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ORIGINAL RESEARCH ARTICLE

# Tralokinumab Provides Clinically Meaningful Responses at Week 16 in Adults with Moderate-to-Severe Atopic Dermatitis Who Do Not Achieve IGA 0/1

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## Abstract

**Background and Objective** Investigator's Global Assessment of clear/almost clear skin (IGA 0/1) is a difficult endpoint to achieve after short-term treatment of chronic moderate-to-severe atopic dermatitis, and does not fully reflect clinically meaningful changes in other parameters. We assessed the impact of tralokinumab versus placebo on other clinically meaningful parameters in patients not achieving IGA 0/1 at week 16 using pooled data from two monotherapy phase III trials, ECZTRA 1 and 2.

**Methods** This post hoc analysis included patients ($n = 1328$) from ECZTRA 1 and 2 who did not achieve the co-primary endpoint, IGA 0/1 at week 16 without rescue medication. Endpoints evaluating atopic dermatitis extent and severity included proportions of patients achieving IGA 0/1, 50%, 75%, and 90% improvement in Eczema Area and Severity Index (EASI-50/75/90); endpoints evaluating patient-reported outcomes included a ≥ 3-point improvement in worst daily pruritus Numerical Rating Scale (NRS), a ≥ 3-point improvement in eczema-related sleep interference (sleep) NRS, a ≥ 4-point improvement in Dermatology Life Quality Index (DLQI), and DLQI ≤ 5. Specifically, clinically meaningful responses were defined as EASI-50, a ≥ 3-point improvement in itch NRS, or a ≥ 4-point improvement in DLQI at week 16.

**Results** Among ECZTRA 1 and 2 patients who did not achieve IGA 0/1 at week 16 without rescue medication, a significantly greater proportion of patients receiving tralokinumab versus placebo achieved EASI-50 (33.0% vs 13.0%), a ≥ 3-point improvement in itch NRS (22.6% vs 9.4%), or a ≥ 4-point improvement in DLQI (41.2% vs 24.5%) at week 16. In addition, compared with placebo, a numerically greater proportion of tralokinumab-treated patients achieved all three measures of clinically meaningful response (30% vs 18%) or a clinically meaningful change in at least one outcome (48.8% vs 28.5%). Significantly greater proportions of patients receiving tralokinumab versus placebo achieved additional clinician-reported and patient-reported outcomes, such as EASI-75 (13.5% vs 4.1%), EASI-90 (3.5% vs 1.1%), DLQI ≤ 5 (22.5% vs 12.5%), and a ≥ 3-point improvement in sleep NRS (24.5% vs 11.5%).

**Conclusions** Tralokinumab provided clinically meaningful responses in patients with moderate-to-severe atopic dermatitis who did not achieve IGA 0/1 at week 16 and/or used rescue medication. Using multiple validated outcome measures of both efficacy and quality of life, alongside IGA scores, can better characterize tralokinumab treatment responses in patients with moderate-to-severe atopic dermatitis. [Video abstract available]

**Clinical Trial Registration** NCT03131648 (ECZTRA 1); study start date: 30 May, 2017; primary completion date: 7 August, 2018; study completion date: 10 October, 2019. NCT03160885 (ECZTRA 2); study start date: 12 June, 2017; primary completion date: 4 September, 2019; study completion date: 14 August, 2019.

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**Key Points**

Atopic dermatitis is a chronic inflammatory disease that can be difficult to evaluate because of its heterogenous presentation. Investigator's Global Assessment of clear/almost clear skin is a required endpoint in most atopic dermatitis clinical trials, but it does not fully reflect the overall patient experience and can underestimate clinically meaningful treatment effects.

A post hoc analysis of patients who did not achieve the co-primary endpoint (Investigator's Global Assessment of clear/almost clear skin at week 16 without rescue medication) in the monotherapy ECZTRA 1 and 2 clinical trials showed greater proportions of tralokinumab-treated patients, compared with placebo, achieved clinically meaningful responses.

Utilization of validated outcome measures of both itch severity and quality of life, in addition to Investigator's Global Assessment scores, more comprehensively assesses the full benefit of tralokinumab treatment.

## 1 Introduction

Atopic dermatitis (AD) is a chronic, type 2 inflammatory skin disease characterized by skin dryness, inflammation, and intense itching [1, 2]. Interleukin-13 has been identified as a key driver of skin inflammation, microbiome dysbiosis, pruritus, and barrier abnormalities in patients with AD [3–5]. Tralokinumab, currently approved in multiple countries, including in Europe, Canada, and the USA [6–10], for the treatment of moderate-to-severe AD in adults, is a fully human, IgG4 high-affinity monoclonal antibody that specifically binds to and neutralizes interleukin-13 [11]. In the ECZTRA 1 and 2 phase III clinical trials with tralokinumab monotherapy in patients with moderate-to-severe AD, one of the co-primary endpoints was an Investigator's Global Assessment [12] of clear/almost clear skin (IGA 0/1) at week 16 without the use of rescue medication. Significantly more patients met the IGA 0/1 endpoint at week 16 with tralokinumab as compared with placebo [12].

