



Tralokinumab Efficacy and Safety, with or without Topical Corticosteroids, in North American Adults with Moderate-to-Severe Atopic Dermatitis: A Subanalysis of Phase 3 Trials ECZTRA 1, 2, and 3

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ABSTRACT

Introduction: In pivotal phase 3 tralokinumab monotherapy (ECZTRA 1/2) and topical corticosteroid (TCS) combination (ECZTRA 3) trials in adults with moderate-to-severe atopic dermatitis (AD), tralokinumab significantly improved signs and symptoms of AD. Geographic region may impact treatment response due to potential differences in race and ethnicity, and based on findings in other therapy areas. Here, we evaluated the efficacy and safety of tralokinumab in the ECZTRA 1/2/3 North American population at week 16, as well as maintenance of responses over time, and compared these data side-by-side with

those of the ECZTRA 1/2/3 non-North American population.

Methods: Primary endpoints were Investigator's Global Assessment score of 0 or 1 (IGA 0/1; clear or almost clear) or at least 75% improvement in Eczema Area and Severity Index (EASI-75) at week 16. At week 16, tralokinumab-treated IGA 0/1 or EASI-75 responders were re-randomized 2:2:1 to tralokinumab 300 mg q2w, or q4w, or placebo (ECZTRA 1/2) and 1:1 to tralokinumab 300 mg q2w or q4w (ECZTRA 3).

Results: Overall, 559/1596 (35%) and 160/380 (42.1%) patients randomized in ECZTRA 1/2 and ECZTRA 3 were from North America, respectively. At week 16, IGA 0/1 and EASI-75 response rates were greater with tralokinumab versus placebo in ECZTRA 1/2 (IGA 0/1: 25.3% vs 15.1%; 95% confidence interval [CI] 3.0, 17.3; $p = 0.012$; EASI-75, 40.1% vs 19.4%; 95%

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CI 12.6, 28.7; $p < 0.001$) and ECZTRA 3 (IGA 0/1, 40.0% vs 25.9%; 95% CI – 0.5, 28.3; $p = 0.074$; EASI-75: 58.1% vs 37.0%; 95% CI 4.9, 37.0; $p = 0.012$) and tralokinumab was well tolerated in the North American population. Patients with IGA 0/1 or EASI-75 response at week 16 demonstrated sustained responses at week 52 and week 32 in ECZTRA 1/2 and ECZTRA 3, respectively. Similar findings were observed in the non-North American trial populations.

Conclusions: Tralokinumab, with or without TCS, displayed similar efficacy and safety in patients with moderate-to-severe AD across the North American population, and was comparable to the non-North American population.

Clinical Trial Registration: NCT03131648 (registered 27-Apr-2017); NCT03160885 (registered 19-May-2017); NCT03363854 (registered 6-Dec-2017).

Keywords: Atopic dermatitis; Geographic region; North America; Patients; Tralokinumab

Key Summary Points

Why carry out this study?

In three pivotal, multinational, phase 3 trials (ECZTRA 1, ECZTRA 2, and ECZTRA 3) in patients with moderate-to-severe atopic dermatitis, tralokinumab, a fully human monoclonal antibody, with or without topical corticosteroids, demonstrated a favorable safety profile and improved signs and symptoms of atopic dermatitis.

Geographic region may influence treatment response in patients with atopic dermatitis; hence, regional analyses are important to identify whether treatment differences exist in clinical trial subpopulations.

This post-hoc analysis evaluated the efficacy and safety of tralokinumab, with or without TCS, in the ECZTRA 1/2 and ECZTRA 3 North American population during the initial treatment period and maintenance of responses over time.

What was learned from the study?

Tralokinumab displayed similar efficacy and safety across the ECZTRA 1/2 and ECZTRA 3 North American population, comparable to that of the non-North American population (all patients in ECZTRA 1/2 and ECZTRA 3, excluding patients from North America).

This post-hoc analysis provides important region-specific evidence of the therapeutic efficacy of tralokinumab monotherapy and combination topical corticosteroid therapy, which could strengthen clinical decision-making and benefit patients with moderate-to-severe atopic dermatitis from North America.

INTRODUCTION

Atopic dermatitis is a chronic inflammatory skin disease that displays a high degree of clinical heterogeneity [1, 2]. Generally, studies investigating safety and efficacy of treatments for atopic dermatitis are analyzed at the multinational level [3–5]. However, clinical presentations of atopic dermatitis are known to be influenced by multiple factors, including race, ethnicity, and geographic region, all of which may also impact treatment response [6–8]. Additionally, regional differences in treatment outcomes have been reported for other conditions, including metabolic and autoimmune diseases, such as type 2 diabetes and multiple sclerosis, respectively [9, 10]. Analysis of efficacy and safety by region is, therefore, necessary to identify whether treatment differences exist in clinical trial subpopulations and for making better informed, region-specific clinical decisions for patients.

Tralokinumab is a first-in-class, fully human immunoglobulin G4 monoclonal antibody that specifically binds with high affinity to interleukin (IL)-13, thus neutralizing it and inhibiting its signaling capabilities [11]. Having recently been approved in the EU, UK, US, and Canada, tralokinumab is a targeted treatment

option that can provide long-term efficacy and safety for adults with moderate-to-severe atopic dermatitis [12–15].

In recent pivotal, multinational, phase 3 tralokinumab monotherapy (ECZTRA 1, NCT03131648; ECZTRA 2, NCT03160885) and topical corticosteroid (TCS) combination therapy (ECZTRA 3, NCT03363854) trials in adult patients with moderate-to-severe atopic dermatitis, significantly more tralokinumab-treated patients achieved the primary endpoints of Investigator's Global Assessment score of 0 or 1 (IGA 0/1; clear or almost clear) or at least 75% improvement in Eczema Area and Severity Index (EASI-75) at week 16 [16, 17].

The objective of this post-hoc analysis was to evaluate the efficacy and safety of tralokinumab 300 mg every 2 weeks (q2w), with or without TCS, in the ECZTRA 1/2 and ECZTRA 3 North American subpopulations at week 16 and maintenance of response over time. Equivalent data are provided for the ECZTRA 1/2 and ECZTRA 3 non-North American populations in the electronic supplementary material [ESM] to facilitate side-by-side comparisons of outcomes in the North American trial populations with the non-North American trial populations.

