Tralokinumab prevents flares in moderate-to-severe atopic dermatitis: post hoc analyses of a randomized phase 3 clinical trial (ECZTRA 3)

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Introduction

- Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by periods of acute symptomatic worsening (flares)[1,2]
- Tralokinumab is a fully human, high-affinity, monoclonal antibody that specifically neutralizes interleukin (IL)-13, a key driver of cutaneous barrier dysfunction, inflammation and dysbiosis in AD[3-7]
- Severe AD flares prompt rescue therapy with high-potency topical corticosteroids (TCS), systemic steroids, and antibiotics, and can lead to both emergency room visits and hospitalizations[8,9]
- Flare prevention is one of the primary goals for long-term control of AD. Flares are commonly defined as worsening of AD requiring treatment intensification or escalation that may impact the flare frequency measured, particularly in moderate-to-severe AD[10,11]

Objective

To assess the impact of tralokinumab treatment on flare prevention in adults with moderate-to-severe AD from the ECZTRA 3 trial (NCT03363854)

Methods

Study design (Figure 1)

- Patients were randomly assigned 2:1 to receive either subcutaneous tralokinumab 300 mg + TCS or placebo + TCS every 2 weeks (Q2W) for an initial treatment period of 16 weeks
- The treatment during the continuation period depended on the regimen received in the initial treatment period and on the subject's clinical response (IGA 0/1 or EASI-75) at Week 16
- During the initial and continuation treatment periods, all subjects applied a thin film of a supplied TCS (mometasone furoate, US: Class 4 [mid-strength]; Europe: Class 3 [potent]) once daily to areas with active lesions as needed; lower potency TCS or topical calcineurin inhibitors could be prescribed if needed on body areas where the supplied TCS was not advisable or on areas where continued treatment with TCS was considered unsafe
- Topical therapy was discontinued when skin lesions were cleared
- All tralokinumab arms during Weeks 16-32 were pooled together for these post hoc analyses

Endpoints and analyses

- Time to first flare from Week 0 to 16 according to the following definitions:
  - **Rescue flare[a]**: treatment intensification to either high-potency TCS, oral corticosteroids, and other systemic treatments
  - **AE flare[a]**: adverse event (AE) reporting of 'dermatitis atopic' or 'dermatitis infected' was analyzed to reflect AD worsening to a degree beyond normal fluctuation
  - **Rescue×AE flare[a]**: combined analysis of Rescue flare and AE flare, whichever occurred first
  - **Per protocol flare[b]**: AD flares, defined as worsening of the disease that required escalation/intensification of AD treatment including initiation or intensification of the supplied TCS
- Proportion of patients with flares from Week 0 to 32

Time to first flare was analyzed using a Cox proportional hazard model stratified by region and baseline IGA with planned treatment as covariate

[a]Post hoc analyses
[b]Pre-specified analysis

Results

Patient characteristics

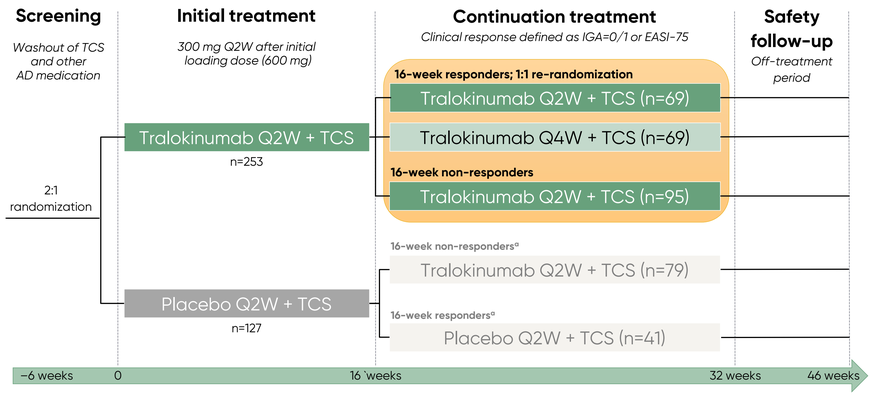
Patients had a long duration of AD and nearly 50% had severe AD (IGA-4) at baseline **(Table 1)**

