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ORIGINAL RESEARCH ARTICLE

Tralokinumab Efficacy Over 1 Year in Adults with Moderate-to-Severe Atopic Dermatitis: Pooled Data from Two Phase III Trials

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Abstract

Background Two phase III trials, ECZTRA 1 and 2, confirmed the efficacy and safety of tralokinumab versus placebo in adults with moderate-to-severe atopic dermatitis (AD). To further explore the long-term efficacy of tralokinumab for AD, a pooled analysis of these trials was conducted.

Methods ECZTRA 1 and 2 patients ($n = 1596$ total) were randomized to tralokinumab 300 mg or placebo every 2 weeks (q2w) over 16 weeks. Patients achieving Investigator's Global Assessment of clear/almost clear skin (IGA 0/1) and/or 75% improvement in the Eczema Area and Severity Index (EASI-75) at Week 16, were re-randomized to tralokinumab q2w, every 4 weeks (q4w), or placebo (tralokinumab withdrawal) for another 36 weeks. Patients not achieving the response criteria at Week 16 received open-label tralokinumab q2w plus optional topical corticosteroids (TCS). A pooled, prespecified analysis assessed the proportions of Week 16 responders that maintained IGA 0/1 and/or EASI-75 at Week 52. Pooled data from all patients initiated with tralokinumab, regardless of the response at Week 16 or dosing regimen received thereafter, were analyzed post hoc.

Results In patients who achieved the primary endpoints at Week 16, IGA 0/1 responses were maintained at Week 52 without rescue treatment (including TCS) by 55.9%, 42.4%, and 34.0% of patients re-randomized to tralokinumab q2w, q4w, or placebo (tralokinumab withdrawal), respectively, while EASI-75 responses were maintained by 57.3%, 50.4%, and 26.4%, respectively (prespecified analysis). In a post hoc analysis of all patients initiated with tralokinumab, response rates improved over time with continued tralokinumab treatment beyond Week 16 to Week 52 for EASI-50 (63.1–82.7%), EASI-75 (37.6–61.8%), EASI-90 (20.4–37.3%), and IGA 0/1 (23.0–36.2%).

Conclusions Tralokinumab treatment provides progressive and sustained improvement over 1 year in the extent and severity of AD in patients with moderate-to-severe AD.

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.

Extended author information available on the last page of the article

Infographic

American Journal of Clinical Dermatology

Tralokinumab efficacy over 1 year in adults with moderate-to-severe atopic dermatitis: Pooled data from two phase III trials

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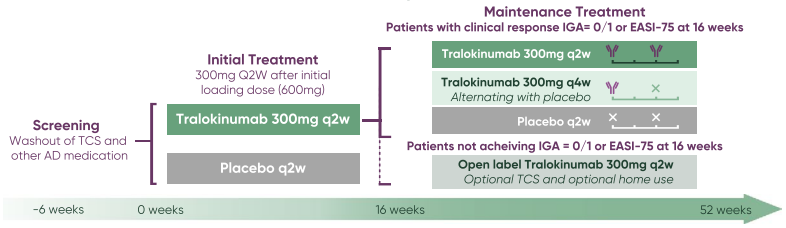
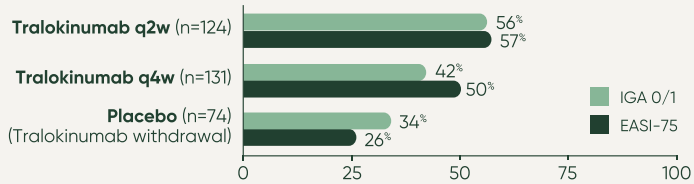
ECZTRA 1 and 2 were identically designed 52-week monotherapy trials



Maintained response at Week 52 (Week 16 tralokinumab responders)

Proportion of patients with maintained response at Week 52 (%)
with continued tralokinumab monotherapy q2w/q4w or treatment withdrawal Week 16-52

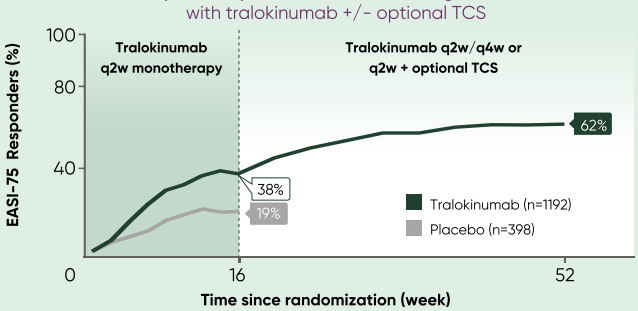


Patients who received rescue medication (including TCS) and patients with missing data were consdidered to be non-responders

Response rates continue to improve through Week 52 (All tralokinumab)

Post hoc analysis following all 1192 patients initiated on tralokinumab through Week 52 as one pooled arm regardless of Week 16 response or dosing regimen (blinded q2w, q4w or open-label q2w + optional TCS) showed that response rates progressively improved beyond Week 16.

Proportion of patients with EASI-75 through Week 52
with tralokinumab +/- optional TCS



These analyses were based on the pre-specified treatment policy estimated approach (using data as observed, regardless of rescue medication and multiple imputations for missing data) until Week 16. From Week 16-52, patients re-randomized to placebo at Week 16 were set missing and imputed from the similar responder populations re-randomized to tralokinumab q2w or q4w at Week 16.

Clinical Implication

- Less frequent q4w dosing can be suffficient to sustain a response in some patients that have achieved clear or almost clear skin with initial q2w tralokinumab
- Week 16 may be too early for evaluating the full benefit of tralokinumab in some patients, a finding which may help inform clinical decision regarding when to continue, discontinue, or modify treatment

EASI: Eczema Area and Severity Index. EASI-50/75/90: at least 50%/75%/90% improvement in EASI. IGA: Investigator's Global Assessment. n: number of subjects in analysis set. TCS: topical corticosteroids. q2w: once every 2 weeks. q4w: once every 4 weeks. The graphical abstract represents the opinion of the authors. For a full list of declarations, including funding and author disclosure statements, please see the full text online.