METHODS

Studies

Three multinational, double-blind, randomized, placebo-controlled, phase 3 trials of tralokinumab, ECZTRA 1, ECZTRA 2, and ECZTRA 3, were included in the subanalysis. Detailed ECZTRA 1/2 and ECZTRA 3 trial designs, endpoints, and results for the primary study populations were reported previously [16, 17]. Briefly, patients were stratified by region and baseline disease severity and randomized 3:1 (ECZTRA 1/2) to receive subcutaneous tralokinumab 300 mg or placebo q2w, and 2:1 (ECZTRA 3) to subcutaneous tralokinumab 300 mg plus TCS as needed or placebo plus TCS as needed q2w for an initial treatment period of 16 weeks. All patients randomized to tralokinumab and placebo received a 600 mg loading dose of tralokinumab or placebo,

respectively, on Day 0. After the initial 16-week treatment period, tralokinumab-treated patients who achieved clinical response, defined as an IGA 0/1 or EASI-75 response at Week 16, were re-randomized 2:2:1 to tralokinumab 300 mg q2w or q4w, or placebo (in ECZTRA 1/2) and 1:1 to tralokinumab 300 mg q2w or q4w (in ECZTRA 3) for a maintenance treatment period of 36 weeks in ECZTRA 1/2 or 16 weeks in ECZTRA 3.

In ECZTRA 3, all patients were instructed to apply a thin layer of TCS (mometasone furoate 0.1% cream; Europe Class 3 [potent]; US Class 4 [mid-strength]), supplied at each visit in kit sizes 180–200 g q2w) once daily to active lesions, as needed. To measure the amount of TCS used, patients were instructed to return used and unused TCS tubes at each trial visit. To control intolerable atopic dermatitis symptoms, rescue medication use was permitted at the discretion of the investigator from Day 0. In ECZTRA 1/2, TCS, topical calcineurin inhibitors (TCI), and systemic treatments were considered rescue; in ECZTRA 3, higher potency TCS (Europe Class > 3; US Class < 4) and systemic treatment were considered rescue. The ECZTRA 1, 2, and 3 studies were 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 trials were approved by institutional review boards or ethics committees at each study site and followed the Consolidated Standards of Reporting Trials reporting guideline. All participants provided informed consent to participate in the trials.

Study Population

Detailed inclusion and exclusion criteria have been described previously [16, 17]. Patients were ≥ 18 years of age, with diagnosed atopic dermatitis for ≥ 1 year, and an inadequate response to topical medications < 1 year prior to screening. Patients were required to have an IGA score of ≥ 3 , EASI ≥ 12 at screening and

≥ 16 at baseline, involvement of $\geq 10\%$ body surface area at screening and baseline, and worst daily pruritus numeric rating scale (NRS) average score of ≥ 4 during the week prior to baseline.

Endpoints and Post-Hoc Analysis

The primary endpoints were IGA score of 0 (clear) or 1 (almost clear) or at least 75% improvement in EASI (EASI-75) at week 16 [16, 17]. Secondary endpoints included: change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD), Dermatology Life Quality Index (DLQI), and weekly average worst daily pruritus NRS score, as well as proportions of patients achieving ≥ 4 -point reduction of weekly average worst daily pruritus NRS and at least 90% improvement in EASI (EASI-90). Maintenance endpoints at week 52 (in ECZTRA 1/2) and week 32 (in ECZTRA 3) were IGA 0/1 in patients with IGA 0/1 at week 16 and EASI-75 in patients with EASI-75 at week 16. These analyses were performed post hoc for the North American trial subpopulations. Equivalent analyses were performed for the non-North American trial populations to facilitate side-by-side comparisons of the North American and non-North American trial populations.

Statistical Analyses

Post-hoc analyses were based on the ECZTRA 1, 2, and 3 North American populations and were considered exploratory; no adjustments for multiplicity testing were made, hence, p-values obtained for these analyses are nominal. ECZTRA 1 and ECZTRA 2 study data were pooled for the North American subanalysis. For binary endpoints, the difference in response rates between treatment groups was analyzed using the Cochran–Mantel–Haenszel test, stratified by baseline IGA and study identification for ECZTRA 1 and ECZTRA 2, and by baseline IGA for ECZTRA 3. Patients receiving rescue medication, including TCS in ECZTRA 1/2, prior to week 16 or with missing data were considered non-responders.

For the pooled ECZTRA 1/2 data and ECZTRA 3 data, continuous endpoints were assessed using a linear mixed model for repeated measures, including baseline IGA and treatment-by-week interaction as factors and interaction between week and baseline value as covariates for ECZTRA 1/2 and ECZTRA 3 as well as interactions between week and study identification for ECZTRA 1/2. An unstructured covariance matrix was used to model within-patient variation. Data collected after permanent discontinuation of investigational medicinal product or after initiation of rescue medication were excluded from the analysis.

Adverse events (AEs) were assessed at baseline and each subsequent visit until completion of the trial. Descriptive statistics were used to present baseline demographics, baseline disease characteristics, and safety assessments.

Side-by-side comparison was used to compare the efficacy and safety of tralokinumab in the ECZTRA 1/2 and ECZTRA 3 North American populations with that in the non-North American populations.

RESULTS

Patients

Overall, 1596 and 380 patients were randomized in ECZTRA 1/2 and ECZTRA 3, respectively, of whom 559 (35%) and 160 (42.1%) patients were from North America, respectively. The North American population in ECZTRA 1/2 and ECZTRA 3 had similar baseline disease characteristics and demographics, although there were some variations compared with the non-North American population (Table 1 and Table S1, see ESM). Across treatment groups, the median baseline body surface area involvement and proportion of patients with severe atopic dermatitis (IGA 4) were lower in the North American population (ECZTRA 1/2: 38–39% and 40.7–40.8%; ECZTRA 3: 33–36% and 37.7–38.9%) compared with the non-North American population (ECZTRA 1/2: 57–60% and 54.1–56.2%; ECZTRA 3, 50–51% and 51.7–53.4%). In the ECZTRA 1/2 and ECZTRA 3 North American population, median duration

Table 1 Patient demographics and disease characteristics of all randomized patients from the ECZTRA 1/2 and ECZTRA 3 North American population at baseline

