IGA) score of 0/1 (clear/almost clear) and >75% improvement in Eczema Area and Severity Index (EASI-75) from Week 16 to Week 248
- A summary of the number of AEs, the rate of AEs, the number (percentage) of patients with any treatment-emergent adverse events (TEAEs), deaths, SAEs, and withdrawals from the trial due to AEs are presented
- AESIs were predefined in the trial based on areas of safety interest for monoclonal antibodies in AD: skin infections requiring systemic treatment, eczema herpeticum, malignancies, and eye disorders. Other safety areas of interest were captured retrospectively using MedDRA searches of all AEs

Results

Patients, Demographics, and Clinical Characteristics

- Patients had up to 42 months of tralokinumab exposure (including PTs plus ECZTEND) with a median time on tralokinumab total of 131.5 weeks (approximately 31 months; IQR 83.4-161.8 weeks), at the time of data cut-off

Table 1. ECZTEND interim analysis baseline demographic and disease characteristics

	ECZTEND interim safety analysis set *n*=1442	
Age Median years (IQR)	38.0 (27.0; 50.0)	
Sex n (%)		
Male	831 (57.6)	
Female	611 (42.4)	
Race n (%)[a]		
White	1093 (75.9)	
Black	108 (7.5)	
Asian	203 (14.1)	
Parent trial n (%)		
ECZTRA 1	450 (31.2)	
ECZTRA 2	293 (20.3)	
ECZTRA 3	282 (19.6)	
ECZTRA 4	31 (2.1)	
ECZTRA 5	149 (10.3)	
ECZTRA 7	237 (16.4)	
Age at onset of AD Median years (IQR)	3.0 (1.0; 15.0)	
Duration of AD Median years (IQR)	27.0 (18.0; 39.0)	
Patients who permanently discontinued ECZTEND n (%)	330 (22.9)	
	Parent Trial Baseline	**ECZTEND Baseline**
IGA severity n (%)		
Clear/minimal (score=0/1)	–	442 (30.6)
Mild (score=2)	–	524 (36.3)
Moderate (score=3)	765 (53.1)	391 (27.1)
Severe (score=4)	677 (46.9)	85 (5.9)
EASI Median (IQR)	26.8 (20.5; 37.6)	4.8 (1.7; 12.0)
SCORAD Median (IQR)	67.7 (60.0; 77.9)	30.2 (18.7; 45.0)
DLQI[b] Median (IQR), n	16.0 (11.0; 22.0), 1391	5.0 (2.0; 10.0), 1400
Worst weekly pruritus NRS[c] Median (IQR), n	7.9 (6.8; 8.8), 1257	5.0 (3.0; 7.0), 1440

[a]Available in 1440 patients. [b]Subjects from the ECZTRA 4 parent trial did not have DLQI assessments in the parent trial, and thus are missing parent trial baseline for DLQI assessments. [c]In PTs, worst pruritus NRS is assessed daily; in ECZTEND, worst pruritus NRS is assessed based on recall of the previous week before the visit.

Summary of safety in ECZTEND

- Long-term use of tralokinumab 300 mg Q2W was well-tolerated, and no new safety signals were identified with up to 42 months of treatment relative to initial treatment in parent trials (**Figure 2**)
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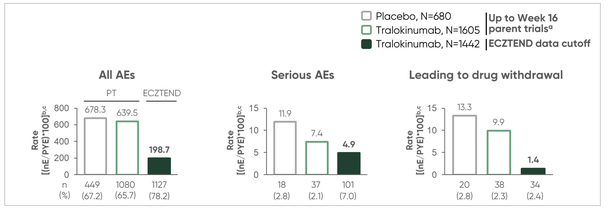
- The pattern of frequently reported AEs in ECZTEND (≥5.0% of patients) was similar to that observed with tralokinumab in the PTs, including viral upper respiratory tract infection, atopic dermatitis, upper respiratory tract infection, headache, and conjunctivitis (reported by preferred term)
  - No events of conjunctivitis AEs were SAEs; only 4 patients discontinued due to conjunctivitis AEs (0.3 %)

Figure 2. Long-term use of tralokinumab 300 mg Q2W was well-tolerated in ECZTEND

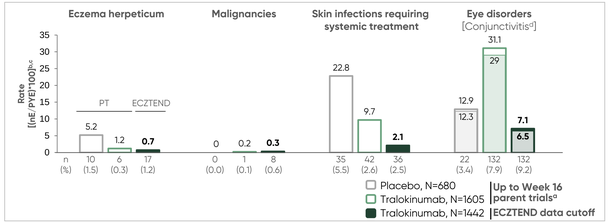


[a]Pooled safety analysis set includes patients from parent trials ECZTRA 1, 2, 3, 5, and Phase 2b. [b]Rate calculated by number of events divided by PYE, multiplied by 100. [c]For PTs, Cochran-Mantel-Haenszel weights were applied to calculate adjusted AE incidences and rates to account for different randomization ratios across PTs. [d]Conjunctivitis reported by preferred term.

