
Long-term 2-year safety and efficacy of tralokinumab in adults with moderate-to-severe atopic dermatitis: Interim analysis of the ECZTEND open-label extension trial



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Background: Additional long-term treatments are needed for moderate-to-severe atopic dermatitis (AD). An ongoing, open-label, 5-year extension trial, ECZTEND (NCT03587805), assesses tralokinumab plus optional topical corticosteroids in participants from previous tralokinumab parent trials (PTs) with moderate-to-severe AD.

Objective: To evaluate the safety and efficacy of up to 2 years tralokinumab treatment in a *post hoc* interim analysis.

Methods: Safety analyses included adults from completed PTs enrolled in ECZTEND, regardless of tralokinumab exposure duration. Efficacy analyses included adult participants treated with tralokinumab in ECZTEND for ≥ 1 year and subgroup analyses of those on tralokinumab for 2 years (1 year from PT, 1 year in ECZTEND). Primary end point was the number of adverse events with additional efficacy end points.

Results: Participants on tralokinumab had an exposure-adjusted rate of 237.8 adverse events/100 patient-years' exposure ($N = 1174$) in the safety analysis set. Exposure-adjusted incidence rates of common adverse events were comparable to PTs, although at lower rates. With 2 years of tralokinumab, improvements in extent and severity of AD were sustained, with Eczema Area and Severity Index (EASI-75) in 82.5% of participants ($N = 345$).

Limitations: Possible selection bias; no placebo arm; some participants experienced treatment gaps between PTs and ECZTEND.

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Funding sources: The ECZTEND clinical trial was sponsored by LEO Pharma A/S. Richard B. Warren is supported by the Manchester NIHR Biomedical Research Centre.

IRB approval status: Reviewed and approved by Advarra.

Accepted for publication July 5, 2022.

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Published online September 12, 2022.

0190-9622

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<https://doi.org/10.1016/j.jaad.2022.07.019>

Conclusion: Over 2 years, tralokinumab was well tolerated and maintained long-term control of AD signs and symptoms. (J Am Acad Dermatol 2022;87:815-24.)

Key words: atopic dermatitis; biologic therapy; efficacy; IL-13; long-term; monoclonal antibody; open label; safety; tralokinumab.

INTRODUCTION

Atopic dermatitis (AD), a chronic inflammatory skin disease,¹ may persist throughout life,² and over half of adults with moderate-to-severe AD report effects on health-related quality of life.^{3,4} While treatment options exist,⁵ few are recommended for long-term use due to safety concerns and modest long-term efficacy.¹

Tralokinumab is a high-affinity monoclonal antibody that selectively inhibits interleukin 13 (IL-13), a key driver of AD pathogenesis.⁶⁻⁸ Safety and efficacy of tralokinumab monotherapy and in combination with topical corticosteroids (TCSs) and topical calcineurin inhibitors were demonstrated through phase 2 and 3 trials up to 1 year duration.⁹⁻¹¹ Recently, tralokinumab was approved in Europe, Canada, and the United States for treatment of adults with moderate-to-severe AD.¹²⁻¹⁴

The ongoing, 5-year, open-label, extension trial ECZTEND (NCT03587805) investigates long-term safety and efficacy of tralokinumab in participants with AD from tralokinumab parent trials (PTs). We report interim safety results of the overall ECZTEND adult population, the longest analysis of safety to date with selective IL-13 inhibition. We also report interim efficacy results of participants who completed 1 year of tralokinumab 300 mg every 2 weeks (approved dosing) in ECZTEND, with a focus on the subgroup of participants with 2 years tralokinumab treatment (1 year in PT, 1 year in ECZTEND), the largest participant cohort with the longest total treatment duration available.

PARTICIPANTS AND METHODS

Trial design

ECZTEND is an ongoing, 5-year, open-label, single-arm, multicenter, long-term extension trial in

participants who completed tralokinumab PT (ECZTRA 1-8 and TraSki). At the data cutoff for this *post hoc* interim analysis (April 30, 2020, cutoff date for drug approval regulatory submissions), ECZTRA 1, 2, 3, and 5 were completed; these included adult participants exclusively. After PT completion, participants at sites in ECZTEND were invited to enroll/provide consent for the long-term extension.