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Plain Language Summary

Atopic dermatitis (AD) is a chronic inflammatory disease characterized by excessively dry and itchy skin, resulting in a considerable burden of disease. Patients with AD often require long-term treatment. Tralokinumab is an injectable antibody treatment that targets a protein called interleukin-13, which substantially contributes to the signs and symptoms of AD. In the ECZTRA 1 and 2 phase III clinical trials, funded by LEO Pharma A/S, adults with moderate-to-severe AD treated with tralokinumab every other week for 16 weeks showed significant improvement in disease extent and severity compared with patients receiving placebo. To further explore the long-term efficacy of tralokinumab for AD, we performed a new analysis combining the almost 1600 patients of ECZTRA 1 and 2. A large proportion of patients treated with tralokinumab who achieved clear or almost clear skin at Week 16 were able to maintain clear or almost clear skin at Week 52 with less frequent dosing (every 4 weeks). Additionally, combining all patients treated with tralokinumab, regardless of Week 16 response or dose frequency thereafter, showed that most patients achieved a significant reduction in disease extent and severity at Week 52. These results demonstrate that many tralokinumab-treated patients continue to improve beyond Week 16, and highlight that efficacy results at Week 16 may not be representative of the outcome of longer-term tralokinumab treatment. These findings may help health care providers better advise patients regarding when to modify treatment with tralokinumab.

Key Points

Atopic dermatitis (AD) is a chronic disease that often requires long-term therapy. Placing too great an emphasis on achievement of efficacy endpoints after short-term treatment may misinterpret the clinical value provided over time by novel long-term treatment options.

A prespecified analysis of ECZTRA 1 and 2 trials showed that a large proportion of patients who achieved the primary endpoints at Week 16 and were re-randomized to tralokinumab monotherapy every 4 weeks maintained response at Week 52 without use of topical corticosteroids (Investigator's Global Assessment of clear/almost clear skin [IGA 0/1]: 42.4%; 75% improvement in the Eczema Area and Severity Index [EASI-75]: 50.4%). This suggests that less frequent dosing can be sufficient to sustain treatment response in some patients who achieve clear or almost clear skin with initial dosing of tralokinumab every 2 weeks.

Post hoc analyses combining all patients initiated on tralokinumab, regardless of Week 16 response or dosing regimen thereafter, showed that response rates progressively improved beyond Week 16, with most patients achieving a clinically relevant benefit at Week 52. These data suggest Week 16 is too early for evaluating the full benefit of tralokinumab in some patients, a finding that may help inform clinical decisions regarding when to continue, discontinue, or modify tralokinumab treatment.

1 Introduction

Atopic dermatitis (AD), a chronic inflammatory skin disease with significant disease burden, often requires long-term therapy [1–3]. The two most common primary endpoints for evaluating therapeutic candidates for AD are an Investigator's Global Assessment of clear/almost clear skin (IGA 0/1) and 75% improvement in the Eczema Area and Severity Index (EASI-75), typically assessed around Week 16 [4, 5]. Emerging evidence, however, indicates that evaluation at Week 16 may be too early to capture the full effect of biologics on the extent and severity of lesions in patients with moderate-to-severe AD [6, 7]. Therefore, longer-term assessments beyond Week 16 can help inform clinical decisions regarding when to continue, discontinue, or modify treatment.

Previous work has identified interleukin (IL)-13, a type 2 cytokine, as playing a key role in AD pathogenesis [8–11]. Skin barrier dysfunction, immune dysregulation, and microbiome dysbiosis observed in AD are associated with overexpression of IL-13 in lesional and non-lesional skin [8, 12]. Tralokinumab, a fully human immunoglobulin (Ig) G4 high-affinity monoclonal antibody that specifically neutralizes IL-13 [13], is currently approved in multiple countries, including Europe, Canada, and the US, for treatment of adults with moderate-to-severe AD [14–18], and is recommended in the current European guidelines for treatment of moderate-to-severe AD [19]. In phase III clinical trials, tralokinumab every 2 weeks (q2w) with or without topical corticosteroids (TCS) was well-tolerated and showed significant improvement in adult patients with moderate-to-severe AD achieving the primary endpoints (IGA 0/1 and EASI-75) at Week 16 compared with placebo [20, 21]. Safety outcomes for ECZTRA 1 and 2, as well as a pooled analysis of five phase II and III tralokinumab trials, were previously reported [21, 22].

In this study, results of a pooled analysis of the two tralokinumab monotherapy phase III trials (ECZTRA 1 and 2) were evaluated. To gain a more comprehensive view of the impact of long-term tralokinumab treatment, a post hoc analysis following all patients initiated on tralokinumab and continued through Week 52 was conducted, regardless of Week 16 response or the dosing regimen received thereafter.

2 Methods

2.1 Trial Design and Patient Population

This was a pooled analysis of two large, identically designed, double-blinded, randomized, placebo-controlled, 52-week, phase III trials of tralokinumab monotherapy in adults with moderate-to-severe AD—ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885). The design and methodology have previously been published in detail [21]. Briefly, in the initial treatment period, patients were randomized 3:1 to receive either subcutaneous tralokinumab 300 mg (after an initial 600 mg loading dose on Day 0) or placebo q2w for 16 weeks. Tralokinumab-treated patients who achieved the prespecified primary endpoints (IGA 0/1 or EASI-75) at Week 16 were re-randomized 2:2:1 to tralokinumab 300 mg q2w or every 4 weeks (q4w), or placebo (tralokinumab withdrawal) for a 36-week maintenance treatment period. Patients who achieved the clinical response criteria with placebo at Week 16 continued to receive placebo q2w to maintain blinding of the study. Patients who did not meet IGA 0/1 or EASI-75 at Week 16 were considered non-responders and were transferred to the open-label arm (tralokinumab q2w + optional TCS) after Week 16. During the 36-week maintenance treatment period, patients who exhibited a predefined decline relative to their Week 16 response over a 4-week period (Methods S1 in the electronic supplementary material [ESM]) were transferred to the open-label arm (Fig. 1).

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 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.

