LEO 6

# Efficacy and safety of tralokinumab with concomitant topical corticosteroids in North American adults with moderate-to-severe atopic dermatitis: a subanalysis of the ECZTRA 3 trial

Boni E. Elewski,[1] Matthew J. Zirwas,[2] Richard G. Langley,[3] Andrew F. Alexis,[4] Karen A. Veverka,[5] John Zoidis,[5] Azra Kurbasic,[6] Jonathan I. Silverberg[7]

[1]University of Alabama, Birmingham, AL, USA; [2]Probity Medical Research, Columbus, OH, USA; [3]Dalhousie University, Halifax, Nova Scotia, Canada; [4]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [5]LEO Pharma, Madison, NJ, USA; [6]LEO Pharma A/S, Ballerup, Denmark; [7]The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

## Introduction

- Atopic dermatitis (AD) is a common, chronic inflammatory skin disease, characterized by excessive pruritus and sleep disturbance, among other symptoms[1–3]
- Tralokinumab is a fully human monoclonal antibody that specifically neutralizes interleukin-13 (IL-13), a key cytokine of the chronic type 2 inflammation underlying AD; IL-13 is overexpressed in lesional and non-lesional AD skin[4–6]
- ECZTRA 3 (NCT03363854) was a Phase 3, randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of subcutaneous tralokinumab 300 mg every 2 weeks (q2w) vs. placebo (after a loading dose of 600 mg), in combination with topical corticosteroids (TCS) as needed, for an initial treatment period of 16 weeks in adults with moderate-to-severe AD across Europe and North America
  - Significantly more patients achieved the primary endpoints of Investigator's Global Assessment (IGA) score of 0/1 (clear/almost clear) and/or a 75% improvement in Eczema Area and Severity Index (EASI-75) at week 16 with tralokinumab plus TCS compared with placebo plus TCS
  - Tralokinumab demonstrated improvements vs. placebo across key secondary endpoints in patient-reported outcomes (Dermatology Life Quality Index [DLQI], pruritus Numeric Rating Scale [NRS], and SCORing Atopic Dermatitis [SCORAD]) at week 16
  - Cumulative TCS use in tralokinumab-treated patients was lower than that of those who received placebo at week 16, suggesting achievement of endpoints was not likely attributable to TCS use alone

## Objective

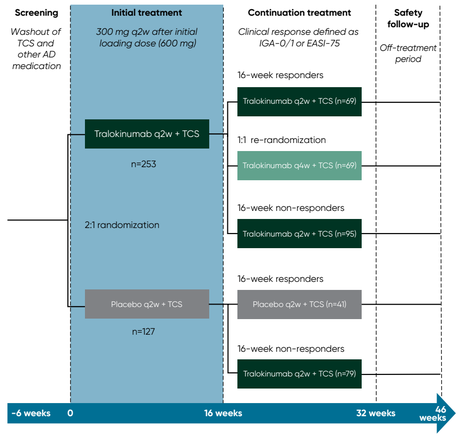
- To evaluate the efficacy and safety of tralokinumab 300 mg q2w in combination with TCS in the ECZTRA 3 North American subpopulation at week 16

## Methods

### Study design and patients

- ECZTRA 3 was a randomized, double-blind, placebo-controlled, 32-week trial in adult patients with moderate-to-severe AD (**Figure 1**)
- Patients were enrolled from Europe (Belgium, Germany, The Netherlands, Poland, Spain, and UK) and North America (USA and Canada)
- Eligible patients were ⩾18 years of age, with a confirmed diagnosis of AD for >1 year and AD involvement of ⩾10% of body surface area, EASI score of ⩾12 at screening and ⩾16 at baseline, IGA score of ⩾3, pruritus NRS score of ⩾4, and were candidates for systemic therapy due to a recent (within 1 year) history of inadequate response or intolerance to topical treatment
- Patients were stratified by region and baseline disease severity (IGA-3 [moderate] or IGA-4 [severe]) and were randomized 2:1 to receive subcutaneous tralokinumab 300 mg or placebo q2w (after a loading dose of 600 mg), plus TCS as needed, for an initial treatment period of 16 weeks
- Use of TCS (mometasone furoate: US Class 4 [midstrength]) was permitted as early as day 0, after a washout period of 2 weeks for TCS
- Rescue treatment, which included higher-potency TCS (e.g. clobetasol), was permitted in the form of topical and systemic medications to control intolerable AD symptoms