Table 1. Baseline characteristics[a]

	Placebo Q2W + TCS (n=127)	Tralokinumab Q2W + TCS (n=253)
Mean age, years	37.7	39.8
Male, %	66	49
Mean duration of AD, years	28.7	28.0
Median age of AD onset, years	2.0	4.0
Mean BSA involvement with AD, %	49.0	47.6
Severe disease (IGA-4), %	47	46
Mean EASI	30.4	28.8
Mean weekly average worst daily pruritus NRS score	7.9	7.7

[a]All randomized subjects (2 subjects were not dosed and therefore not included in the analyses)

Figure 1. ECZTRA study design (modified)



Key inclusion criteria

- History of AD for ≥1 year
- Recent history of inadequate response to treatment with topical medications
- BSA involvement ≥10%
- EASI score ≥12 at screening and ≥16 at baseline
- IGA score ≥3 at screening and at baseline
- Worst daily pruritus NRS average score of ≥4 prior to baseline

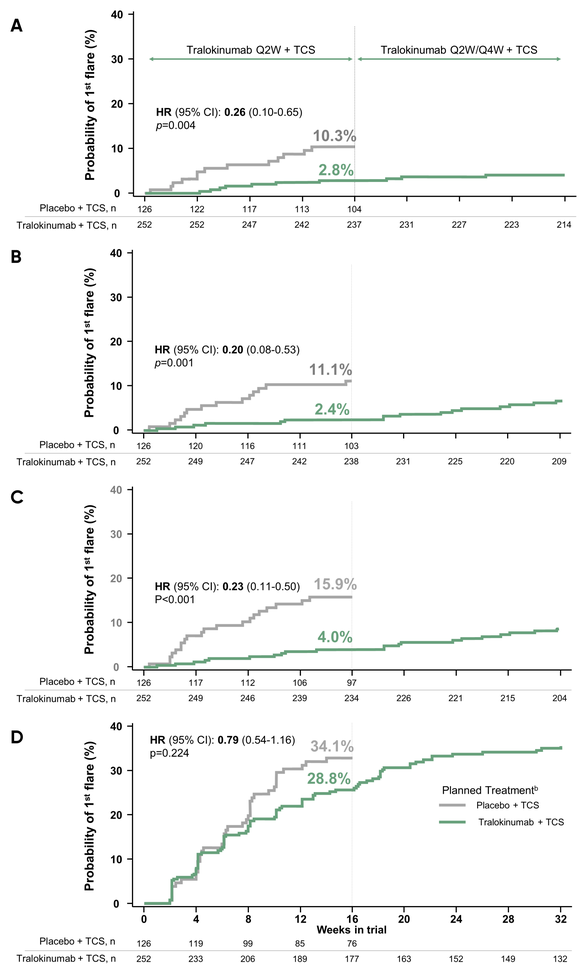
[a]To maintain blinding of the study, placebo patients who achieved the clinical response criteria at week 16 continued to receive placebo (Q2W) and patients not achieving the clinical response criteria were assigned tralokinumab Q2W plus TCS as needed. These patients were not included in analyses after week 16

AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroid

AD flare analyses (Week 0 to 16)

- Overall, 7 (2.8%) patients experienced a 'rescue flare' in the tralokinumab + TCS group compared to 13 (10%) in the placebo + TCS group during the first 16 weeks, corresponding to a 74% risk reduction with tralokinumab
- Similarly, 6 (2.4%) patients experienced an 'AE flare' in the tralokinumab + TCS group versus 14 (11%) with placebo + TCS during the first 16 weeks, corresponding to an 80% risk reduction with tralokinumab
- The risk of a 'rescue×AE flare' was 77% lower with tralokinumab
- The proportion of patients with a 'per protocol flare' during the initial 16-week treatment period was numerically lower in the tralokinumab + TCS group (28%, 70/252) compared to the placebo + TCS group (34%, 43/126)

Figure 2. Time to first flare (Week 0 to 32)[a] according to the following endpoint definitions: **A**. Rescue flare. **B.** AE flare. **C**. Rescue×AE flare. **D.** Per protocol flare.