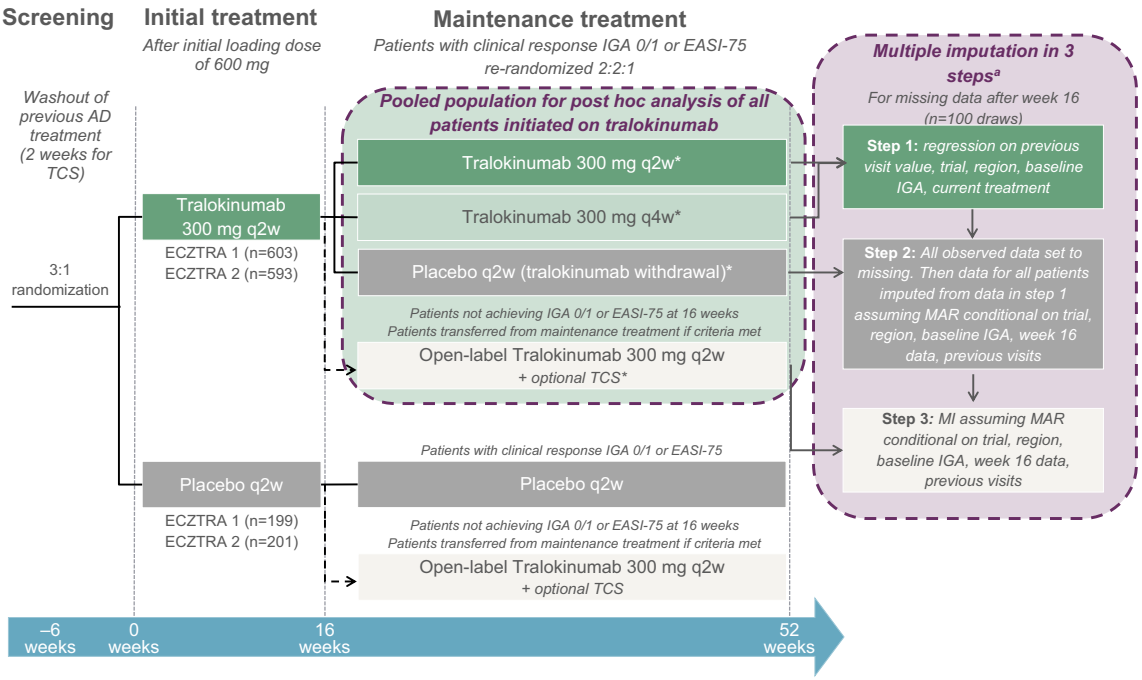

Fig. 1 Pooled analysis of ECZTRA 1 and 2. ECZTRA 1 and 2 trial design. *In a post hoc analysis, all 1192 patients initially treated with tralokinumab q2w (four patients were not dosed) were followed from Weeks 0 to 52 as one pooled arm (green box). Patients achieving IGA 0/1 and/or EASI-75 at Week 16 and re-randomized to placebo (tralokinumab withdrawal) through Week 52 were set missing, and imputed from the similar responder populations re-randomized to continue on blinded tralokinumab q2w or q4w at Week 16 (purple box; see "Methods" section for details). *AD* atopic dermatitis, *EASI* Eczema Area Severity Index, *IGA* Investigator's Global Assessment, *MI* multiple imputation, *q2w* once every 2 weeks, *q4w* once every 4 weeks, *TCS* topical corticosteroids

2.2 Endpoints

Primary endpoints for ECZTRA 1 and 2 were IGA 0/1 and EASI-75 at Week 16; maintenance endpoints assessed at Week 52 were IGA 0/1 and EASI-75 in patients initially randomized to tralokinumab, who achieved the primary endpoints at Week 16 without rescue medication (including TCS) [21]. Additional endpoints evaluating AD extent and severity included the proportion of patients achieving 50% and 90% improvement in EASI (EASI-50/90), and the percentage improvement in EASI from baseline. Additionally, the proportion of patients who initiated TCS use (various strengths) was evaluated.

2.3 Statistical Analysis

Presented data are from the full analysis set, which comprised all dosed patients. Data as per the United States Prescribing Information (USPI) are provided in the ESM.

2.3.1 Prespecified Efficacy Statistical Analysis

Analyses of the primary endpoints at Week 16 were performed using the full analysis set, which included all dosed patients in both trials. The prespecified primary analytical approach for the binary endpoints at Week 16 considered patients who received rescue medication (including TCS) and patients with missing data to be non-responders. The difference in response rates between treatment groups was analyzed using the Cochran–Mantel–Haenszel test stratified by region, baseline disease severity (IGA score of 3 or 4), and trial, as well as a prespecified treatment policy estimand approach using data as observed, regardless of rescue medication and other intercurrent events, and multiple imputation (MI) for missing data.

Analysis of the maintenance endpoints at Week 52 were performed in tralokinumab-treated patients who met the primary endpoints at Week 16 and were subsequently re-randomized to continue on tralokinumab q2w or q4w, or placebo (tralokinumab withdrawal). Patients who received rescue

Table 1 Baseline characteristics for pooled ECZTRA 1 and 2 patients

	All randomized [$N=1596$]	Initially randomized to tralokinumab q2w [$n=1196$]	Initially randomized to placebo [$n=400$]
Mean age, years (SD)	37.8 (14.4)	37.9 (14.2)	37.2 (14.8)
Male [*n* (%)]	947 (59.3)	710 (59.4)	237 (59.3)
Mean BSA involvement, % (SD)	52.9 (24.9) [$n=1595$]	52.7 (24.8)	53.6 (25.3) [$n=399$]
Mean duration of AD, years (SD)	28.2 (15.2) [$n=1594$]	28.1 (15.2) [$n=1195$]	28.5 (14.9) [$n=399$]
IGA 4, severe [*n* (%)]	794 (49.7)	591 (49.4)	203 (50.8)
Mean EASI (SD)	32.29 (13.97) [$n=1590$]	32.15 (14.01) [$n=1192$]	32.72 (13.86) [$n=398$]
Mean weekly average worst daily pruritus NRS (SD)	7.81 (1.43) [$n=1577$]	7.79 (1.45) [$n=1182$]	7.84 (1.37) [$n=395$]

AD atopic dermatitis, *BSA* body surface area, *EASI* Eczema Area Severity Index, *IGA* Investigator's Global Assessment, *NRS* numeric rating score, *q2w* every 2 weeks, *SD* standard deviation

Table 2 IGA 0/1 and EASI-75 responders at Week 16 (full analysis set; pooled ECZTRA 1 and 2 patients)