Investigator's Global Assessment of clear/almost clear skin is a difficult endpoint to achieve after short-term treatment of moderate-to-severe AD and does not fully capture clinically meaningful changes in all of the patient domains impacted by this heterogeneous disease. Additional instruments include: (1) Eczema Area and Severity Index (EASI), a clinician-administered assessment of the extent and severity of the physical signs of AD across each of the four body regions [13, 14]; (2) worst daily pruritus Numerical Rating Scale (NRS), a patient-reported scale assessing the intensity of worst itch experienced during the previous 24 h; and (3) Dermatology Life Quality Index (DLQI), a patient-reported questionnaire assessing patients' perception of the impact of AD on their health-related quality of life over the previous week [15, 16]. Importantly, previous work defines clinically meaningful responses as a $\geq$ 50% improvement in EASI (EASI-50) [17], a $\geq$ 3-point improvement in peak daily itch NRS [18, 19], or a $\geq$ 4-point improvement in DLQI [20]. These domains are especially important to assess in patients because AD is a multifaceted disease [5, 21] that carries a substantial disease burden. Individuals with AD demonstrate a worse quality of life than several other common chronic diseases, including heart disease, diabetes mellitus, and hypertension [18]. As a result of disease heterogeneity and significant patient burden, clinicians often rely more heavily on their experience and care than assessment of formalized outcome parameters [2], and include a scale component (scoring system), a functional component, and a social component in the guideline definition of "candidates for systemic therapy" [22]. As such, there are ongoing efforts to resolve the current lack of standardization in the clinical trial assessment of AD that propose a multidimensional assessment, including, but not limited to, clinician-reported signs, patient-reported symptoms, and quality of life [23, 24].

Placing too great an emphasis on the achievement of clinician-assessed endpoints (e.g., IGA 0/1) after short-term treatment may underestimate the benefits of systemic therapies for AD. Phase III clinical trials in adults [25] and adolescents [26] revealed a substantial proportion of dupilumab-treated patients, who did not achieve IGA 0/1 at week 16 of treatment, still exhibited clinically relevant responses in measures of signs, symptoms, and quality of life. Results from phase IIb and phase III clinical trials with abrocitinib monotherapy showed that patients who did not achieve IGA 0/1 at week 12 of treatment still demonstrated clinically meaningful improvements across several other validated measures of efficacy and quality of life [27]. Patients not achieving optimal responses with short-term treatment often exhibit improvements in AD signs and symptoms from

continued treatment with either dupilumab [28] or tralokinumab [29] beyond the initial treatment period. Here, utilizing data from two pivotal phase III studies (ECZTRA 1 and 2), we assessed the impact of tralokinumab versus placebo on other clinically meaningful parameters in patients not achieving IGA 0/1 at week 16.

## 2 Methods

### 2.1 Study Design and Patient Population

This post hoc analysis included patients from ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885) who did not achieve IGA 0/1 at week 16 and/or used rescue medication during the first 16 weeks (referred to as IGA > 1). The ECZTRA 1 and 2 trials were previously described in detail [12]. Briefly, ECZTRA 1 and 2 were identically designed, multinational, double-blinded, randomized, placebo-controlled, 52-week phase III trials of tralokinumab monotherapy in adults with moderate-to-severe AD. Adult patients were randomized 3:1 to receive either subcutaneous tralokinumab 300 mg (after an initial 600-mg loading dose on day 0) or placebo every other week, with the primary endpoints (IGA 0/1 and EASI-75) being assessed at week 16 [12] (Fig. S1 of the Electronic Supplementary Material [ESM]). The trials were sponsored by LEO Pharma A/S (Ballerup, Denmark) and conducted in accordance with the ethical principles derived from the Declaration of Helsinki and Good Clinical Practice guidelines and were approved by the local institutional review board or ethics committee of each institution. All patients provided written informed consent.

### 2.2 Endpoints

Endpoints evaluating AD extent and severity included the proportion of patients achieving IGA 0/1, 50%, 75%, and 90% improvement in EASI (EASI-50/75/90), whereas endpoints evaluating patient-reported outcomes included a ≥ 3-point improvement in worst daily pruritus NRS, a ≥ 3-point improvement in eczema-related sleep interference (sleep) NRS, a ≥ 4-point improvement in DLQI, and DLQI ≤5.

Clinically meaningful responses were defined as EASI-50 [17], a ≥ 3-point improvement in itch NRS [19, 30], or a ≥ 4-point improvement in DLQI [20] at week 16 based on previously published work examining minimal clinically relevant responses exhibited by patients with AD.

Presented data are from the full analysis set, which comprised all dosed patients (ECZTRA 1, $n = 798$; ECZTRA 2, $n = 792$). A sensitivity analysis was conducted in alignment with the population described in the United States Prescribing Information (USPI) where data from two US sites of the ECZTRA 2 trial were excluded from the full analysis set. Results from the USPI population (ECZTRA 1, $n = 798$; ECZTRA 2, $n = 770$) analysis were consistent with the full analysis set and are provided in the ESM.