Participants were eligible regardless of previous treatment in PT (tralokinumab or placebo) or treatment response. Participants in ECZTEND must have completed PT treatment period and complied with PT protocols⁹⁻¹¹; further eligibility criteria are described in Supplementary Material, available via Mendeley at <https://doi.org/10.17632/ms9xg8cb9g.1>.

ECZTEND participants received subcutaneous tralokinumab 300 mg every 2 weeks after a 600 mg loading dose of tralokinumab; all adult participants received this loading dose as prior treatment status is blinded at ECZTEND entry.

Visits occurred at weeks 0, 2, 4, 8, 12, 16, and every 8 weeks afterward, whereas the PTs had shorter gaps between visits.⁹⁻¹¹

The primary end point of ECZTEND is the number of adverse events (AEs) during the treatment period from baseline up to week 268 (5 years); secondary end points are the proportion of participants achieving an Investigator's Global Assessment (IGA) score of 0/1 (clear/almost clear skin) and the proportions of participants achieving at least 75% improvement in Eczema Area and Severity Index (EASI) relative to PT baseline (EASI-75). Other analyses included the percentage improvement in EASI relative to PT baseline, proportion of participants achieving EASI-90, worst weekly pruritus Numeric Rating Scale (NRS), eczema-related sleep interference NRS, and Dermatology Life Quality Index.

Optional TCS (US class ≥ 4 or Europe class ≤ 3) or topical calcineurin inhibitor was permitted as concomitant medication at the investigator's discretion. Rescue treatment (TCS US class < 4 or Europe

CAPSULE SUMMARY

- Over 2 years, tralokinumab was well tolerated and maintained long-term control of atopic dermatitis in adults. The safety data reported in ECZTEND are consistent with the placebo-controlled parent trials, with adverse events occurring at lower rates.
- These results support the long-term, continuous use of tralokinumab in adults with moderate-to-severe atopic dermatitis.

Abbreviations used:

AD:	atopic dermatitis
AEs:	adverse events
EASI:	Eczema Area and Severity Index
IGA:	Investigator's Global Assessment
IL:	interleukin
IQR:	interquartile range
NRS:	Numeric Rating Scale
PT:	parent trial
PYE:	patient-years of exposure
SAE:	severe adverse event
TCS:	topical corticosteroids

class >3) was allowed to control intolerable AD symptoms at the investigator's discretion; additional details are provided in Supplementary Material.

This trial is sponsored by LEO Pharma A/S and conducted in accordance with the ethical principles derived from the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the local institutional review board or ethics committee of each institution. All participants provided written informed consent.

Analysis populations

The interim safety analysis set included all adult participants enrolled in ECZTEND from ECZTRA 1, 2, 3, and 5 at the data cutoff regardless of treatment response or duration of tralokinumab exposure (Fig 1). Therefore, this population is heterogeneous, with some participants first receiving tralokinumab at ECZTEND baseline and others on tralokinumab for the entirety of PT.

The interim 1-year efficacy analysis set included adult participants treated with tralokinumab in ECZTEND for at least 1 year regardless of PT treatment or treatment response. To examine efficacy in a homogenous group of participants with the longest tralokinumab treatment duration, a 2-year subgroup composed of participants on tralokinumab for 52 weeks in PT ECZTRA 1 and 2 and for 56 Weeks in ECZTEND (enrolled ≥ 60 weeks) regardless of treatment response was analyzed (Supplementary Fig 1, available via Mendeley at <https://doi.org/10.17632/ms9xg8cb9g.1>). Participants in PT ECZTRA 3 and 5 did not receive 52 weeks of tralokinumab and therefore were not included in the 2-year efficacy analysis set.

Initially, there was a 14-week safety follow-up period between PT and ECZTEND. A protocol amendment enabled all eligible participants to enter ECZTEND directly after completing the treatment period in PT (Fig 1). To account for variability in the interval between PTs and ECZTEND, participants were assessed in 3 groups: interval <36 days (≤ 5 weeks, continuous treatment), 36-105 days (6-

15 weeks, interrupted treatment), and >105 days (>15 weeks, washout); 15 weeks is 5 half-lives of tralokinumab.

Safety and efficacy analyses

All AEs were recorded, coded according to the Medical Dictionary for Regulatory Activities, and classified by severity, causality, and outcome. Event rates are presented as the number of events per 100 patient-years of exposure (PYE). Additional information was collected for AEs of special interest.