	Composite estimand Non-responder imputation for missing data and after rescue use (including TCS)		Treatment policy estimand Data analyzed as observed; multiple imputation used for missing data	
Outcome	Tralokinumab q2w [$n=1192$]	Placebo [$n=398$]	Tralokinumab q2w [$n=1192$]	Placebo [$n=398$]
IGA 0/1 responders [*n* (%)]	226/1192 (19.0)	36/398 (9.0)	273.5/1192 (22.9)	45.0/398 (11.3)
Difference vs. placebo [% (95% CI)][a]	9.8 (6.4–13.3); $p<0.001$		11.5 (7.4–15.7); $p<0.001$	
EASI-75 responders [*n* (%)]	346/1192 (29.0)	48/398 (12.1)	447.5/1192 (37.5)	78.0/398 (19.6)
Difference vs. placebo [% (95% CI)][a]	16.9 (12.8–20.9); $p<0.001$		17.8 (12.5–23.0); $p<0.001$	

CI confidence interval, *EASI* Eczema Area and Severity Index, *EASI-75* at least 75% improvement in EASI, *IGA* Investigator's Global Assessment, *q2w* every 2 weeks, *TCS* topical corticosteroids

[a]Mantel–Haenszel risk differences stratified by region, baseline IGA, and trial. *P*-value for composite estimand: Mantel–Haenszel test stratified by region, baseline IGA, and trial. *P*-value for treatment policy estimand: combined inference from multiple Mantel–Haenszel risk differences and associated standard errors

medication (including TCS) and patients with missing data were considered to be non-responders. The differences in response rates were analyzed using the Cochran–Mantel–Haenszel test stratified by region and trial.

2.3.2 Post Hoc Efficacy Statistical Analysis

In patients who initially received tralokinumab and were transferred to open-label tralokinumab plus optional TCS at Week 16, post hoc analyses of the proportion of patients achieving IGA 0/1 and EASI-75 responses through Week 52 were conducted using a prespecified treatment policy analysis using data as observed, regardless of rescue medication and other intercurrent events, and MI for missing data.

Post hoc efficacy analysis assessing the response in all patients initiated with tralokinumab 300 mg q2w ($n=1192$) [ESM Table S1] through Week 52, and through Week 16 for all patients initiated with placebo ($n=398$), was conducted. As shown by the green box in Fig. 1, the data were pooled from all patients initiated on tralokinumab treatment regardless of the response achieved at Week 16, the dosing regimen (i.e., blinded q2w or q4w tralokinumab monotherapy, or open-label tralokinumab q2w plus optional TCS), or whether data were missing. In these analyses, only data from every second visit (where data were available from patients assigned to the open-label arm) were considered after Week 16. These analyses were based on the prespecified treatment policy estimand approach until Week 16. As shown in Fig. 1, after Week 16, MI was performed in three steps. First, Week 16 responders randomized to tralokinumab q2w or q4w were pooled. Missing data within these two arms were imputed from a model accounting for previous visit value, trial, region, baseline IGA, and current treatment. The latter was a time-dependent variable and allowed for switches to the open-label arm, thereby ensuring these patients had their data imputed from similar patients switching to the open-label arm. Next, data for Week 16 responders randomized to placebo (tralokinumab withdrawal) were all set to missing and subsequently imputed from Week 16 responders randomized to the two tralokinumab arms (q2w/q4w). This method allowed the data of these patients to be imputed as if they were re-randomized to tralokinumab q2w/q4w, and was justified due to the Week 16 randomization. Lastly, missing data for patients with no assigned maintenance treatment and patients in the open-label arm were imputed from Weeks 12 to 16 data while accounting for trial, region, and baseline IGA. Since these two patient groups exhibited similar data until Week 16, we determined it was appropriate to pool them for imputations after Week 16. Furthermore, this approach was more conservative than simply excluding the data of these patients.

After the above imputations, data after Week 16 can be considered to represent patients who received tralokinumab q2w or q4w with or without optional TCS. All data after Week 16 were analyzed as one tralokinumab q2w/q4w arm.

Binary endpoints were analyzed using the Cochran–Mantel–Haenszel method stratified for trial, region, baseline IGA, and treatment, and then combined using Rubins' rule. Continuous endpoints were analyzed using analysis of covariance (ANCOVA) accounting for trial, region, baseline IGA, baseline outcome value, and treatment, and then combined using Rubins' rule.

2.3.3 Post Hoc Analysis of Topical Corticosteroid (TCS) Use

Cumulative frequency plots over time of patients initiating TCS were generated to support the interpretation of efficacy results. As for other post hoc analyses, all patients were followed through to Week 52. After Week 16, actual TCS use for patients re-randomized to placebo and for patients not assigned to maintenance treatment were replaced by imputations. That is, TCS use for the Week 16 responders re-randomized to placebo were imputed from Week 16 responders re-randomized to tralokinumab q2w/q4w (i.e., same proportion of TCS use assumed in both arms at each timepoint).

Table 3 Maintenance of IGA 0/1 and EASI-75 response at Week 52 (Week 16 responder population; pooled ECZTRA 1 and 2 patients)

Outcome	Tralokinumab q2w to tralokinumab q2w	Tralokinumab q2w to tralokinumab q4w	Tralokinumab q2w to placebo
IGA 0/1 responders [*n* (%)][a]	52/93 (55.9)	36/85 (42.4)	16/47 (34.0)
Difference vs. placebo [% (95% CI)][b]	22.8 (5.6–39.9); $p=0.013$	7.8 (−9.4 to 25.1); $p=0.38$	
EASI-75 responders [*n* (%)][c]	71/124 (57.3)	66/131 (50.4)	19/72 (26.4)
Difference vs. placebo [% (95% CI)][b]	28.7 (15.6–41.9); $p<0.001$	22.3 (9.4–35.3); $p=0.002$	

Composite estimand; non-responder imputation for missing data and after rescue use including TCS

CI confidence interval, *EASI* Eczema Area and Severity Index, *EASI-75* at least 75% improvement in EASI, *IGA* Investigator's Global Assessment, *q2w* every 2 weeks, *q4w* every 4 weeks, *TCS* topical corticosteroids

[a]Considering patients who achieved IGA 0/1 at Week 16

[b]Mantel–Haenszel risk differences stratified by region and trial

[c]Considering patients who achieved EASI-75 at Week 16

Likewise, TCS use for patients not assigned to a maintenance treatment were imputed from the open-label tralokinumab arm. This follows a similar logic as imputations for efficacy.