### 2.3 Statistical Analysis

Two estimands were considered: (1) the pre-specified primary composite estimand using non-responder imputation (NRI) for patients who utilized rescue medication or had missing data and (2) data as observed (AO) ignoring missing data and using observed data as is regardless of rescue medication use. Response rates are lower with NRI versus AO as many patients who exhibited responses utilized rescue medication (hence set to non-response with NRI method, but not AO). Comparisons between the tralokinumab and placebo groups were analyzed using the chi-square test. Note that this comparison was performed although the two groups were not necessarily balanced with respect to baseline characteristics because of the selection of subjects based on a week 16 response (i.e., randomization no longer applies).

## 3 Results

### 3.1 Patient Disposition and Baseline Characteristics

At week 16, 19.0% (226/1192) of patients treated with tralokinumab and 9.0% (36/398) of patients treated with placebo met IGA 0/1 at week 16 without rescue medication, whereas 81.0% (966/1192) of patients treated with tralokinumab and 91.0% (362/398) of patients treated with placebo did not achieve IGA 0/1 at week 16 and/or used rescue medication by NRI [AO: tralokinumab 79.9% (901/1127), placebo 90.1% (328/364)] (Table 1).

Of the 1192 tralokinumab-treated patients in the ECZTRA 1 and 2 trials at week 16, 305 (25.6%) patients had IGA >1 and used rescue medication; 563 (47.2%) had IGA > 1, but did not use rescue medication; 31 (2.6%) patients met IGA 0/1, but used rescue medication; 226 (19.0%) patients met IGA 0/1 without rescue medication; and 67 (5.6%) patients were missing an IGA score at week 16 (Table 1).

Baseline characteristics were similar between tralokinumab-treated and placebo-treated patients for both responders (IGA 0/1 at week 16 without rescue medication) and non-responders (did not achieve IGA 0/1 at week 16 and/or used rescue medication, referred to as IGA > 1). Of note, most tralokinumab-treated non-responders presented substantial disease severity at baseline as 54.0% of patients met IGA 4 (severe) whereas 30.5% of tralokinumab-treated

**Table 1** Baseline characteristics for ECZTRA 1 and 2 responders (IGA 0/1 without rescue medication) versus non-responders at week 16

| | IGA >1[a] At week 16 | | | | IGA 0/1[b] At week 16 | |
|---|---|---|---|---|---|---|
| | NRI dataset | | AO dataset[c] | | NRI and AO datasets[d] | |
| | Tralo ($N = 966$) | PBO ($N = 362$) | Tralo ($N = 901$) | PBO ($N = 328$) | Tralo ($N = 226$) | PBO ($N = 36$) |
| Mean age, years (SD) | 38.0 (14.3) | 37.4 (15.0) | 38.1 (14.3) | 37.2 (14.4) | 37.5 (14.1) | 35.1 (13.1) |
| Male, *n* (%) | 587 (60.8) | 214 (59.1) | 555 (61.6) | 193 (58.8) | 121 (53.5) | 22 (61.1) |
| Race, *n* (%) | | | | | | |
| White | 629 (65.2) | 240 (66.9) | 590 (65.6) | 221 (68.0) | 167 (74.2) | 20 (55.6) |
| Black or African American | 65 (6.7) | 22 (6.1) | 52 (5.8) | 16 (4.9) | 19 (8.4) | 12 (33.3) |
| Asian | 238 (24.7) | 88 (24.5) | 229 (25.4) | 81 (24.9) | 36 (16.0) | 4 (11.1) |
| American Indian or Alaska Native | 3 (0.3) | 0 (0.0) | 3 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Native Hawaiian or other Pacific Islander | 5 (0.5) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 1 (0.4) | 0 (0.0) |
| Other | 25 (2.6) | 9 (2.5) | 24 (2.7) | 7 (2.2) | 2 (0.9) | 0 (0.0) |
| Missing data | 1 | 3 | 1 | 3 | 1 | 0 |
| Mean duration of AD, years (SD) | 28.1 (15.2) | 29.0 (15.0) | 28.1 (15.2) | 29.3 (14.7) | 28.0 (15.3) | 23.1 (14.0) |
| Mean BSA involvement with AD, % (SD) | 55.4 (24.8) | 55.4 (25.1) | 55.5 (24.6) | 55.8 (24.8) | 40.7 (21.3) | 35.9 (19.0) |
| IGA, *n* (%) | | | | | | |
| IGA 3 (moderate) | 444 (46.0) | 168 (46.4) | 408 (45.3) | 150 (45.7) | 157 (69.5) | 27 (75.0) |
| IGA 4 (severe) | 522 (54.0) | 194 (53.6) | 493 (54.7) | 178 (54.3) | 69 (30.5) | 9 (25.0) |
| Mean EASI (SD) | 33.6 (14.4) | 33.6 (13.9) | 33.7 (14.4) | 33.7 (13.8) | 25.9 (10.2) | 23.8 (9.4) |
| Mean weekly average worst daily pruritus NRS (SD) | 7.9 (1.4), $n = 958$ | 7.9 (1.3), $n = 360$ | 7.8 (1.4), $n = 896$ | 7.9 (1.3), $n = 326$ | 7.5 (1.5), $n = 224$ | 7.2 (1.6), $n = 35$ |
| Mean SCORAD (SD) | 71.3 (13.1) | 71.9 (12.2) | 71.4 (13.1) | 71.9 (12.1) | 65.5 (12.5) | 62.5 (10.7) |
| Mean DLQI (SD) | 17.6 (7.1), $n = 956$ | 17.8 (6.8), $n = 359$ | 17.6 (7.1), $n = 893$ | 17.8 (6.8), $n = 326$ | 15.6 (6.9), $n = 222$ | 13.4 (7.8), $n = 35$ |
| Mean eczema-related sleep interference (sleep) NRS (SD) | 7.1 (2.0), $n = 958$ | 7.1 (2.0), $n = 360$ | 7.1 (2.0), $n = 896$ | 7.1 (2.0), $n = 326$ | 6.8 (2.0), $n = 224$ | 6.1 (2.4), $n = 35$ |