Characteristic	ECZTRA 1/2 North American population		ECZTRA 3 North American population	
	Tralokinumab q2w (<i>n</i> = 419)	Placebo q2w (<i>n</i> = 140)	Tralokinumab q2w + TCS (<i>n</i> = 106)	Placebo q2w + TCS (<i>n</i> = 54)
Median age, years (IQR)	39.0 (27.0–53.0)	37.0 (25.0–53.5)	39.0 (28.0–54.0)	34.5 (24.0–53.0)
Male, <i>n</i> (%)	218 (52.0)	73 (52.1)	49 (46.2)	29 (53.7)
Race, <i>n</i> (%)				
White	229 (54.7)	70 (50.0)	66 (62.3)	22 (40.7)
Black or African American	79 (18.9)	34 (24.3)	19 (17.9)	10 (18.5)
Asian	87 (20.8)	30 (21.4)	13 (12.3)	18 (33.3)
American Indian or Alaska native	3 (0.7)	0	–	–
Native Hawaiian or other Pacific Islander	6 (1.4)	0	1 (0.9)	1 (1.9)
Other	15 (3.6)	6 (4.3)	7 (6.6)	3 (5.6)
Median duration of atopic dermatitis, years (IQR)	26.0 (16.0–40.0)	25.0 (16.0–40.0)	25.0 (13.0–39.0)	24.0 (17.0–39.0)
Median BSA involvement, % (IQR)	39.0 (23.0–58.0)	38.0 (22.0–62.0)	36.0 (25.0–50.0)	33.0 (22.0–68.0)
Median EASI (IQR)	24.2 (18.4–33.3)	24.9 (18.4–37.5)	21.6 (17.9–30.7)	24.9 (19.4–32.4)
IGA, <i>n</i> (%)				
Moderate (IGA 3)	248 (59.2)	82 (58.6)	65 (61.3)	33 (61.1)
Severe (IGA 4)	171 (40.8)	57 (40.7)	40 (37.7)	21 (38.9)
Median SCORAD score (IQR)	65.5 (58.9–73.6)	67.3 (59.7–77.5)	63.4 (56.5–74.9)	66.2 (59.5–77.7)
Median DLQI (IQR)	17.0 (12.0–23.0)	17.0 (11.0–24.0)	16.0 (11.0–22.0)	18.0 (12.0–24.0)
Median weekly average worst daily pruritus NRS score (IQR)	8.0 (7.0–9.1)	8.1 (7.1–9.0)	8.0 (6.9–8.7)	8.5 (7.1–9.4)

BSA body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *IQR* interquartile range, *NRS* numeric rating scale, *q2w* every 2 weeks, *SCORAD* SCORing Atopic Dermatitis, *TCS* topical corticosteroid

of atopic dermatitis was 25–26 years and 24–25 years and median EASI was 24.2–24.9 and 21.6–24.9, respectively, across treatment groups. The ECZTRA 1/2 and ECZTRA 3 North American population was more racially diverse than the non-North American population, with ~ 30–52% of patients from ethnic minority groups across treatment groups (ECZTRA 1/2: ~ 19–24% black/African American, ~ 21% Asian; ECZTRA 3: ~ 18% black/African American, ~ 12–33% Asian).

Primary Outcomes of the ECZTRA 1/2 and ECZTRA 3 North American Population

At week 16, a greater proportion of tralokinumab-treated patients in ECZTRA 1/2 (25.3% vs 15.1%; difference 10.2%; 95% confidence interval [CI] 3.0, 17.3; $p = 0.012$), and

numerically greater proportion of patients in ECZTRA 3 (40.0% vs 25.9%; difference 13.9%; 95% CI – 0.5, 28.3; $p = 0.074$) achieved IGA 0/1 compared with those who received placebo (Fig. 1a). Similarly, a higher proportion of tralokinumab-treated patients achieved EASI-75 compared with placebo in ECZTRA 1/2 (40.1% vs 19.4%; difference 20.6%; 95% CI 12.6, 28.7; $p < 0.001$) and ECZTRA 3 (58.1% vs 37.0%; difference 21.0%; 95% CI 4.9, 37.0; $p = 0.012$) (Fig. 1b).

In the ECZTRA 3 North American population, cumulative TCS use was approximately 50% lower at weeks 15–16 in patients receiving tralokinumab compared with placebo (geometric mean 60.7 g vs 118.5 g; $p = 0.012$) (Fig. 2), which could account for the high placebo response at week 16 in ECZTRA 3; this needs to

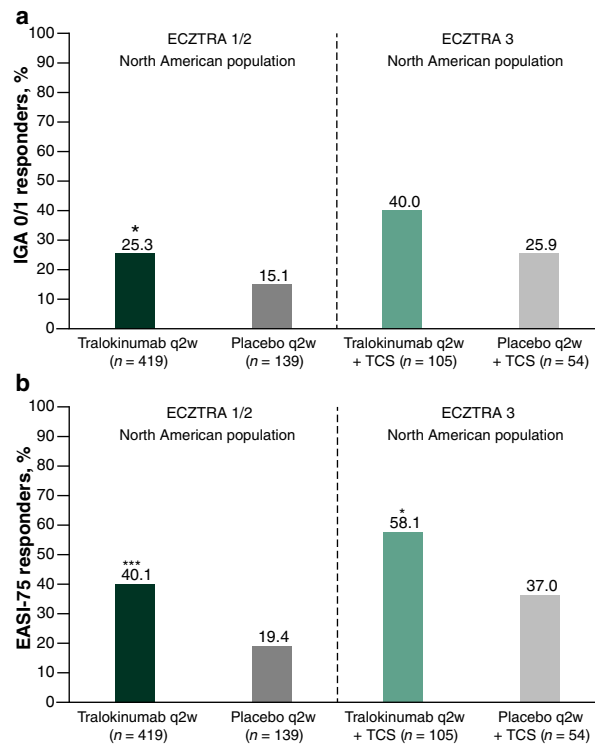


Fig. 1 Achievement of **a** IGA score of 0/1 and **b** EASI-75 response in the ECZTRA 1/2 and ECZTRA 3 North American population at week 16. Patients who received rescue medication prior to week 16 or with missing data were considered non-responders. The Cochran–Mantel–Haenszel test was used to test risk difference, stratified

by baseline IGA and study identification for ECZTRA 1 and ECZTRA 2, and baseline IGA for ECZTRA 3. Based on the full analysis set. * $p < 0.05$ vs placebo; *** $p < 0.001$ vs placebo. EASI-75 at least 75% improvement in Eczema Area and Severity Index, IGA Investigator’s Global Assessment, q2w every 2 weeks, TCS topical corticosteroid

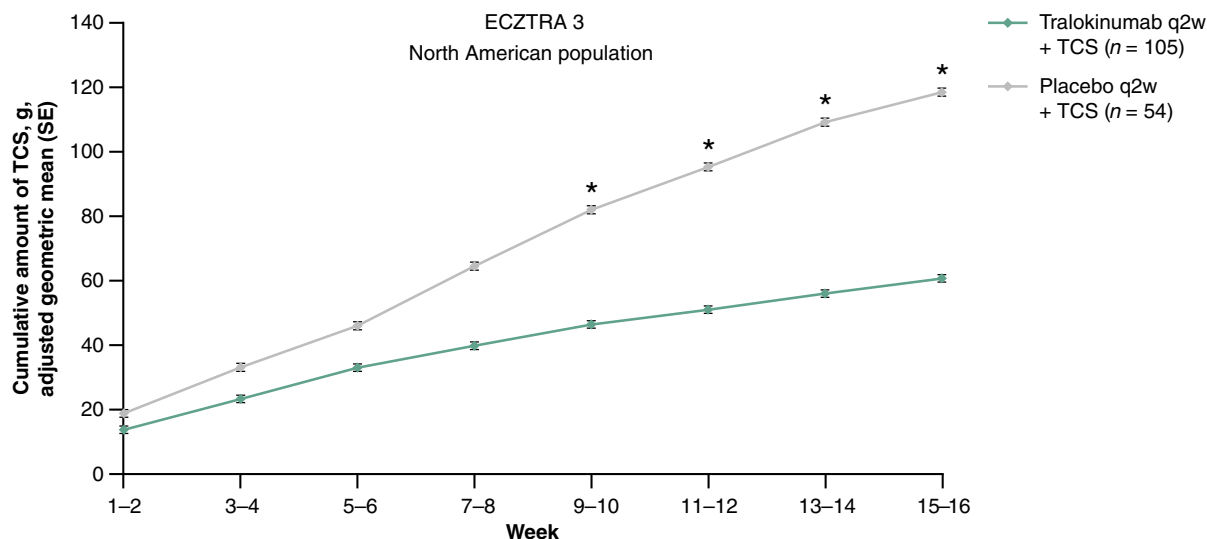


Fig. 2 Cumulative amount of TCS used in the ECZTRA 3 North American population by visit, assuming no TCS used from non-returned tubes, initial treatment period, full analysis set. Data collected after permanent discontinuation of investigational medicinal product or initiation of