3 Results

3.1 Patient Disposition and Baseline Characteristics

Overall, 1596 adult patients were randomized to tralokinumab 300 mg q2w ($n = 1196$) or placebo ($n = 400$) in the initial treatment period. Four patients randomized to tralokinumab and two patients randomized to placebo were not dosed and were not included in the full analysis set. After Week 16, patients who achieved the primary endpoints of IGA 0/1 and/or EASI-75 with tralokinumab q2w were re-randomized to tralokinumab q2w ($n = 160$), tralokinumab q4w ($n = 166$), or placebo (tralokinumab withdrawal; $n = 81$). Patients who did not achieve the primary endpoints at Week 16 were transferred to tralokinumab q2w open-label treatment with optional TCS ($n = 686$). Disposition for patients initially randomized to tralokinumab q2w at specific timepoints from Week 16 to Week 52 is shown in ESM Table S1. Ninety-nine patients (8%) discontinued and were not assigned any treatment after Week 16; these patients were included in the analysis at all timepoints using imputation for missing data as described in the "Methods" section.

Baseline demographics and disease characteristics were similar across treatment groups (Table 1). Patients generally exhibited substantial disease severity at baseline, as 50% of patients had severe disease (IGA 4), while the mean body surface area involvement and EASI were 53% and 32, respectively.

3.2 Prespecified Analysis of the Primary Endpoints at Week 16

At Week 16, tralokinumab monotherapy significantly improved the proportions of patients achieving IGA 0/1 and EASI-75 compared with placebo (IGA 0/1: 19.0% vs. 9.0%, $p < 0.001$; EASI-75: 29.0% vs. 12.1%, $p < 0.001$) [Table 2]. Additionally, results from a treatment policy estimand approach irrespective of rescue medication are presented here to better reflect real-world treatment scenarios where TCS is often used as part of clinical practice (Table 2). Consistent results were obtained in the sensitivity analysis considering the USPI population (ESM Table S4).

3.3 Prespecified Analysis of the Maintenance Endpoints at Week 52

A substantial proportion of patients who achieved IGA 0/1 or EASI-75 with tralokinumab q2w at Week 16, who were then re-randomized to blinded tralokinumab q2w or q4w, maintained response at Week 52 without rescue medication

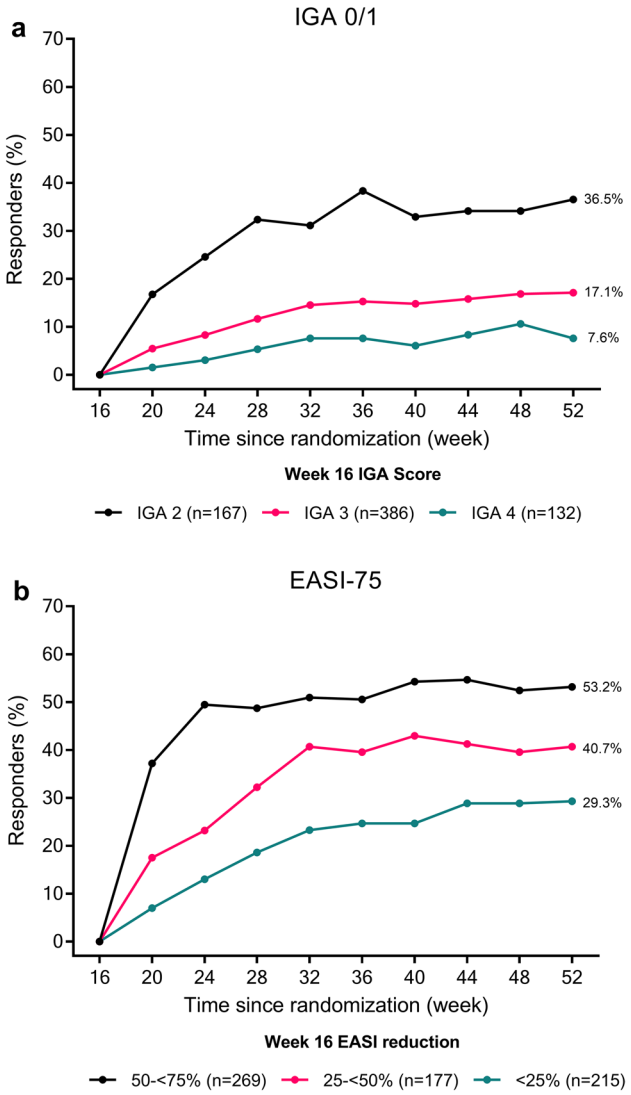

Fig. 2 Proportions of pooled ECZTRA 1 and 2 patients in the open-label arm who achieved (**a**) IGA 0/1 or (**b**) EASI-75 over 36 weeks with tralokinumab q2w + optional TCS, among those who did not achieve IGA 0/1 or EASI-75 at Week 16 with tralokinumab 300 mg q2w monotherapy. Treatment policy estimand used data as observed, regardless of rescue medication and other intercurrent events, and multiple imputation for missing data. *EASI* Eczema Area and Severity Index, *EASI-75* at least 75% improvement in EASI, *IGA* Investigator's Global Assessment, *n* number of subjects in the analysis set, *q2w* every 2 weeks, *TCS* topical corticosteroids

(including TCS). For patients with IGA 0/1 responses at Week 16, these responses were maintained by 55.9%, 42.4%, and 34.0% of patients re-randomized to tralokinumab q2w, q4w, or placebo (tralokinumab withdrawal), respectively, and EASI-75 responses were maintained by 57.3%, 50.4%, and 26.4%, respectively (Table 3). Consistent results were obtained in the sensitivity analysis considering the USPI population (ESM Table S5).

3.4 Post Hoc Analyses of the Open-Label Arm

Among patients who did not achieve IGA 0/1 or EASI-75 at Week 16 with initial short-term tralokinumab q2w treatment and continued treatment with open-label tralokinumab q2w plus optional TCS, cumulative response rates by Week 52 were 38.6% and 63.7%, respectively (ESM Fig. S1). When analyzed by the response achieved at Week 16, 36.5% (95% confidence interval [CI] 29.6–44.4) of patients with IGA 2 at