**Figure 1. ECZTRA 3 trial design**




**Primary endpoints**
- IGA-0/1 and/or EASI-75 at week 16

**Secondary endpoints**
- Change in SCORAD from baseline to week 16
- Change in DLQI score from baseline to week 16
- Reduction of worst daily pruritus NRS (weekly average) ⩾4 from baseline to week 16
- Adverse events/serious adverse events by preferred term

### Endpoints

- Primary endpoints were defined as IGA-0/1 and/or EASI-75 at week 16
- Key secondary endpoints included reduction of worst daily pruritus NRS (weekly average) of at least 4 from baseline to week 16 and change from baseline to week 16 in SCORAD and DLQI

### Safety assessments

- Adverse events were collected from the first trial-related activity after patients provided informed consent until completion of the clinical trial

### Statistical analysis

- For binary endpoints, the difference in response rates between treatment groups was analyzed using the Cochran-Mantel-Haenszel test, stratified by baseline IGA score; patients receiving rescue medication prior to week 16 or with missing data were considered non-responders
- Continuous endpoints were assessed using a mixed-effect model for repeated measurements, with an unstructured covariance matrix to model within-patient variation and the mean change modeled as: change from baseline = treatment*week + baseline*week + baseline IGA; denominator degrees of freedom were estimated using Kenward-Roger approximation
  - Data collected after permanent discontinuation of investigational medicinal product or after initiation of rescue medication were excluded from the analysis
- Descriptive statistics were used to present baseline demographics, baseline disease characteristics, and safety assessments

## Results

### Patient characteristics

- In total, 380 patients were randomized in ECZTRA 3, with 160 patients (42.1%) from North America (**Table 1**)

**Table 1. Patient demographics and disease characteristics at baseline**

| | North America (n=160) | |
|---|---|---|
| | Tralokinumab q2w + TCS (n=106) | Placebo + TCS (n=54) |
| Mean age (SD) | 42.4 (17.6) | 39.5 (16.2) |
| Male, % | 46.2 | 53.7 |
| Mean duration of AD, years (SD) | 27.1 (18.3) | 27.7 (15.7) |
| IGA score of 4, % | 37.1 | 38.9 |
| Mean EASI score (SD) | 26.2 (11.4) | 28.3 (11.4) |
| Mean SCORAD (SD) | 65.2 (13.4) | 67.5 (13.2) |
| Mean DLQI (SD) | 16.5 (7.3) | 18.0 (7.1) |
| Mean weekly average worst daily pruritus NRS score (SD) | 7.7 (1.6) | 8.2 (1.6) |
| Mean BSA involvement with AD, % (SD) | 41.0 (20.6) | 41.2 (23.6) |

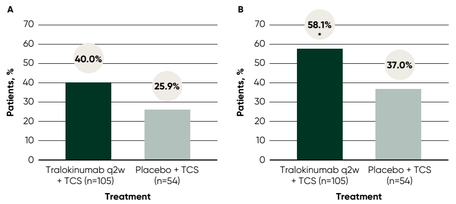
BSA, body surface area; SD, standard deviation.