rescue medication not included. Repeated measurements model: $\log[\text{cumulative TCS amount} + 1] \text{ (g)} = \text{Treatment} \times \text{Week} + \text{Baseline IGA}$. * $p < 0.05$ vs tralokinumab. IGA Investigator’s Global Assessment, *q2w* every 2 weeks, SE standard error, TCS topical corticosteroid

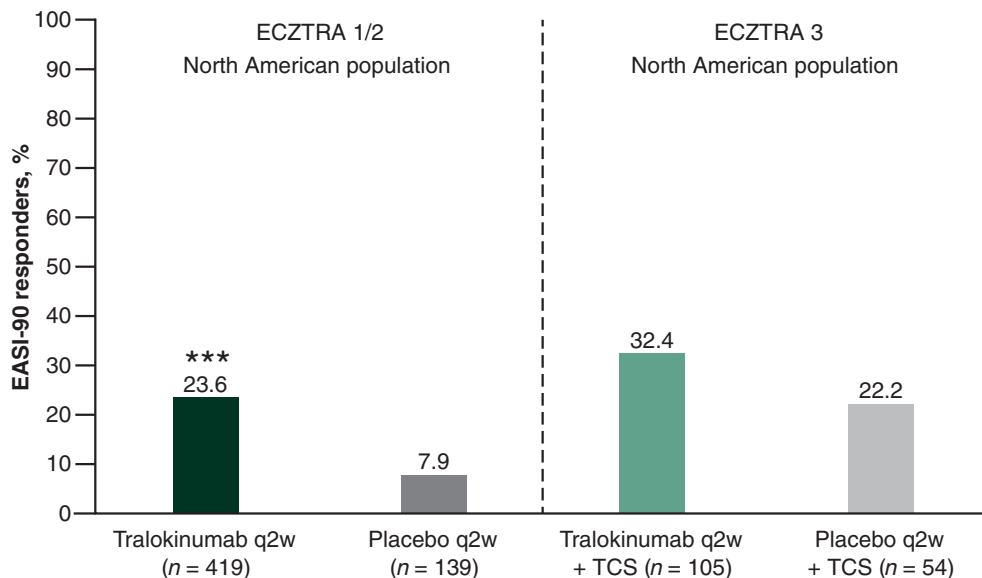
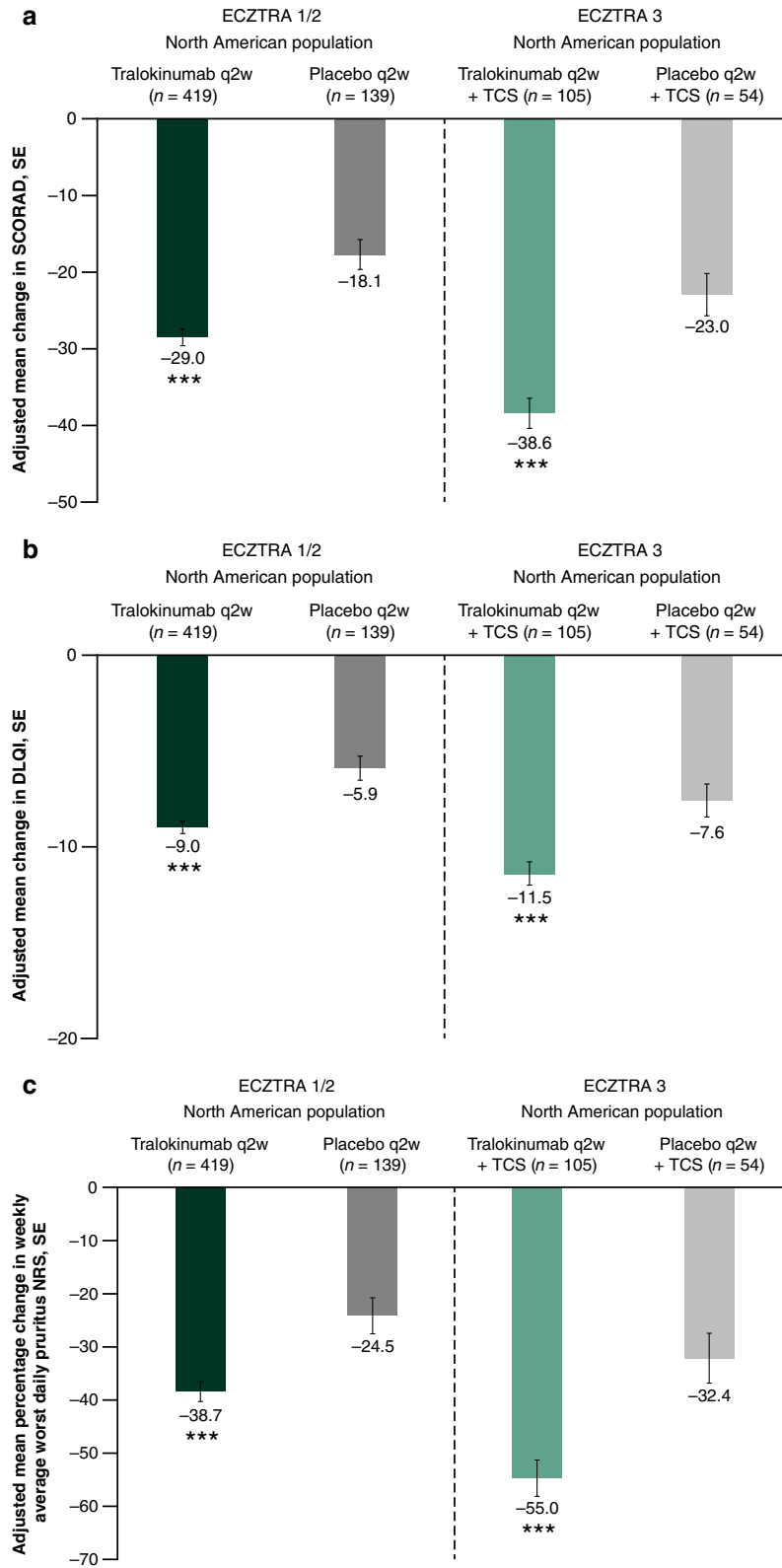