*AO* as observed, *AD* atopic dermatitis, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *NRI* non-responder imputation, *NRS* numeric rating scale, *n* number of subjects in analysis set, *PBO* placebo, *Q2W* every 2 weeks, *SCORAD* SCORing Atopic Dermatitis, *SD* standard deviation, *Tralo* tralokinumab

[a]Patients who did not achieve IGA 0/1 at week 16 and/or used rescue medication

[b]Without rescue medication

[c]Fewer patients compared to the NRI dataset because patients with missing observations were omitted

[d]For the responder population, the AO and NRI datasets are identical

responders met IGA 4 at baseline. Furthermore, tralokinumab-treated non-responders displayed mean EASI, pruritus NRS, DLQI, and SCORAD scores of 33.6, 7.9, 17.6, and 71.3 at baseline, respectively, whereas the mean EASI, pruritus NRS, DLQI, and SCORAD scores at baseline for tralokinumab-treated responders were 25.9, 7.5, 15.6, and 65.5, respectively (Table 1).

Baseline characteristics were comparable between non-responders who achieved at least one clinically meaningful response and non-responders who did not (Table S1 of the ESM). Consistent results were obtained in the USPI population analysis (Tables S3–4 of the ESM).

### 3.2 Clinically Meaningful Responses in Patients Who Did Not Achieve IGA 0/1 at Week 16 and/or Used Rescue Medication

At week 16, significantly greater proportions of IGA>1 patients receiving tralokinumab versus placebo achieved EASI-50, a ≥ 3-point improvement in itch NRS, or a ≥ 4-point improvement in DLQI (each $p < 0.0001$ vs placebo). Specifically, 33.0% of tralokinumab-treated patients met EASI-50, 22.6% achieved a ≥ 3-point improvement in itch NRS, and 41.2% achieved a ≥ 4-point improvement in DLQI by NRI (AO: 54.5%, 39.9%, and 72.2%) [Fig. 1]. There were 48.8% of patients in the tralokinumab group compared with 28.5% in the placebo group who achieved a clinically meaningful change in at least one outcome by NRI (AO: tralokinumab 82.2% vs placebo 64.9%). A numerically greater proportion of IGA >1 patients achieved all three measures of clinically meaningful response (EASI-50, a ≥ 3-point improvement in itch NRS, and a ≥ 4-point improvement in DLQI) at week 16 with tralokinumab versus placebo (NRI: 30% vs 18%; AO: 29% vs 19%) [Fig. 2]. Consistent results were obtained in the USPI population analysis (Figs. S2–3 of the ESM).

Additionally, at week 16, significantly greater proportions of IGA >1 patients receiving tralokinumab versus placebo also achieved EASI-75 ($p < 0.0001$), EASI-90 ($p = 0.0188$), a ≥ 3-point improvement in sleep NRS ($p < 0.0001$), and DLQI ≤ 5 ($p < 0.0001$). Specifically, 13.5% of tralokinumab-treated patients met EASI-75, 3.5% achieved EASI-90, 24.5% achieved a ≥ 3-point improvement in sleep NRS, and 22.5% achieved DLQI ≤5 by NRI (AO: 23.2%, 7.3%, 44.5%, and 37.2%, respectively) (Fig. 3). By NRI at week 16, tralokinumab-treated IGA > 1 patients displayed mean EASI, pruritus NRS, sleep NRS, DLQI, and SCORAD scores of 24.4, 6.5, 5.7, 13.1, and 57.6, respectively, corresponding to an absolute mean improvement from baseline of 9.2, 1.4, 1.4, 4.5, and 13.7, respectively (Table S2 of the ESM). Consistent results were obtained in the USPI population analysis (Fig. S4 and Table S5 of the ESM).