- Overall, the North American and primary study populations had similar baseline demographics, although there was slight variation in the baseline disease characteristics:[7]
  - The percentage of severe AD (IGA-4) was slightly lower in the North American population, although mean EASI scores did not objectively differ
  - Mean body surface area involvement with AD was slightly lower in the North American population

### IGA and EASI-75 at week 16

- At week 16, a numerically higher proportion of tralokinumab-treated patients in the North American population achieved IGA-0/1 compared with placebo (40.0% vs. 25.9%) [**Figure 2**]
- A higher proportion of tralokinumab-treated patients in the North American population achieved EASI-75, compared with placebo (58.1% vs. 37.0%) at week 16

**Figure 2. (A) IGA-0/1 and (B) EASI-75 in the ECZTRA 3 North American population at week 16**

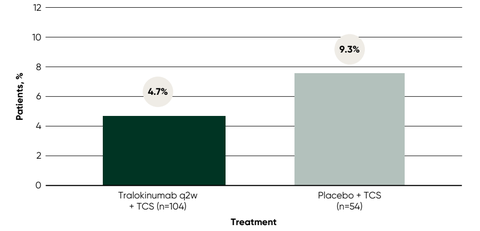



*P<0.05 vs. placebo + TCS.
Patients receiving rescue medication prior to week 16 or with missing data were considered non-responders.

### Use of rescue medication

- Use of rescue medication, which included higher-potency TCS or systemic treatment for AD, was low in the North American population during the initial treatment period (**Figure 3**)
  - When compared with placebo, rescue medication use was lower in tralokinumab-treated patients (4.7% vs. 9.3%)

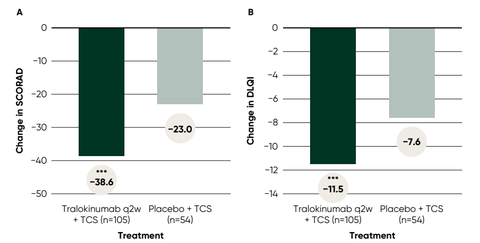
**Figure 3. Rescue medication use in the ECZTRA 3 North American population during the initial 16-week treatment period**




### Change in SCORAD, DLQI, and pruritus NRS

- Reduction in SCORAD (−38.6 vs. −23.0) and DLQI (−11.5 vs. −7.6) were greater with tralokinumab compared with placebo in the North American population from baseline to week 16 (**Figure 4**)

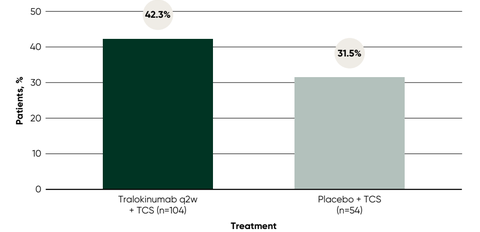
**Figure 4. Change in (A) SCORAD and (B) DLQI in the ECZTRA 3 North American population at week 16**




***P<0.001 vs. placebo + TCS.
Data collected after permanent discontinuation of investigational medicinal product or initiation of rescue medication not included. Repeated measurements model: change from baseline = treatment*week + baseline*week + baseline IGA.

- A numerically greater proportion of the North American population treated with tralokinumab achieved a worst daily pruritus NRS reduction of ⩾4 at week 16 compared with placebo (42.3% vs. 31.5%) [**Figure 5**]

**Figure 5. Proportion of patients achieving a reduction in pruritus NRS ⩾4 in the ECZTRA 3 North American population at week 16**




Patients receiving rescue medication prior to week 16 or with missing data were considered non-responders.

### Safety

- The overall rate of adverse events was similar between tralokinumab and placebo groups in the North American population (**Table 2**)
- Most adverse events were mild to moderate in severity

**Table 2. Adverse events in the initial 16-week treatment period**

| n (%) | North America (n=160) | |
|---|---|---|
| | Tralokinumab q2w + TCS (n=105) | Placebo + TCS (n=54) |
| At least one adverse event | 60 (57.1) | 28 (51.9) |
| At least one serious adverse event | 0 | 1 (1.9) |
| Adverse event leading to withdrawal from trial | 2 (1.9) | 0 |
| Severity | | |
| Mild | 50 (47.6) | 20 (37.0) |
| Moderate | 18 (17.1) | 12 (22.2) |
| Severe | 0 | 3 (5.6) |
| Outcome | | |
| Not recovered/not resolved | 18 (17.1) | 5 (9.3) |
| Recovering/resolving | 2 (1.9) | 2 (3.7) |
| Recovered/resolved | 55 (52.4) | 25 (46.3) |
| Recovered/resolved with sequelae | 1 (1.0) | N/A |

N/A, not available.