Fig. 3 Achievement of EASI-90 in the ECZTRA 1/2 and ECZTRA 3 North American population at week 16. Patients who received rescue medication prior to week 16 or with missing data were considered non-responders. The Cochran–Mantel–Haenszel test was used to test risk difference, stratified by baseline IGA and study

identification for ECZTRA 1/2, and by baseline IGA for ECZTRA 3. Based on the full analysis set. *** $p < 0.001$ vs placebo. EASI-90 at least 90% improvement in Eczema Area and Severity Index, IGA Investigator’s Global Assessment, *q2w* every 2 weeks, TCS topical corticosteroid



◀**Fig. 4** Change in **a** SCORAD score, **b** DLQI, and **c** percentage change in weekly average worst daily pruritus NRS score in the ECZTRA 1/2 and ECZTRA 3 North American population at week 16. Data collected after permanent discontinuation of investigational medicinal product or initiation of rescue medication not included. Repeated measures model: ECZTRA 1/2, Change from baseline = Treatment*Week + Baseline*Week + Baseline IGA + Study Identification*Week; ECZTRA 3, Change from baseline = Treatment*Week + Baseline*Week + Baseline IGA. Based on the full analysis set. *** $p < 0.001$ vs placebo. *DLQI* Dermatology Life Quality Index, *IGA* Investigator’s Global Assessment, *NRS* numeric rating scale, *q2w* every 2 weeks, *SCORAD* SCORing Atopic Dermatitis, *SE* standard error, *TCS* topical corticosteroids

be considered when comparing other week 16 endpoints in this trial.

A summary of tralokinumab efficacy in the ECZTRA 1/2 and ECZTRA 3 non-North American population at week 16 can be found in Table S2 (see ESM).

Secondary Outcomes of the ECZTRA 1/2 and ECZTRA 3 North American Population

EASI-90 was achieved by a greater proportion of tralokinumab-treated patients in ECZTRA 1/2 (23.6% vs 7.9%; difference 15.6%; 95% CI 9.6, 21.6; $p < 0.001$) and numerically greater proportion of tralokinumab-treated patients in ECZTRA 3 (32.4% vs 22.2%; difference 10.1%; 95% CI - 4.3, 24.5; $p = 0.18$) versus those who received placebo at week 16 (Fig. 3). The adjusted mean change from baseline to Week 16 in SCORAD (standard error [SE]) was greater with tralokinumab versus placebo in ECZTRA 1/2 (- 29.0 [1.08] vs - 18.1 [2.03]; difference -10.9; 95% CI - 15.4, - 6.4; $p < 0.001$) and ECZTRA 3 (-38.6 [1.98] vs - 23.0 [2.77]; difference - 15.6; 95% CI - 22.4, - 8.9; $p < 0.001$) (Fig. 4a). Similarly, adjusted mean change from baseline to week 16 in DLQI (SE) was greater with tralokinumab versus placebo in ECZTRA 1/2 (- 9.0 [0.35] vs - 5.9 [0.66]; difference - 3.1; 95% CI - 4.6, - 1.7; $p < 0.001$) and ECZTRA 3 (- 11.5

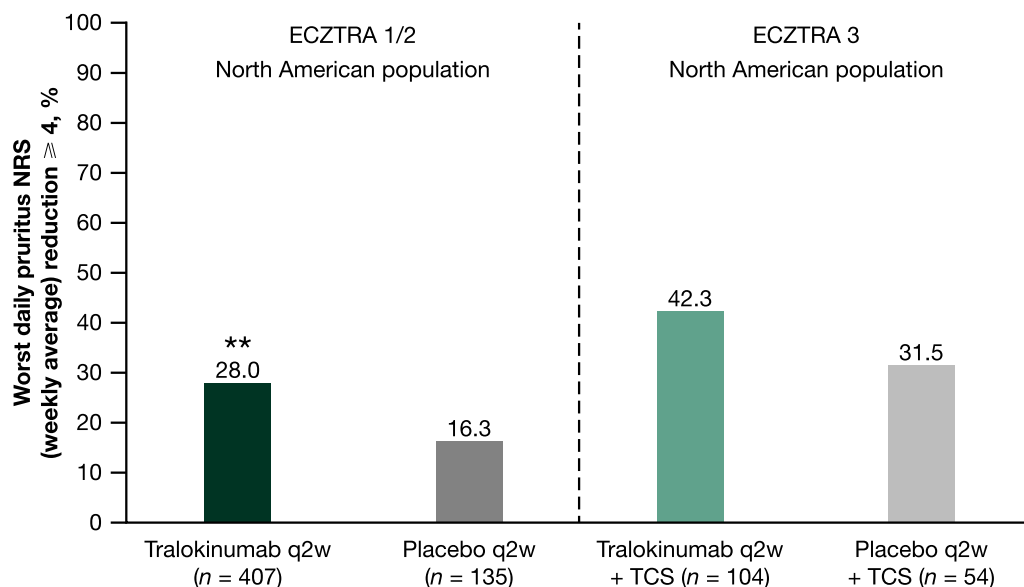


Fig. 5 Reduction in pruritus NRS ≥ 4 in the ECZTRA 1/2 and ECZTRA 3 North American population at week 16. Patients who received rescue medication prior to week 16 or with missing data were considered non-responders. The Cochran–Mantel–Haenszel test was used to test risk difference, stratified by baseline IGA and study

identification for ECZTRA 1/2, and by baseline IGA for ECZTRA 3. Based on the full analysis set with a baseline pruritus NRS average of ≥ 4 . ** $p < 0.01$ vs placebo. *IGA* Investigator’s Global Assessment, *NRS* numeric rating scale, *q2w* every 2 weeks, *TCS* topical corticosteroid

Table 2 Rescue medication use in the initial 16-week treatment period in the ECZTRA 1/2 and ECZTRA 3 North American population, safety analysis set

<i>n</i> (%)	ECZTRA 1/2 North American population		ECZTRA 3 North American population	
	Tralokinumab q2w (<i>n</i> = 419)	Placebo q2w (<i>n</i> = 140)	Tralokinumab q2w + TCS (<i>n</i> = 106)	Placebo q2w + TCS (<i>n</i> = 54)
Any rescue medication	74 (17.7)	46 (32.9)	5 (4.7)	5 (9.3)
Immunosuppressants	3 (0.7)	6 (4.3)	0	2 (3.7)
Cyclosporin	1 (0.2)	4 (2.9)	0	2 (3.7)
Methotrexate	0	2 (1.4)	NA	NA
Topical	70 (16.7)	41 (29.3)	4 (3.8)	3 (5.6)
Corticosteroids	59 (14.1)	38 (27.1)	3 (2.8)	3 (5.6)
Corticosteroids combined with antiseptics	0	1 (0.7)	NA	NA
Other dermatologic preparations	16 (3.8)	4 (2.9)	1 (0.9)	0

Rescue medication was permitted at the discretion of the investigator. In ECZTRA 1/2, TCS, topical calcineurin inhibitors, and systemic treatment were considered rescue; in ECZTRA 3, higher potency TCS (Europe Class > 3; US Class < 4) and systemic treatment were considered rescue
q2w every 2 weeks, *NA* not available, *TCS* topical corticosteroid

[0.61] vs -7.6 [0.86]; difference -3.9 ; 95% CI $-6.0, -1.9$; $p < 0.001$) (Fig. 4b).