[a]Treatments are re-assigned at Week 16. Hence, the placebo arm is only followed up to Week 16. The tralokinumab arm is followed beyond Week 16 as the different dosing (Q2W or Q4W) is ignored

CI, confidence interval; HR, hazard ratio

Table 2. Proportion of subjects experiencing flares from Week 0 to 16

	Placebo (n=126)	Tralokinumab Q2W (n=252)	Hazard ratio (HR) [95% CI]	*p*-value
Rescue flare[a]	13 (10.3%)	7 (2.8%)	0.26 [0.10-0.65]	0.004
AE flare[a]	14 (11.1%)	6 (2.4%)	0.20 [0.08-0.53]	0.001
Rescue×AE flare[a]	20 (15.9%)	10 (4.0%)	0.23 [0.11-0.50]	<0.001
Per protocol flare[b]	43 (34.1%)	70 (28.8%)	0.79 [0.54-1.16]	0.224

[a]Post hoc analyses
[b]Pre-specified analysis

AD flare analyses (Week 0 to 32)

- Among patients who received tralokinumab + TCS during the entire 32-week treatment period, nearly all did not experience a 'rescue flare' (96%) or an 'AE flare' (94%) during the 32 weeks; the majority (65%) did not have a 'per protocol flare'

TCS use by the end of the initial treatment period (Week 0 to 16)

- Mean amount of TCS used during Weeks 15-16 in the tralokinumab + TCS group was 50% less compared with the placebo + TCS group ($p<0.001$)
- The cumulative amount of TCS used over 16 weeks was approximately 30% lower in tralokinumab + TCS group compared to the placebo + TCS group ($p<0.05$)

TCS use with continued trakolinumab treatment (Week 16 to 32)

- Estimated use of TCS among patients continuing on tralokinumab Q2W/Q4W remained low, 9.2-13.6 g (SE: 1.2-2.0) per each 2-week period

Conclusions

- Tralokinumab treatment reduced the risk of 'rescue flares' by 74% relative to placebo when used in combination with TCS in adults with moderate-to-severe AD
- Nearly all patients (96%) remained free of 'rescue flares' with tralokinumab + TCS during the entire 32-week treatment period
- We propose 'rescue flares' as a clinically relevant flares outcome measure in moderate-to-severe AD that highlights flares where moderate potency TCS treatment intensification is insufficient

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Disclosures

- Jonathan Silverberg is a consultant/advisory board member for LEO Pharma and has acted as a consultant for, and/or has received grants/honoraria from, AbbVie, AnaptysBio, Asana Biosciences, Galderma Research and Development, GlaxoSmithKline, Glenmark, Kiniksa, LEO Pharma, Lilly, MedImmune, Menlo Therapeutics, Pfizer, PuriCore, Regeneron, and Sanofi
- Sebastien Barbarot is a consultant/advisory board member for Sanofi-Genzyme, Abbvie, Novartis, Janssen, Leo Pharma, Pfizer, Eli Lilly, and UCB Pharma
- Julia Welzel participated in the ECZTRA study as a principal investigator and reports honoraria for lectures and consulting from LEO Pharma
- Mahreen Ameen is a consultant for LEO Pharma, Abbvie, Pfizer, and Eli Lilly
- Jacob Thyssen reports is a consultant /advisory board member for Abbvie, Pfizer, Leo Pharma, Sanofi-Genzyme, Eli Lilly, and Regeneron
- Mark Lomaga has no conflicts of interest to report
- Christina Kurre Olsen, Thomas Mark, and Joshua Corriveau are employees of LEO Pharma A/S
- Joseph Merola is a consultant and/or investigator for Abbvie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Bristol-Myers Squibb/Celgene, Sanofi, Regeneron, Biogen, Pfizer, and Leo Pharma

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