Summary of AESIs in ECZTEND

- AESIs were observed at rates similar to or lower than reported in PTs (**Figure 3**, **Table 2**)
- The most frequent eye disorder was conjunctivitis, including bacterial, allergic and viral types
- There was no clustering in type of malignancy and none reported in more than 2 patients
- There was no specific clustering in any type of skin infection requiring systemic treatment
- Other areas of interest, based on common concerns for those with AD, were:
  - Injection site reaction: reported for 35 patients [2.4%, 2.5 vs 22.9 and 4.0 (nE/PYE)*100 in ECZTEND vs PT tralokinumab and placebo]
  - Rates for herpes simplex, oral herpes and herpes zoster: similar or lower than placebo up to week 16 and rates decreased over time [2.0/1.6/1.3 vs 5.2/3.1/1.4 and 3.7/8.1/2.0 (nE/PYE)*100 in ECZTEND vs PT tralokinumab and placebo]

Figure 3. AESIs in ECZTEND at April 30, 2021 data cut-off



[a]Pooled safety analysis set includes patients from parent trials ECZTRA 1, 2, 3, 5, and Phase 2b. [b]Rate calculated by number of events divided by PYE, multiplied by 100. [c]For PTs, Cochran-Mantel-Haenszel weights were applied to calculate adjusted AE incidences and rates to account for different randomization ratios across PTs. [d]Conjunctivitis category includes several preferred terms, such as conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial and conjunctivitis viral.

Table 2. AESIs in ECZTEND at April 30, 2021 data cut-off

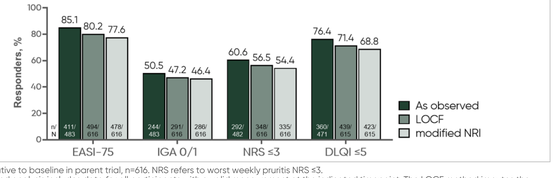
	AEs in ECZTEND interim safety analysis set: Tralokinumab Q2W + optional TCS (*n*=1442; PYE=2446.2; 131.5 weeks median exposure)				AEs up to Week 16 in parent trials initial tralokinumab treatment[a]: Tralokinumab Q2W ± TCS (*n*=1605; PYE=473.2)				Placebo Q2W ± TCS (*n*=680; PYE=193.1)			
	n (%)	Rate[b] [(nE/PYE)*100]	E	Rate [(nE/PYE)*100]	*n* (adj. %)[c]	E	Adj. Rate[b,c] [(nE/PYE)*100]	E	*n* (adj. %)[c]	E	Adj. Rate[b,c] [(nE/PYE)*100]	E
Eczema herpeticum	17 (1.2)	0.7	18	0.7	6 (0.3)	6	1.2	10	10 (1.5)	10	5.2	10
Malignancies	8 (0.6)	0.3	8	0.3	1 (0.1)	1	0.2	0	0 (0)	0	0	0
Skin infections requiring systemic treatment	36 (2.5)	1.5	51	2.1	42 (2.6)	46	9.7	55	35 (5.5)	42	22.8	42
Eye disorders	132 (9.2)	5.8	174	7.1	132 (7.9)	155	31.1	227	22 (3.4)	24	12.9	24
Conjunctivitis[d]	125 (8.7)	5.4	160	6.5	126 (7.5)	145	29.0	211	21 (3.2)	23	12.3	23
Keratoconjunctivitis	8 (0.6)	0.3	8	0.3	5 (0.3)	5	1.2	0	0 (0)	0	0	0
Keratitis	6 (0.4)	0.2	6	0.2	4 (0.2)	5	0.9	1	1 (0.2)	1	0.6	1

[a]Pooled safety analysis set includes patients from parent trials ECZTRA 1, 2, 3, 5, and Phase 2b. [b]Rate calculated by number of events divided by PYE, multiplied by 100. [c]For PTs, Cochran-Mantel-Haenszel weights were applied to calculate adjusted AE incidences and rates to account for different randomization ratios across PTs. [d]Conjunctivitis category includes several preferred terms, such as conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial and conjunctivitis viral.

Sustained improvement in AD signs and symptoms

- Tralokinumab demonstrated sustained long-term improvement in AD signs and symptoms in patients who reached the 2-year time point (Week 104), or would have reached that time point had they not discontinued earlier, prior to data cutoff April 30, 2021 (**Figure 4**)

Figure 4. Proportion of patients achieving EASI-75, IGA 0/1, Worst Weekly Pruritus NRS ≤3, and DLQI ≤5 with tralokinumab at Week 104



Data is relative to baseline in parent trial, n=616. NRS refers to worst weekly pruritis NRS ≤3.
The observed analysis includes data for all participants with a valid measurement at the indicated timepoint. The LOCF method imputes the value recorded at the participant's last visit for subsequent missed timepoints. The modified NRI method considers participants who discontinue from trial due to adverse event(s) or lack of efficacy as non-responders, and other missing are imputed with LOCF.

Conclusions

- This analysis of 1442 patients with up to 42 months of treatment supports the long-term benefit-risk profile of targeted IL-13 inhibition with tralokinumab for patients with moderate-to-severe AD, with no new safety signals identified
- Exposure-adjusted incidence rates of AEs of special interest were generally similar to or lower than rates reported during the short-term, placebo-controlled period up to Week 16 and declined over time
- Overall, tralokinumab demonstrated sustained long-term improvement in extent and severity of atopic dermatitis over 104 weeks of treatment in ECZTEND

Abbreviations

%, percentage of patients with ≥1 event; AD, atopic dermatitis; adj., adjusted; AE, adverse event; AESI, adverse event of special interest; DLQI, Dermatology Life Quality Index; E, number of adverse events; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; LOCF, last observation carried forward; n, number of patients with ≥1 event; nE, number of events; nP, number of patients; NRI, non-responder imputation; NRS, Numeric Rating Scale; PYE, patient-years of exposure; PT, parent trial; Q2W, every 2 weeks; TCS, topical corticosteroids.

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