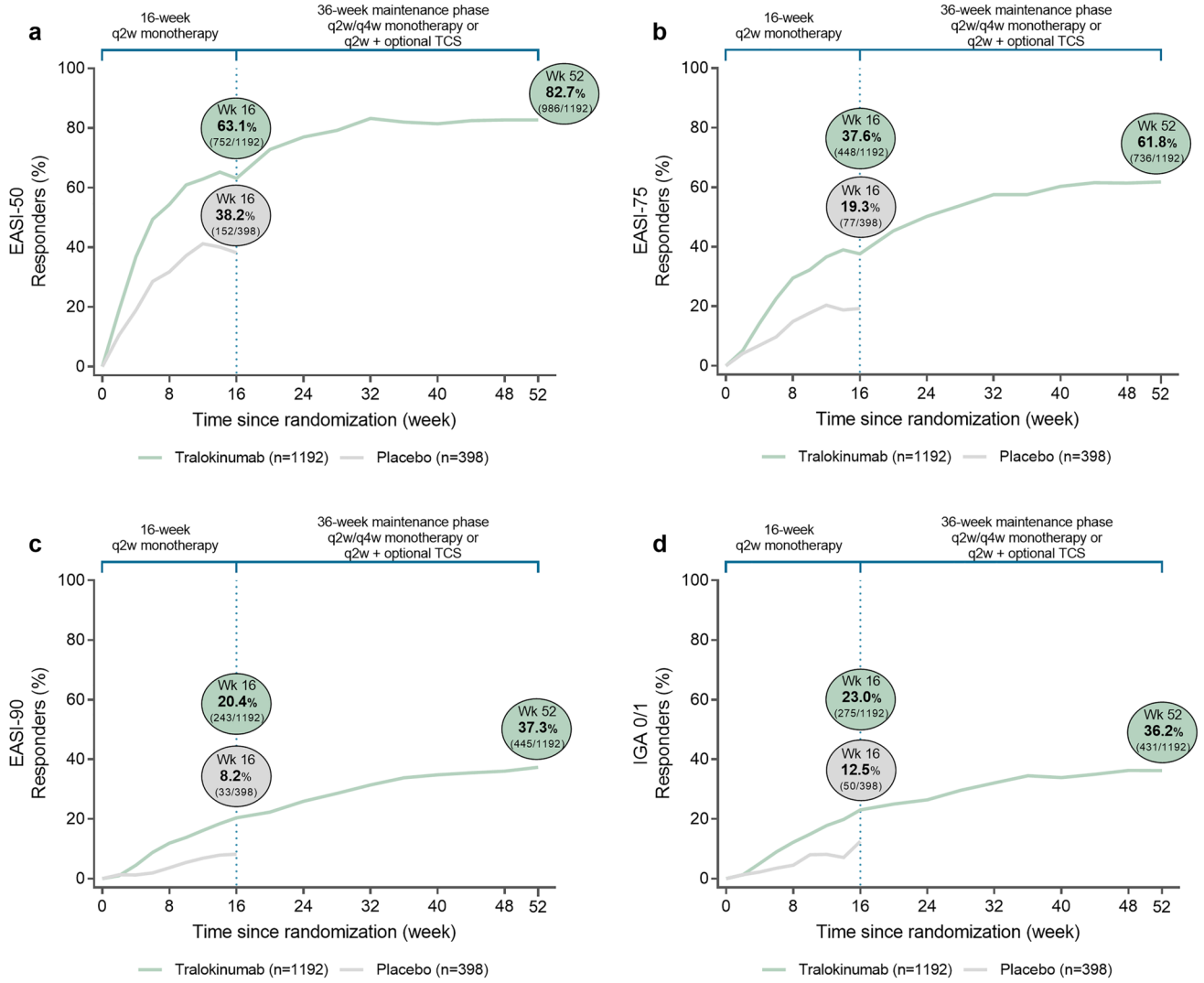

Fig. 3 **a** EASI-50, **b** EASI-75, **c** EASI-90, and **d** IGA 0/1 over 52 weeks for pooled ECZTRA 1 and 2 patients (full analysis set). In this post hoc analysis, all 1192 patients initially treated with tralokinumab q2w (four patients were not dosed) were followed from Weeks 0 to 52 as one pooled arm. Patients re-randomized to placebo at Week 16 were set missing, and imputed from the similar responder populations re-randomized to tralokinumab q2w or q4w at Week 16 (see "Methods" section for details). *EASI* Eczema Area and Severity Index, *EASI-50* at least 50% improvement in EASI, *EASI-75* at least 75% improvement in EASI, *EASI-90* at least 90% improvement in EASI, *IGA* Investigator's Global Assessment, *q2w* every 2 weeks. *q4w* every 4 weeks, *TCS* topical corticosteroids, *Wk* week

Week 16 achieved IGA 0/1 at Week 52. Furthermore, 53.2% (95% CI 47.2–59.0) of patients with EASI-50 to < EASI-75 at Week 16 achieved EASI-75 at Week 52, and 40.7% (95% CI 33.7–48.0) of patients with EASI-25 to < EASI-50 at Week 16 achieved EASI-75 at Week 52 (Figs. 2a, b).

3.5 Post Hoc Analysis Following All Patients Initiated on Tralokinumab from Weeks 0 to 52

In a pooled analysis of all patients initiated on tralokinumab, irrespective of the response achieved at Week 16 and the dosing regimen received in the maintenance treatment period (i.e., blinded q2w or q4w tralokinumab monotherapy, or open-label tralokinumab q2w plus optional TCS; $n = 1192$), response rates continued to improve from Week 16 to Week 52 for EASI-50 (63.1–82.7%), EASI-75 (37.6–61.8%), EASI-90 (20.4–37.3%), and IGA 0/1 (23.0–36.2%) (Fig. 3a–d; ESM Table S2). Similarly, mean percentage improvement in EASI from baseline continued to increase from 56.1% at Week 16 to 73.4% at Week 52 (Fig. 4). Consistent results were obtained in the sensitivity analysis considering the USPI population (ESM Figs. S3, S4).

3.6 TCS Use

The cumulative proportion of patients who used concomitant TCS (any strength) as rescue therapy during the first 16 weeks was lower with tralokinumab (27.0%) versus placebo (41.5%) (Fig. 5a). Over 52 weeks, the cumulative proportion of tralokinumab-treated patients who used any TCS was 45.5%, of which 12.5% used low potency TCS and 4.6% used a high potency TCS (Fig. 5a–c). Initiation of TCS increased after Week 16, as it was permitted as optional concomitant medication for patients continuing in the open-label arm. Consistent results were obtained in the sensitivity analysis considering the USPI population (see Fig. S5 in the ESM).