## 4 Discussion

Despite not meeting the pre-specified co-primary endpoint of IGA 0/1 at week 16 without utilization of rescue medication, a significantly greater proportion of adult patients with moderate-to-severe AD receiving tralokinumab versus placebo exhibited clinically meaningful improvements in AD signs, symptoms, or quality of life (as measured by

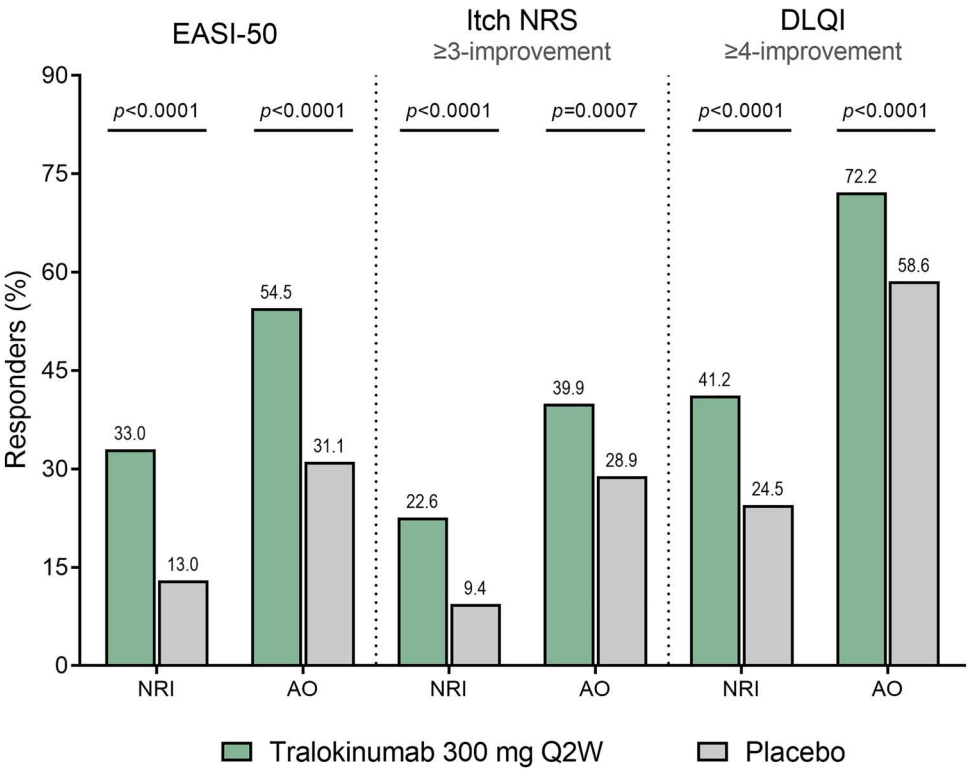


**Fig. 1** Greater proportion of tralokinumab-treated patients achieved clinically meaningful responses relative to placebo at week 16. Patients who did not achieve Investigator's Global Assessment of clear/almost clear skin (IGA 0/1) at week 16 and/or used rescue medication. *P*-values compare tralokinumab (non-responder imputation [NRI]: $n = 966$; as observed [AO]: $n = 901$) with placebo (NRI: $n = 362$; AO: $n = 328$). *DLQI* Dermatology Life Quality Index, *EASI-50* at least 50% improvement in the Eczema Area and Severity Index, *NRS* numeric rating scale, *Q2W* every 2 weeks