In the initial 16-week treatment period, tralokinumab-treated patients achieved a greater adjusted mean percentage change from baseline in weekly average worst daily pruritus NRS (SE) versus those who received placebo in ECZTRA 1/2 (-38.7 [1.82] vs -24.5 [3.41]; difference -14.1 ; 95% CI $-21.7, -6.5$; $p < 0.001$) and ECZTRA 3 (-55.0 [3.36] vs -32.4 [4.70]; difference -22.6 ; 95% CI $-34.1, -11.2$; $p < 0.001$) (Fig. 4c). Additionally, a greater proportion of patients in the tralokinumab group in ECZTRA 1/2 (28.0% vs 16.3%; difference 11.8%; 95% CI 4.3, 19.4; $p = 0.006$) and numerically greater proportion of patients in ECZTRA 3 (42.3% vs 31.5%; difference 10.8%; 95% CI $-4.9, -26.6$; $p = 0.19$) achieved a ≥ 4 -point reduction in weekly average worst daily pruritus NRS versus those in the placebo group (Fig. 5). Notably, the placebo group in ECZTRA 3 used twice as much of the supplied

TCS at weeks 15–16 compared with the tralokinumab group (Fig. 2).

Rescue Medication Use in the ECZTRA 1/2 and ECZTRA 3 North American Population

During the initial 16-week treatment period, tralokinumab-treated patients used less rescue medication compared with those who received placebo in ECZTRA 1/2 (17.7% vs 32.9%). TCS was the most commonly used rescue medication in ECZTRA 1/2. In ECZTRA 3, where an increase in TCS potency or systemic therapy were considered rescue, tralokinumab-treated patients used less rescue medication compared with placebo (4.7% vs 9.3%) during the initial treatment period (Table 2). Higher potency TCS was the most commonly used rescue medication in ECZTRA 3. A smaller proportion of patients in the tralokinumab group used immunosuppressants as rescue medication

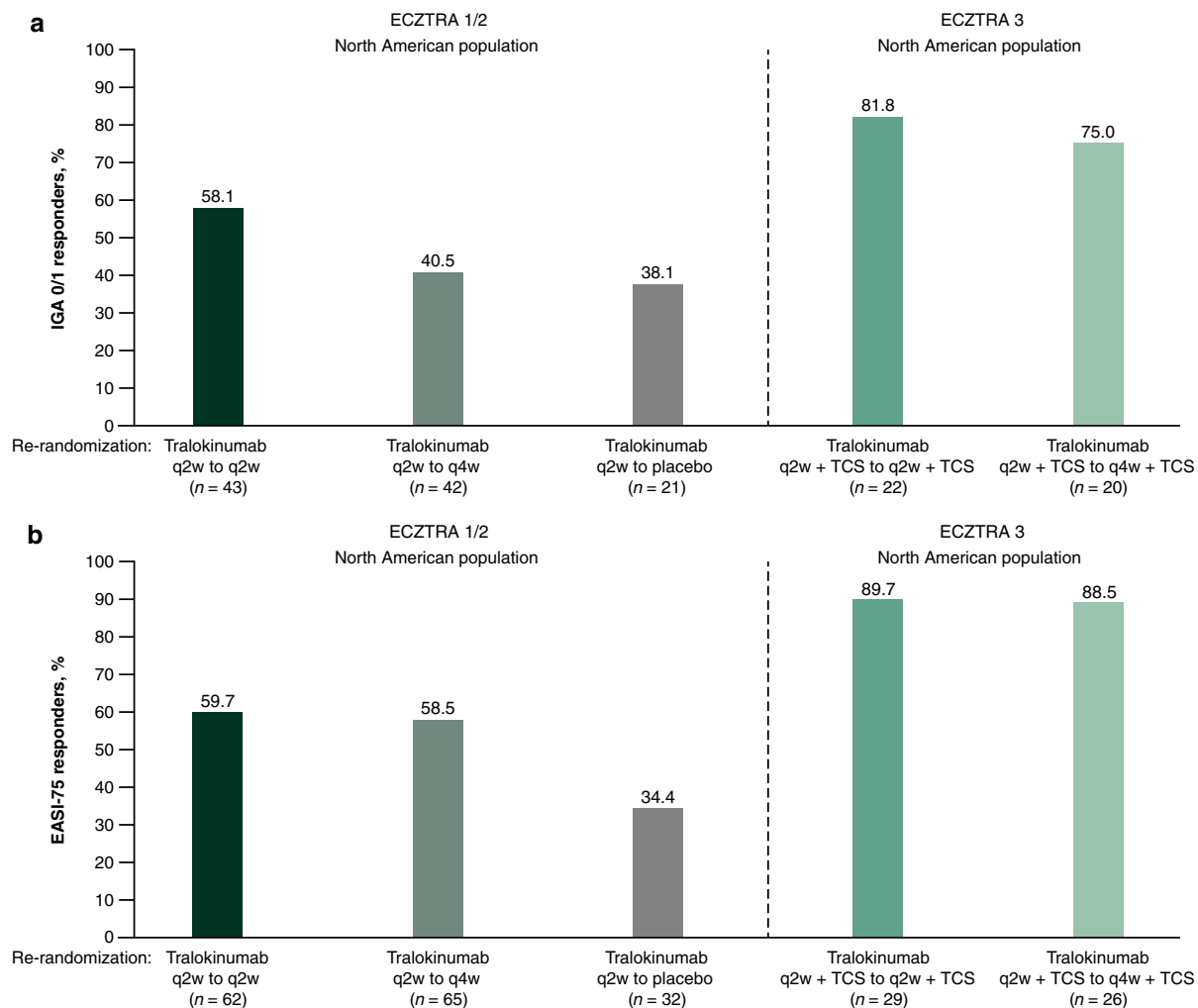


Fig. 6 Efficacy outcomes^a in patients achieving IGA 0/1 or EASI-75 response without rescue medication at week 16 in the ECZTRA 1/2 and ECZTRA 3 North American population, maintenance treatment period, full analysis set. ^aAt week 52 in ECZTRA 1/2 and week 32 in ECZTRA 3. Patients who received rescue medication or were

transferred to open-label treatment or with missing data were considered non-responders. *EASI-75* at least 75% improvement in Eczema Area and Severity Index, *IGA* Investigator’s Global Assessment, *q2w* every 2 weeks, *TCS* topical corticosteroid

compared with those in the placebo group in ECZTRA 1/2 (0.7% vs 4.3%) and ECZTRA 3 (0% vs 3.7%) (Table 2).