4 Discussion

Data used in this analysis were derived from two large identically designed, double-blinded, randomized, placebo-controlled, phase III, 52-week monotherapy trials—ECZTRA 1 and 2. In these trials, topical treatments were considered as prohibited medication and could only be used as rescue medication if considered medically necessary (i.e., to control intolerable AD symptoms) by the investigator. Optional TCS use was allowed for only in the patients who did not achieve the primary endpoints at Week 16, and subsequently continued into the open-label arm. Tralokinumab q2w monotherapy significantly improved the proportions of patients achieving the primary endpoints IGA 0/1 and/or EASI-75 versus placebo at Week 16, consistent with the previously described results of the individual trials [21]. A majority of patients who achieved the primary endpoints at Week 16 and continued to receive blinded tralokinumab monotherapy q2w following re-randomization maintained IGA 0/1 and EASI-75 response at Week 52. Similarly, 50% of the patients who were re-randomized to continue with tralokinumab monotherapy q4w maintained EASI-75 at Week 52, suggesting that less frequent q4w dosing can be sufficient to sustain a response in some patients who have achieved clear or almost clear skin with initial q2w dosing. Importantly, these results were achieved using the strict primary analyses method considering patients who received any rescue medication (including TCS) and patients with missing data to be non-responders.

Among patients who did not achieve the primary endpoints after short-term treatment with tralokinumab monotherapy, continued treatment with tralokinumab q2w with optional TCS was associated with further improvement in the extent and severity of AD through Week 52 in most patients. To assess the contribution of the addition of optional TCS use versus extended tralokinumab treatment alone, we compared the response rates in the open-label arm ignoring optional TCS use or treating optional TCS use as non-response. Doing so, we found that improved clinical response was largely driven

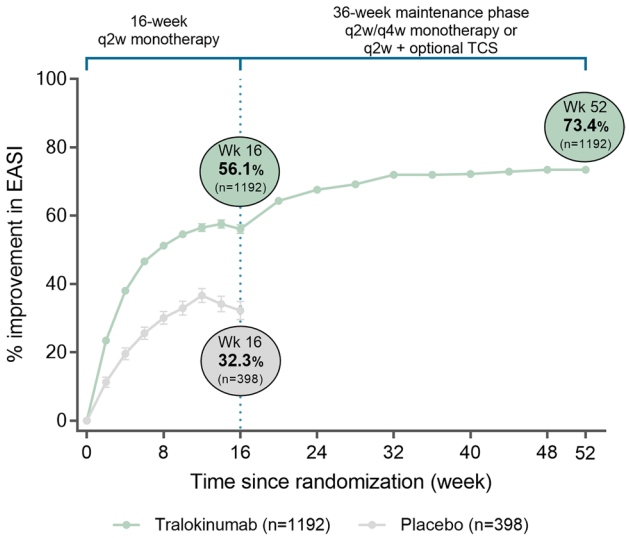

Fig. 4 Percentage improvement in EASI from baseline over 52 weeks for pooled ECZTRA 1 and 2 patients (full analysis set). In this post hoc analysis, all 1192 patients initially treated with tralokinumab q2w (four patients were not dosed) were followed from Weeks 0 to 52 as one pooled arm. Patients re-randomized to placebo at Week 16 were set missing, and imputed from the similar responder populations re-randomized to tralokinumab q2w or q4w at Week 16 (see "Methods" section for details). Least squares means ± standard error are shown. *EASI* Eczema Area and Severity Index, *q2w* every 2 weeks, *q4w* every 4 weeks, *TCS* topical corticosteroids