For EASI-75/90 and IGA 0/1, results are presented using observed data, as well as last observation carried forward and nonresponder imputation as 2 separate sensitivity analyses to account for missing data during ECZTEND. Dropouts during PT were not accounted for in the analyses. The observed analysis includes data for all participants with a valid measurement at the indicated timepoint. The last observation carried forward method imputes the value recorded at the participant's last visit for subsequent missed time points. The nonresponder imputation method considers all participants in ECZTEND with missing data as nonresponders at the indicated time point; participants who discontinue treatment are imputed as nonresponders at all subsequent time points. Rescue therapy use during ECZTEND was not automatically considered as nonresponse; only individuals whose rescue use met the stopping rules would permanently discontinue tralokinumab and thus lead to missing data in the nonresponder analysis.* This approach seeks to reflect a real-world representation of long-term AD management. Further, 52-week PT data analyses were restricted to PT completers at 52 weeks.

RESULTS

Baseline demographics

ECZTEND baseline characteristics of participants in the 2-year efficacy analysis set ($N = 345$) were

*Note: Participants who received topical rescue treatment would continue treatment with tralokinumab, whereas participants who received systemic rescue treatment required discontinuation of tralokinumab until 5 half-lives from the last dose of systemic treatment. If a participant required continuous use of higher potency TCS for >4 weeks, continuous use of systemic rescue treatment for >3 weeks, or had disease severity above or equal to baseline in the PT for a duration of ≥ 8 weeks, participants would permanently discontinue tralokinumab and be withdrawn from the trial. Participants would also permanently discontinue tralokinumab and be withdrawn from the trial in the event of anaphylactic reaction or other severe systemic reaction to tralokinumab injection, an AE that contraindicates further dosing, diagnosis of a malignancy during the trial, evidence of pregnancy, opportunistic infection, or severe laboratory abnormalities.

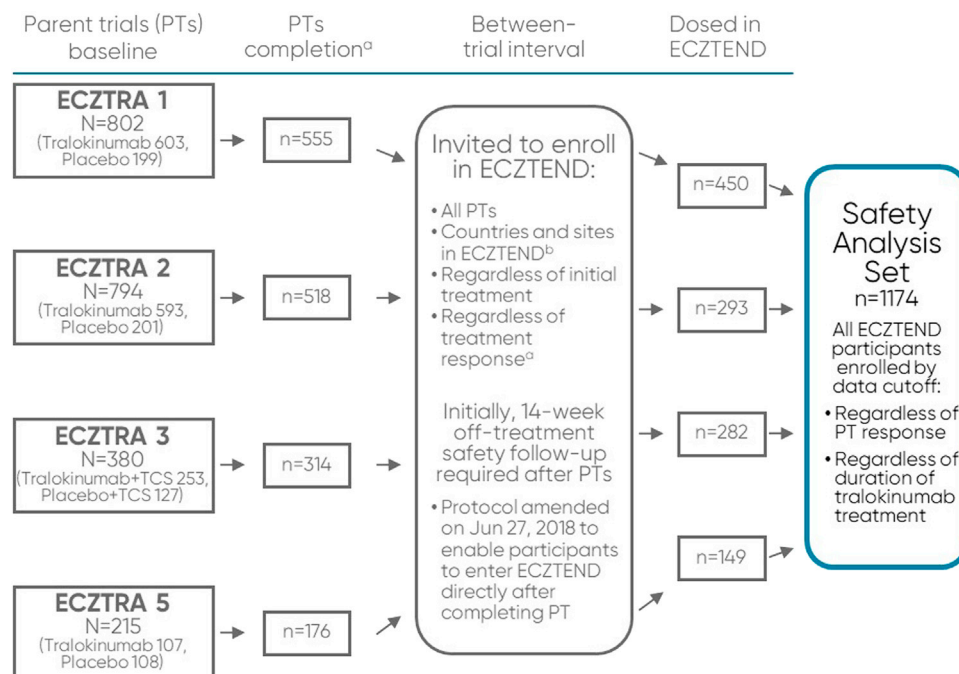


Fig 1. Participant flow from PT ECZTRA 1-3 and 5 into ECZTEND as of April 30, 2020, data cutoff. Additional trials in which eligible participants may opt to enroll in ECZTEND that were ongoing at data cutoff were ECZTRA 4, 6–8, and TraSki. Previous treatment regimens in PTs included tralokinumab every 2 weeks, every 4 weeks, or placebo $\pm$ TCS. ^aParticipants who were nonresponders at week 16 of ECZTRA 1 and 2 on either tralokinumab or placebo went onto open-label tralokinumab every 2 weeks. ^bNot all PT sites and not all countries in PTs participated in ECZTEND. PT, Parent trial.