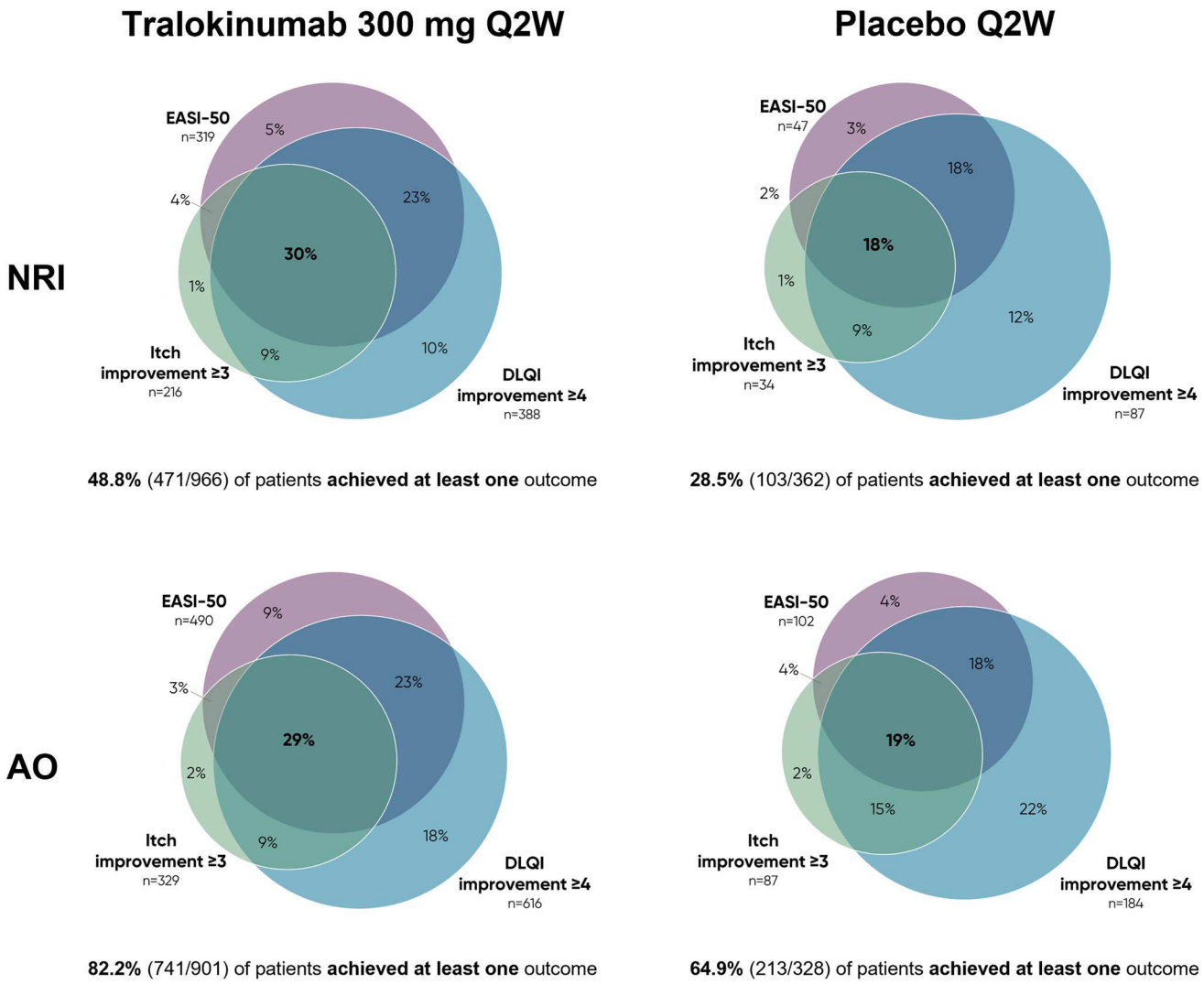


**Fig. 2** A greater proportion of tralokinumab-treated patients achieved all three measures of clinically meaningful response relative to placebo at week 16. Patients who did not achieve Investigator's Global Assessment of clear/almost clear skin (IGA 0/1) at week 16 and/or used rescue medication. *AO* as observed, *DLQI* Dermatology Life Quality Index, *EASI-50* at least 50% improvement in the Eczema Area and Severity Index, *n* number of subjects in analysis set, *NRI* non-responder imputation, *Q2W* every 2 weeks

EASI-50, a ≥ 3-point improvement in itch NRS, and a ≥ 4-point improvement in DLQI). In addition, significantly greater proportions of IGA > 1 patients receiving tralokinumab versus placebo achieved other commonly used endpoints, such as EASI-75, EASI-90, DLQI ≤ 5, and a ≥ 3-point improvement in sleep NRS.

Investigator's Global Assessment scales are widely utilized in AD clinical trials, especially because their assessment is relatively quick to perform, and their results are readily interpreted [31]. However, there are several limitations of this metric, such as the exclusion of assessing body surface area affected and the key patient-reported outcome of pruritus. Additionally, there are several variations of the IGA scale in use today. Notably, the US Food and Drug Administration recommends IGA ≤ 1 as a primary endpoint in US clinical trials, but the European Medicines Agency does not. This difference likely drives the higher utilization of IGA as an endpoint in studies conducted in North America compared to Europe (73% vs 30%) [31].

Investigator's Global Assessment of clear/almost clear skin is a difficult endpoint to achieve after short-term treatment of moderate-to-severe AD, especially in a patient population with close to 50% body surface area involved at baseline. Despite widespread use in AD clinical trials, no data support the exclusive utilization of IGA 0/1 as the marker of treatment success. For example, a new therapy may provide significant relief from itch and/or improvement in quality of life without complete or near-complete clearance of the skin. Moreover, baseline body surface area of patients with moderate AD vary substantially [32], rendering