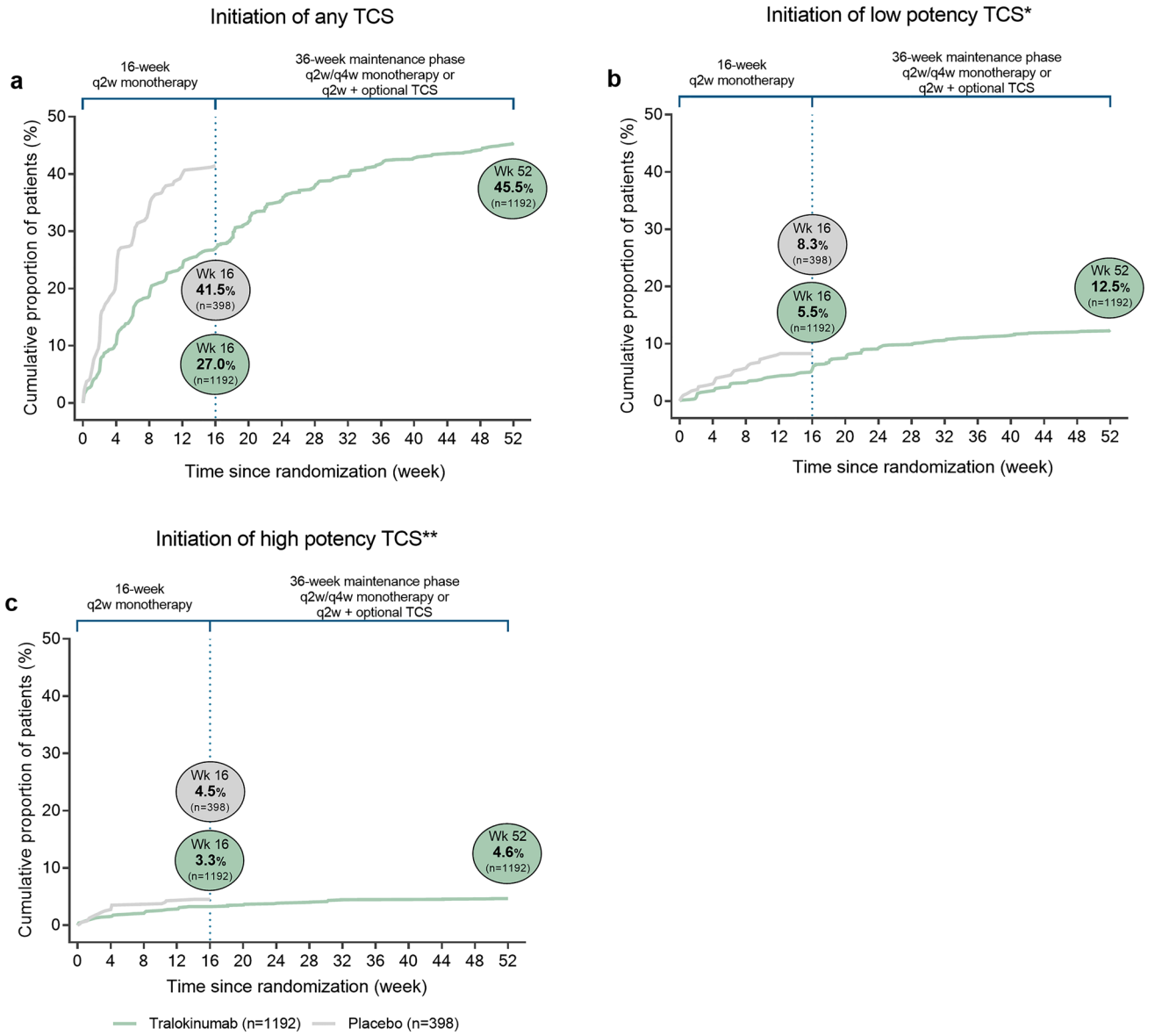

Fig. 5 Cumulative proportion of pooled ECZTRA 1 and 2 patients with initiation of **a** any TCS, **b** low-potency TCS, or **c** high-potency TCS over 52 weeks (full analysis set). In this post hoc analysis, all 1192 patients initially treated with tralokinumab q2w were followed from Weeks 0 to 52 as one pooled arm. Data for patients re-randomized to placebo at Week 16 were imputed from the similar responder populations re-randomized to tralokinumab q2w or q4w at Week 16 (see "Methods" section for details). *Includes ATC codes: D07AA, D07BA, D07CA, or D07XA; **includes ATC codes: D07AD, D07BD, D07CD, or D07XD. *ATC* Anatomical Therapeutic Chemical, *n* number of subjects in the analysis set, *q2w* every 2 weeks, *q4w* every 4 weeks, *TCS* topical corticosteroids, *Wk* week

by continued tralokinumab treatment (ESM Fig. S2). Of note, this subgroup of patients also had greater disease severity at baseline, which likely increased the time required to improve skin barrier integrity and stabilize the disease (ESM Table S3). Indeed, previous work has shown that IL-13 levels in skin and blood correlate with disease severity [10, 11, 23], consistent with its role as the central driver of AD pathogenesis, triggering and maintaining local immune dysregulation, skin barrier dysfunction, microbiome dysbiosis, and itch [8, 9, 12]. Preliminary results of biopsies collected from lesional skin, at baseline and following 16 weeks of tralokinumab treatment in ECZTRA 1, showed shifts in inflammatory mediators and skin barrier markers towards that of uninvolved ('non-lesional') skin. In patients followed up to 2 years—1 year in ECZTRA 1 + 1 year in the ECZTEND open-label extension study (NCT03587805)—the shift was greater than that seen at Week 16 [24]. Interestingly, our analyses also showed that 34% of the patients who achieved a robust response (IGA 0/1) at Week 16 with tralokinumab q2w, and were subsequently withdrawn from tralokinumab (i.e., re-randomized to placebo),

maintained their IGA 0/1 response at Week 52 without any active maintenance medication or rescue use (including TCS) over 36 weeks. One possible explanation is that following a period of clear or almost clear skin achieved with tralokinumab q2w, IL-13-mediated inflammation in the skin is blunted, altering the natural course of the disease. Further studies are needed to determine if some patients can maintain the positive impact for a longer period of time after treatment withdrawal, or experience disease remission with tralokinumab. To reflect clinical practice, we pooled all patients who started on tralokinumab in the initial treatment period irrespective of the response achieved at Week 16. This post hoc analysis showed that 62% of all patients treated with tralokinumab ± optional TCS achieved EASI-75 at Week 52. This result is consistent with the outcome of a corresponding analysis of the ECZTRA 3 phase III trial (TCS combination trial), where 70% of all patients initiated on tralokinumab plus TCS achieved EASI-75 at Week 32 [7]. Furthermore, in an analysis following patients treated with tralokinumab for 1 year in ECZTRA 1 and 2, and subsequently for another year in the open-label extension ECZTEND study, patients maintained high EASI-75 and IGA 0/1 responses (EASI-75: 82.5%; IGA 0/1: 48.1%, as observed) after 2 years of tralokinumab treatment [25].

Importantly, these present analyses indicate that the primary endpoints assessed at Week 16 may not be representative for the outcome of longer-term treatment with tralokinumab since more patients achieve these endpoints with continued treatment. This is clinically relevant, as Week 16 appears to be too early for evaluating the full benefit of tralokinumab on disease control in some patients. Other studies have also shown that response rates improve with continued treatment with biologics beyond Week 16 [6, 7, 26, 27], supporting the idea that Week 16 may be too early to assess optimal responses to a biologic therapy for some patients with AD.

Limitations of the post hoc analyses conducted here include pooling of patients after re-randomization to distinct dosing regimens at Week 16. However, combining data from patients maintained on tralokinumab q2w with those switched to tralokinumab q4w after Week 16 is likely a conservative approach. Furthermore, the switch in tralokinumab dosing frequency from q2w to q4w is likely to occur in clinical practice settings for patients achieving clear or almost clear skin with tralokinumab q2w, as per the approved labels [14–18]. Additionally, data for Week 16 responders re-randomized to placebo (tralokinumab withdrawal) beyond Week 16 were set as missing. However, these patients were imputed based on the tralokinumab q2w and q4w arms, given the expectation that such patients would have responded similarly with continued tralokinumab treatment.

Another limitation was the lack of a placebo comparator arm beyond Week 16 comprised of patients initiated on placebo. To ensure that all patients with uncontrolled moderate-to-severe AD at Week 16 had access to active systemic therapy, the trials were designed so that patients initially randomized to placebo who did not achieve the primary outcome at Week 16 were assigned to receive tralokinumab q2w plus optional TCS from Weeks 16 to 52. This approach prevented the inclusion of patients initiated on placebo in any comparative analyses beyond Week 16. Despite these limitations, the current analyses provide a more complete overview of the benefits of tralokinumab over time, which may help guide clinicians on how and when to assess optimal responses to tralokinumab.

5 Conclusions

In summary, tralokinumab provided progressive and sustained improvements over 52 weeks in the extent and severity of AD in patients with moderate-to-severe AD.

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

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. 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.

Code Availability Not applicable.

Author Contributions Conceptualization: All authors contributed equally. Investigation: All authors contributed equally. Data curation: Thomas Mark (lead). Formal analysis: Thomas Mark (lead), Ann-Marie Tindberg (supporting). Methodology: Thomas Mark (equal), Ann-Marie Tindberg (equal). Visualization: Ann-Marie Tindberg (lead). 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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