consistent with those of the safety analysis set ($N = 1174$) (Table I). For participants in the 2-year subgroup, median time between the last dose in PT and the first dose in ECZTEND was 63.0 days (interquartile range [IQR], 21.0; 105.0). One hundred twenty-six participants had continuous tralokinumab, 133 had interrupted tralokinumab, and 86 had tralokinumab washout. Participants in the 2-year subgroup had robust improvements in AD extent and severity at ECZTEND baseline relative to PT baseline (Table I).

Safety

Long-term use of tralokinumab was well tolerated with a safety profile consistent with PTs. In the safety analysis set, cumulative tralokinumab exposure was 1235.7 patient-years ($N = 1174$; Table II). The exposure-adjusted incidence rate of AEs was 237.8 events/100 PYE (Table II); 71.9% of participants ($n = 844$) had ≥ 1 AE (Table II). Fifty-nine severe adverse events (SAEs) were reported, representing 4.8 SAEs/100 PYE; 4.7% of participants ($n = 55$) experienced ≥ 1 SAE. SAEs were not clustered around any particular system organ class or repeated among participants. One hundred thirty-nine

(11.8%) participants discontinued ECZTEND, with 29 (2.5%) lost to follow-up, 24 (2.0%) due to lack of efficacy, 19 (1.6%) due to AEs, 16 (1.4%) withdrawn by participant choice, and 51 (4.3%) for other reasons (Table II). No deaths occurred during this interim safety analysis of ECZTEND. The majority of AEs were mild or moderate in severity and resolved (Table II). Two hundred eighty-four (24.2%) participants experienced ≥ 1 treatment-related AE.

The most commonly reported AEs ($\geq 2\%$) were viral upper respiratory tract infection (most commonly reported as common cold), AD, and upper respiratory tract infection (Table II). Incidence of AEs of special interest was similar or lower than that reported in PTs. Most conjunctivitis cases in ECZTEND were mild to moderate in severity and resolved with or without ophthalmological treatment during continued tralokinumab treatment. Two (0.2%) participants reported severe conjunctivitis and 1 (0.1%) discontinued tralokinumab because of a conjunctivitis-related AE. Injection site reactions were reported in 2.4% of participants (3.9 events/100 PYE). No new safety signal associated with tralokinumab use was identified.

Table 1. ECZTEND baseline demographics and clinical characteristics with key characteristics from PT baseline

	Safety analysis set* (N = 1174)	2-year efficacy analysis set† (N = 345)
Age		
Median years (IQR)	38.0 (27.0; 50.0)	42.0 (30.0; 52.0)
Sex, n (%)		
Male	675 (57.5)	203 (58.8)
Female	499 (42.5)	142 (41.2)
Race, n (%)		
White	836 (71.3)	258 (74.8)
Black	101 (8.6)	20 (5.8)
Asian	201 (17.2)	55 (15.9)
Parent trial, n (%)		
ECZTRA 1	450 (38.3)	223 (64.6)
ECZTRA 2	293 (25.0)	122 (35.4)
ECZTRA 3	282 (24.0)	N/A
ECZTRA 5	149 (12.7)	N/A
Age at onset of AD		
Median years (IQR)	3.0 (1.0; 15.0)	3.0 (1.0; 15.0)
Duration of AD		
Median years (IQR)	27.0 (18.0; 40.0)	30.0 (19.0; 43.0)
	2-year efficacy analysis set	
	Parent Trials Baseline	ECZTEND Baseline
IGA severity, n (%)		
Clear/minimal (score = 0/1)	-	97 (28.2)
Mild (score = 2)	-	123 (35.7)
Moderate (score = 3)	171 (49.6)	105 (30.4)
Severe (score = 4)	174 (50.4)	20 (5.8)
EASI		
Median (IQR)	26.7 (20.0; 38.0)	4.7 (2.2; 12.3)
SCORAD score		
Median (IQR)	68.1 (60.9; 77.5)	32.8 (20.6; 46.9)
DLQI		
Median (IQR) n	17.0 (11.0; 23.0) 341	5.0 (2.0; 10.0) 326
Worst weekly‡ pruritus NRS		
Median (IQR) n	7.9 (6.9; 8.9) 344	5.0 (3.0; 8.0) 344

AD, Atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IQR, interquartile range; NRS, Numeric Rating Scale; PT, parent trial; SCORAD, SCORing Atopic Dermatitis.