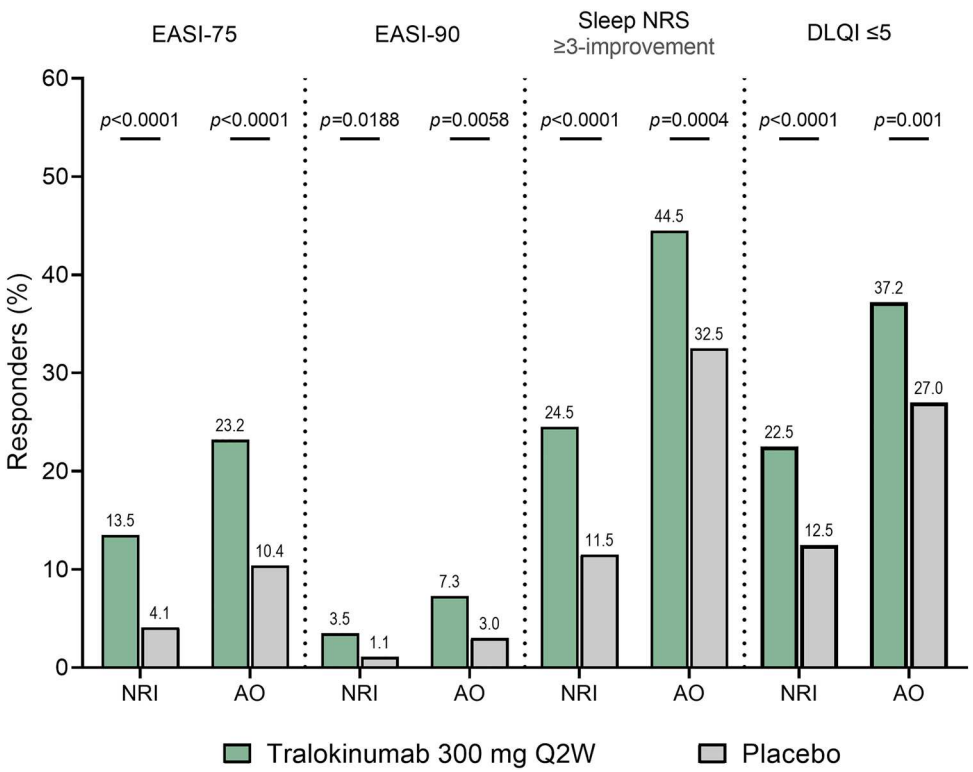


**Fig. 3** At week 16 greater proportions of tralokinumab-treated patients relative to placebo achieved at least a 75% improvement in the Eczema Area and Severity Index (EASI-75), at least a 90% improvement in the Eczema Area and Severity Index (EASI-90), a ≥ 3-point improvement in sleep numeric rating scale (NRS),and Dermatology Life Quality Index (DLQI) ≤ 5. Patients who did not achieve Investigator's Global Assessment of clear/almost clear skin (IGA 0/1) at week 16 and/or used rescue medication. *P*-values compare tralokinumab (non-responder imputation [NRI]: $n = 966$; as observed [AO]: $n = 901$) with placebo (NRI: $n = 362$; AO: $n = 328$). *Q2W* every 2 weeks

complete clearance difficult in many patients. Although no treat-to-target framework currently exists for the optimal use of systemic therapies in AD, an international panel of expert clinicians and patients recently recommended the use of EASI-50, a ≥ 3-point improvement in itch NRS, and a ≥ 4-point improvement in DLQI at 3 months, and EASI-75 and DLQI ≤5 at 6 months as treatment targets to inform clinical decision making [33].

Notably, these recommendations, and the current study, include patient-reported outcomes (e.g., DLQI, itch NRS) as a complement to clinician-evaluated outcomes (e.g., EASI). This is important as the clinician's visual assessment of AD extent or severity can underestimate both the disease burden and extent of treatment benefit in patients [34, 35]. In a heterogeneous and chronic disease like AD, use of clinically meaningful parameters reflecting an improvement in signs, symptoms, and/or quality of life, including patient-reported outcomes, can considerably support clinicians during the treatment decision-making process and may prevent unnecessary switching of treatments. Furthermore, clinical decision making is complex [22, 36] and should incorporate both existing health-related quality of life [37], and safety data [38], including ophthalmological complications such as conjunctivitis [39].

Limitations of this analysis include its post hoc nature; however, two statistical approaches (NRI and AO) were utilized and produced comparable results with similar conclusions. The main difference between the two approaches were the generally lower response rates in NRI versus AO, which is likely driven by the impact of rescue medication usage (NRI, but not AO, accounts for rescue utilization). As such, AO likely better reflects real-world treatment scenarios where rescue medications (e.g., topical corticosteroids) are often used alongside biologics during clinical practice. Additionally, while this article focused on treatment responses at week 16, it is also important to consider longer-term timepoints given the chronic nature of AD. Recent work suggests that evaluation at week 16 does not capture the progressive and sustained improvements in AD signs and symptoms that patients exhibit with continued tralokinumab treatment [29]. Further, tralokinumab was shown to be well tolerated and maintained long-term control of AD signs and symptoms over 2 years of continued treatment [40]. An additional limitation was that patients were selected based on their outcome during the trial (i.e., tralokinumab-treated or placebo-treated patients who did not achieve IGA 0/1 at week 16 without rescue medication). As such, the two groups being examined were not randomized and thus may not be balanced regarding their baseline characteristics. Further, non-responders who received tralokinumab would arguably be harder to treat compared with non-responders who received placebo, as some of the latter would likely have achieved IGA 0/1 at week 16 had they instead received tralokinumab. This results in a different degree of selection on the two non-responder arms making them not directly comparable.

## 5 Conclusions

Patients who did not achieve IGA 0/1 at week 16 without rescue medication exhibited significant, clinically meaningful responses with tralokinumab treatment. Using multiple validated outcome measures of both efficacy and quality of life, including patient-reported outcomes, alongside IGA scores, can better characterize treatment responses in patients with moderate-to-severe AD.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40257-023-00817-0.