## Conclusions

- The North American population represented 42.1% of the overall ECZTRA 3 study population
- In this subanalysis of the ECZTRA 3 trial, tralokinumab 300 mg q2w plus TCS was well tolerated and displayed superior efficacy in patients with moderate-to-severe AD in the North American population compared with placebo
  - Tralokinumab plus TCS demonstrated improvements in AD symptoms and patient quality of life
- Tralokinumab plus TCS was well tolerated in the North American population, suggesting no special considerations in safety for this trial subpopulation are required
- Overall, tralokinumab plus TCS displayed similar efficacy and safety across the North American population comparable to that of the primary study population[7]

## References

1. Weidinger S, Novak N. Lancet 2016; 387: 1109–1122.
2. Silverberg JI et al. Ann Allergy Asthma Immunol 2018; 121: 340–347.
3. Dalgard FJ et al. J Invest Dermatol 2015; 135: 984–991.
4. Bieber T. Allergy 2020; 75: 54–62.
5. Tsoi LC et al. J Invest Dermatol 2019; 139: 1480–1489.
6. Popovic B et al. J Mol Biol 2017; 429: 208–219.
7. Silverberg JI et al. Br J Dermatol 2020; in press.

## Disclosures

- Boni E. Elewski has received honoraria as a consultant from Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, LEO Pharma, Lilly, Menlo Therapeutics, Novartis, Pfizer, Sun, Valeant (Ortho Dermatologics), and Verrica and received research funding from AbbVie, AnaptysBio, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Incyte, LEO Pharma, Lilly, Menlo Therapeutics, Merck, Novartis, Pfizer, Regeneron, Sun, Valeant (Ortho Dermatologics), and Vanda
- Matthew J. Zirwas has acted as a consultant for AbbVie, Aclaris, Arcutis, Asana, Aseptic MD, Avillion, DS Biopharma, Fitbit, Foamix, Genentech, Incyte, Janssen, Leo Pharma, Lilly, L'Oreal, Menlo, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, and UCB
- Richard G. Langley has received honoraria as an advisory board member from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Leo Pharma, Lilly, Merck, Novartis, Pfizer, and UCB, and as a speaker from AbbVie, Amgen, Celgene, Leo Pharma, Merck, Novartis, and Pfizer
- Andrew F. Alexis has acted as a consultant for Beiersdorf, Bristol-Myers Squibb, Celgene, Dermavant, Foamix, Galderma, LEO Pharma, L'Oreal, Menlo Therapeutics, Novartis, Pfizer, Sanofi/Regeneron, Scientis, UCB, Unilever, and Valeant (Bausch Health) and received grants/research support from Almirall, Bristol-Myers Squibb, Cara, Celgene, Galderma, LEO Pharma, Menlo Therapeutics, Novartis, and Valeant (Bausch Health)
- Karen A. Veverka, John Zoidis, and Azra Kurbasic are employees of LEO Pharma
- Jonathan I. Silverberg has received honoraria as a consultant/advisory board member from LEO Pharma and acted as a consultant for, and/or received grants/honoraria from, AbbVie, AnaptysBio, Asana Biosciences, Galderma Research and Development, GlaxoSmithKline, Glenmark Generics, Kiniksa, LEO Pharma, Lilly, MedImmune, Menlo Therapeutics, Pfizer, PuriCore, Regeneron, and Sanofi

## Acknowledgments

- The ECZTRA 3 study was sponsored by LEO Pharma
- Medical writing and editorial assistance were provided by Henna Potigadoo, MSc, and Lauren Smith, BA (Hons), from McCann Health, funded by LEO Pharma

*Fall Clinical Dermatology Conference, Las Vegas, NV, USA, October 29–November 1, 2020*