Rescue medication use in the ECZTRA 1/2 and ECZTRA 3 non-North American population was comparable to the ECZTRA 1/2 and ECZTRA 3 North American population, with lower rescue medication use in the tralokinumab arm compared with the placebo arm (Table S3, see ESM).

Maintenance Outcomes in the ECZTRA 1/2 and ECZTRA 3 North American Population

In tralokinumab-treated patients with IGA 0/1 at week 16 in the ECZTRA 1/2 North American population, IGA 0/1 was maintained at week 52 by 58.1% of patients with continued tralokinumab q2w and 40.5% of patients re-randomized to tralokinumab q4w versus 38.1% of patients re-randomized to placebo (Fig. 6a).

Table 3 Summary of AEs and AESIs in the initial 16-week treatment period in the ECZTRA 1/2 and ECZTRA 3 North American population, safety analysis set

<i>n</i> (%)	ECZTRA 1/2 North American population		ECZTRA 3 North American population	
	Tralokinumab q2w (<i>n</i> = 419)	Placebo q2w (<i>n</i> = 139)	Tralokinumab q2w + TCS (<i>n</i> = 105)	Placebo q2w + TCS (<i>n</i> = 54)
Patients with AEs				
≥ 1 AE	232 (55.4)	83 (59.7)	60 (57.1)	28 (51.9)
≥ 1 SAE	8 (1.9)	4 (2.9)	0	1 (1.9)
Severity				
Mild	191 (45.6)	52 (37.4)	50 (47.6)	20 (37.0)
Moderate	102 (24.3)	60 (43.2)	18 (17.1)	12 (22.2)
Severe	10 (2.4)	6 (4.3)	0	3 (5.6)
AE leading to withdrawal from trial	11 (2.6)	1 (0.7)	2 (1.9)	0
Outcome				
Not recovered/not resolved	41 (9.8)	23 (16.5)	18 (17.1)	5 (9.3)
Recovering/resolving	12 (2.9)	2 (1.4)	2 (1.9)	2 (3.7)
Recovered/resolved	211 (50.4)	77 (55.4)	55 (52.4)	25 (46.3)
Recovered/resolved with sequelae	3 (0.7)	0	1 (1.0)	0
Frequent AEs (> 5% in any treatment group) ^a				
Viral upper respiratory tract infection	44 (10.5)	13 (9.4)	9 (8.6)	3 (5.6)
Upper respiratory tract infection	36 (8.6)	12 (8.6)	6 (5.7)	3 (5.6)
Dermatitis atopic	30 (7.2)	30 (21.6)	2 (1.9)	4 (7.4)
Injection site reaction	20 (4.8)	1 (0.7)	12 (11.4)	0
Injection site pain	19 (4.5)	8 (5.8)	1 (1.0)	0
AESIs				
Eye disorders				
Conjunctivitis	10 (2.4)	2 (1.4)	3 (2.9)	1 (1.9)
Keratoconjunctivitis	0	0	0	0
Keratitis	0	0	0	0
Skin infections requiring systemic treatment	10 (2.4)	9 (6.5)	2 (1.9)	5 (9.3)
Eczema herpeticum	1 (0.2)	0	0	0
Malignancies diagnosed after randomization	0	0	0	0

AE adverse event, *AESI* adverse event of special interest, *q2w* every 2 weeks, *SAE* serious adverse event, *TCS* topical corticosteroid

^aPreferred Term according to the Medical Dictionary for Regulatory Activities, version 20.0

Similarly, in tralokinumab-treated patients with EASI-75 at week 16, EASI-75 was maintained at week 52 by 59.7% with continued tralokinumab q2w and 58.5% of patients re-randomized to tralokinumab q4w, compared with 34.4% of patients re-randomized to placebo (Fig. 6b).

In week 16 tralokinumab responders in the ECZTRA 3 North American population, IGA 0/1 response was maintained at week 32 by 81.8% and 75.0% and EASI-75 response was maintained by 89.7% and 88.5% of patients receiving tralokinumab q2w and q4w, respectively (Fig. 6a and b).

Efficacy outcomes in the ECZTRA 1/2 and ECZTRA 3 non-North American population were comparable with the North American population during the maintenance treatment period (Table S4, see ESM); a slightly lower response was observed in the placebo arm in the ECZTRA 1/2 non-North American and North American populations, possibly due to a small number of patients.

Safety in the ECZTRA 1/2 and ECZTRA 3 North American Population

The overall AE rate was comparable between the tralokinumab and placebo groups during the initial 16-week treatment period in the ECZTRA 1/2 and ECZTRA 3 North American population (Table 3). The majority of AEs were mild or moderate in severity, with ~ 50% resolved or resolving at the end of the treatment period. Of the most frequently reported AEs (> 5% in any treatment groups), viral upper respiratory tract infection (ECZTRA 1/2: 10.5% vs 9.4%; ECZTRA 3: 8.6% vs 5.6%) and injection-site reaction (ECZTRA 1/2: 4.8% vs 0.7%; ECZTRA 3: 11.4% vs 0%) occurred more frequently with tralokinumab versus placebo, and dermatitis atopic (ECZTRA 1/2: 7.2% vs 21.6%; ECZTRA 3: 1.9% vs 7.4%) occurred less frequently with tralokinumab versus placebo.

In the initial 16-week treatment period, conjunctivitis occurred more often with tralokinumab versus placebo (ECZTRA 1/2: 2.4% vs 1.4%; ECZTRA 3: 2.9% vs 1.9%) (Table 3). All cases of conjunctivitis were mild or moderate in severity and most resolved at the end of the

initial treatment period. No cases of keratitis or keratoconjunctivitis were reported (Table 3). Skin infections requiring systemic treatment occurred less frequently with tralokinumab compared with placebo in ECZTRA 1/2 (2.4% vs 6.5%) and ECZTRA 3 (1.9% vs 9.3%) (Table 3).

No marked differences in rates of serious AEs were observed between tralokinumab and placebo in the ECZTRA 1/2 (1.9% vs 2.9%) and ECZTRA 3 (0% vs 1.9%) North American population (Table 3).

In the maintenance treatment period, a slightly higher rate of AEs was reported with tralokinumab q2w in the ECZTRA 1/2 and ECZTRA 3 North American population than in the initial treatment period, although event severity and outcome with tralokinumab q2w was comparable to the initial treatment period (Table 4) and may be an artifact of the small number of patients analyzed.