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## Declarations

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**Conflicts of Interest/Competing interests** Eric L. Simpson reports personal fees from AbbVie, Amgen, Arena Pharmaceuticals, Aslan Pharma, Benevolent AI Bio Limited "BAI", BiomX Ltd, Bluefin Biomedicine Inc, Boehringer-Ingelheim, Boston Consulting Group, Collective Acumen, LLC (CA), Coronado, Dermira, Eli Lilly, Evidera, ExcerptaMedica, Galderma, GlaxoSmithKline, Forte Bio RX, Incyte Dermatologics, Janssen, Kyowa Kirin Pharmaceutical Development, Leo Pharm, Medscape LLC, Merck, Novartis, Ortho Galderma, Pfizer, Physicians World LLC, Pierre Fabre Dermo Cosmetique, Regeneron, Roivant, Sanofi- Genzyme, SPARC India, Trevi therapeutics, WebMD, and Valeant; reports grants (or served as the Principal Investigator) from AbbVie, Amgen, Arcutis, Aslan, Castle Biosciences, Inc Celegene, CorEvitas, Dermavant, Dermira, Eli Lilly, Galderma, Incyte, Kymab, Kyowa Hakko Kirin, Leo Pharmaceuticals, Merck, Novartis, Pfizer, Regeneron, Sanofi, and TARGET-DERM. Andrew Blauvelt has served as a speaker (received honoraria) for AbbVie, Bristol-Myers Squibb, Eli Lilly and Company, Pfizer, Regeneron, and Sanofi, served as a scientific adviser (received honoraria) for AbbVie, Abcentra, Aclaris, Affibody, Aligos, Almirall, Alumis, Amgen, Anaptysbio, Arcutis, Arena, Aslan, Athenex, Bluefin Biomedicine, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Dermavant, EcoR1, Eli Lilly and Company, Escient, Evelo, Evommune, Forte, Galderma, HighlightII Pharma, Incyte, InnoventBio, Janssen, Landos, LEO Pharma, Merck, Novartis, Pfizer, Rani, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, TLL Pharmaceutical, TrialSpark, UCB Pharma, Union, Vibliome, and Xencor, and has acted as a clinical study investigator (institution has received clinical study funds) for AbbVie, Acelyrin, Allakos, Almirall, Alumis, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Concert, Dermavant, Eli Lilly and Company, Evelo, Evommune, Galderma, Incyte, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, Sun Pharma, UCB Pharma, and Ventyx. Jonathan I. Silverberg reports honoraria as a consultant/advisory board member from LEO Pharma and has acted as a consultant for and/or received grants/honoraria from AbbVie, AnaptysBio, Asana Biosciences, Galderma Research and Development, GSK, Glenmark, Kiniksa, LEO Pharma, Lilly, MedImmune, Menlo Therapeutics, Pfizer, PuriCore, Regeneron, and Sanofi. Michael J Cork has served as a clinical trial investigator for Astellas, Galapagos, Johnson & Johnson, LEO Pharma, La Roche-Posay, MSD, Novartis, Perrigo, Regeneron, Sanofi Genzyme, and Stiefel; has served as an advisory board member, consultant, and/or invited lecturer for Pfizer Inc., Amgen, Astellas, Bayer, Johnson & Johnson, LEO Pharma, L'Oréal, MSD, Novartis, Regeneron, Sanofi Genzyme, Stiefel, and Unilever; has received honoraria from Astellas, Johnson & Johnson, LEO Pharma, Novartis, Regeneron, Sanofi Genzyme, and Stiefel; and has received research funding from Bayer. Norito Katoh has received honoraria as a speaker/consultant for Sanofi, Maruho, Abbvie, Ely-Lilly Japan, Taiho Pharmaceutical, Torii Pharmaceutical, and LEO Pharma, and has received grants as an investigator from Maruho, Ely-Lilly Japan, Sun Pharma, Taiho Pharmaceutical, Torii Pharmaceutical, Boehringer Ingelheim Japan, Kyowa Kirin, Jansen Pharma, Boehringer Ingelheim Japan, Abbvie, and LEO Pharma. Thomas Mark was an employee and stockholder of LEO Pharma A/S when conducting the data analyses for this publication. Shannon K.R. Schneider is an employee of LEO Pharma Inc. Andreas Wollenberg has received grants, personal fees, or nonfinancial support from AbbVie, Almirall, Aileens, Beiersdorf, Bioderma, BMS, Chugai, Galapagos, Galderma, GSK, Hans Karrer, Janssen, LEO Pharma, Lilly, L'Oreal, Maruho, MedImmune, Novartis, Pfizer, Pierre Fabre, Regeneron, Santen, and Sanofi-Aventis.

**Ethics Approval** The ECZTRA 1 and 2 trials were sponsored by LEO Pharma A/S (Ballerup, Denmark) and conducted in accordance with the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and in compliance with International Council for Harmonisation guidelines for Good Clinical Practice. The clinical trial was approved by institutional review boards or ethics committees at each study site (see ESM). This trial followed the Consolidated Standards of Reporting Trials reporting guideline.

**Consent to Participate** All patients provided written informed consent.

**Consent for Publication** Not applicable.

**Availability of Data and Material** Data will be made available, upon request to the study sponsor, following review by the external Patient and Scientific Review Board.

**Code Availability** Not applicable.

**Authors' Contributions** Conceptualization: all authors contributed equally; investigation: all authors contributed equally; data curation: TM (lead); formal analysis: TM (lead); methodology: TM (equal), SKRS (equal); writing: all authors contributed equally; review/editing: all authors contributed equally. All authors read and approved the final version of the manuscript.

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