Safety in the ECZTRA 1/2 and ECZTRA 3 non-North American population during the initial and maintenance treatment periods are summarized in Table S5 and Table S6 (see ESM).

DISCUSSION

This is the first phase 3 trial post-hoc analysis evaluating the therapeutic efficacy of an anti-IL-13 biologic, used with or without TCS as needed, in a North American subpopulation of patients with moderate-to-severe atopic dermatitis. Tralokinumab showed greater improvement compared with placebo in all primary and secondary endpoints at week 16 in the ECZTRA 1/2 North American population and most primary and secondary endpoints at week 16 in the ECZTRA 3 North American population. In addition, IGA 0/1 and EASI-75 were sustained with tralokinumab at week 52 (in ECZTRA 1/2) and at week 32 (in ECZTRA 3). These results are similar to those observed in the ECZTRA 1/2 and ECZTRA 3 non-North American population (Table S2 and Table S4, see ESM). While direct comparison is not possible due to lack of head-to-head data, at week 16, 40% and 58.1% of the North American population in ECZTRA 3 achieved IGA 0/1 and EASI-75 with tralokinumab plus TCS as needed,

Table 4 Summary of AEs in the maintenance treatment period in the ECZTRA 1/2 and ECZTRA 3 North American population, safety analysis set

Re-randomization at week 16	ECZTRA 1/2 North American population week 16 tralokinumab responders			ECZTRA 3 North American population week 16 tralokinumab responders	
	Tralokinumab q2w to q2w (<i>n</i> = 65)	Tralokinumab q2w to q4w (<i>n</i> = 68)	Tralokinumab q2w to placebo (<i>n</i> = 33)	Tralokinumab q2w + TCS to q2w + TCS (<i>n</i> = 31)	Tralokinumab q2w + TCS to q4w + TCS (<i>n</i> = 28)
Patients with AEs, <i>n</i> (%)					
≥ 1 AE	41 (63.1)	38 (55.9)	22 (66.7)	22 (71.0)	19 (67.9)
≥ 1 SAE	0	1 (1.5)	0	2 (6.5)	0
Severity, <i>n</i> (%)					
Mild	32 (49.2)	29 (42.6)	17 (51.5)	19 (61.3)	14 (50.0)
Moderate	20 (30.8)	14 (20.6)	10 (30.3)	6 (19.4)	6 (21.4)
Severe	1 (1.5)	0	0	1 (3.2)	0
Outcome, <i>n</i> (%)					
Not recovered/not resolved	13 (20.0)	8 (11.8)	6 (18.2)	3 (9.7)	7 (25.0)
Recovering/resolving	4 (6.2)	6 (8.8)	3 (9.1)	0	1 (3.6)
Recovered/resolved	34 (52.3)	31 (45.6)	18 (54.5)	21 (67.7)	14 (50.0)
Recovered/resolved with sequelae	0	1 (1.5)	0	0	0

AE adverse event, *q2w* every 2 weeks, *SAE* serious adverse event, *TCS* topical corticosteroid

respectively, which is similar to week 16 dupilumab plus TCS IGA 0/1 (39%) and EASI-75 (69%) response rates in the LIBERTY AD CHRONOS study [18]. However, compared with LIBERTY AD CHRONOS, placebo response rates were greater in the ECZTRA 3 North American population. This may be due to a number of factors, including: (1) a higher proportion of patients with moderate atopic dermatitis (IGA 3) at baseline; (2) the nature of the ECZTRA 3 study, where all patients had continued access to TCS; and (3) the greater amount of TCS use in patients receiving placebo compared with tralokinumab.

During the initial treatment period, rescue medication use was ~ 50% lower in tralokinumab-treated patients compared with those who received placebo in the ECZTRA 1/2 and ECZTRA 3 North American population. Of note, a considerably smaller proportion of the ECZTRA 1/2 North American population used rescue medications compared with the non-North American population (Table S3, see ESM). Overall, rescue medication use was low in the ECZTRA 3 North American and non-North American populations, possibly due to continued access to TCS. Greater tralokinumab responses were observed in the North American

population in ECZTRA 3 compared with ECZTRA 1/2 at week 16, also likely due to TCS use as needed as an adjunct to treatment with tralokinumab. These ECZTRA 3 data reflect how moderate-to-severe atopic dermatitis might be treated in real-world settings, i.e., with a biologic combined with TCS [17].

Tralokinumab, with or without TCS, was well tolerated in the ECZTRA 1/2 and ECZTRA 3 North American population, with an overall safety profile consistent with the non-North American population (Table S5 and Table S6, see ESM). Of note, the proportion of patients experiencing ≥ 1 AE was lower in the North American population compared with the non-North American population. This may be explained by the greater proportion of patients with moderate disease, who are less likely to experience flares and skin infections compared to patients with severe disease [19, 20]. Additionally, regardless of treatment groups, conjunctivitis occurred with lower frequency in the ECZTRA 1/2 and ECZTRA 3 North American population compared with the non-North American population. This may reflect the lower proportion of patients in the North American population with severe disease at baseline, which has been identified as a risk factor for conjunctivitis in an analysis of five tralokinumab trials in adult patients with moderate-to-severe atopic dermatitis [21].

Limitations of this study include the small North American population sample sizes and multiplicity testing; only analyses included in the pre-specified ECZTRA 1/2 and ECZTRA 3 testing hierarchy were considered statistically significant. Although this post-hoc analysis of the North American population was exploratory in nature, differences were observed between treatment groups for most primary and secondary outcomes, comparable to the primary study population, where all primary and secondary endpoints were met [16, 17]. Of note, there was a difference between the proportion of ethnic minorities in the ECZTRA 1/2 and ECZTRA 3 North American population compared with the non-North American population. Approximately 30–52% of patients had skin of color in the ECZTRA 1/2 and ECZTRA 3 North American population compared with

approximately 5–25% in the non-North American population across treatment groups. This is an important finding and represents a strength of this North American subanalysis, providing safety and efficacy data across several ethnicities in three large phase 3 programs.

CONCLUSIONS

Tralokinumab, with or without TCS, displayed similar efficacy and safety in patients with moderate-to-severe atopic dermatitis across the ECZTRA 1/2 and ECZTRA 3 North American population, comparable to that of the non-North American population. Tralokinumab, with or without TCS, was well tolerated in ethnically diverse North American populations, suggesting no special treatment considerations may be required for this subpopulation. Confirmation of the region-specific therapeutic efficacy and safety of tralokinumab may strengthen clinical decision-making, thereby benefiting patients from North America with moderate-to-severe atopic dermatitis.

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Compliance with Ethics Guidelines. The ECZTRA 1, 2, and 3 studies were 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 trials were approved by institutional review boards or ethics committees at each study site and followed the Consolidated Standards of Reporting Trials reporting guideline. All participants provided informed consent to participate in the trials.

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

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