*Safety analysis set includes all participants from PT ECZTRA 1, 2, 3, and 5 enrolled in ECZTEND.

†2-year subgroup includes participants who received tralokinumab for the full 52 weeks in the PT ECZTRA 1 and ECZTRA 2, regardless of treatment response, and had been treated with tralokinumab for 56 weeks in ECZTEND (enrolled ≥60 weeks) for a total of 108 weeks (2 years) of tralokinumab treatment; ECZTRA 3 and ECZTRA 5 participants did not have 2 years of exposure at the time of the data cutoff, and, as such, were not included in the 2-year efficacy analysis set.

‡In parent trials, worst pruritus NRS is assessed daily, in ECZTEND, worst pruritus NRS is assessed based on recall of the previous week before the visit.

Efficacy

Progressive and sustained improvements in AD signs and symptoms were reported in participants treated with tralokinumab for up to 2 years. For the 1-year efficacy analysis set (N = 612), EASI-75 and EASI-90 were achieved in 82.8% and 61.0% of participants, respectively, and IGA scores of 0/1 (clear/almost clear skin) were achieved in 49.7% (Supplementary Fig 2, available via Mendeley at <https://doi.org/10.17632/ms9xg8cb9g.1>, as observed, n = 513). Participants treated with tralokinumab for 2 years (N = 345) maintained high EASI-75, EASI-90, and IGA 0/1 response rates (overall: EASI-75, 82.5%; EASI-90, 59.8%; IGA 0/1, 48.1%, as observed, n = 291) (Fig 2, Supplementary Fig 4, available via Mendeley at <https://doi.org/10.17632/ms9xg8cb9g.1>). Sensitivity analyses suggested responses were sustained at similar levels in both the 1- and 2-year analyses regardless of imputation method (Fig 2, Supplementary Fig 2, Supplementary Fig 4). Similar results were observed for continuous, interrupted, and washout cohorts (Fig 2, Supplementary Fig 4). Approximately one-third of patients reported using mild or moderate TCS (US class ≥4 or Europe class ≤3) or topical calcineurin inhibitors within the previous week at any point of the follow-up (ranging from 29.4% to 35.4% of participants).

For the 2-year subgroup, median (IQR) percentage improvement in EASI after 1 year of tralokinumab in PTs was 88.0% (78.4, 96.1) (Fig 3, Supplementary Table I, available via Mendeley at <https://doi.org/10.17632/ms9xg8cb9g.1>). At 2 years of tralokinumab treatment, median (IQR) EASI improvements were 92.7% (83.3, 98.2), 91.7% (83.3, 97.8), and 92.7% (74.9, 97.9) in the continuous (n = 126), interrupted (n = 133), and washout groups (n = 86), respectively, relative to PT baseline (Fig 3, Supplementary Table I). By week 12 in ECZTEND, after reinitiation of treatment for interrupted or washout groups, participants regained improvements similar to the end of PTs (Fig 3). Median EASI reduced from moderate-to-severe disease severity at PT baseline to mild-to-moderate severity at ECZTEND baseline and was sustained over time in ECZTEND (Supplementary Fig 4, Supplementary Table II, available via Mendeley at <https://doi.org/10.17632/ms9xg8cb9g.1>).

At 1 year in the PTs, 75.9% (n/N 262/345) of participants achieved EASI ≤7 (mild AD). Improvements were sustained over 2 years of tralokinumab treatment, with 77.6% (83/107), 82.9% (92/111), and 74.0% (54/73) of participants in the continuous, interrupted, or washout groups with EASI ≤7, respectively.

Table II. Summary of AEs in ECZTEND (safety analysis set)

	ECZTEND safety analysis set		Pooled safety analysis set of initial treatment period in parent trials*			
	Tralokinumab every 2 weeks (<i>n</i> = 1174; PYE = 1235.7)		Tralokinumab every 2 weeks (<i>N</i> = 1605; PYE, 473.19)		Placebo (<i>N</i> = 680; PYE, 193.1)	
	<i>n</i> (%)	Rate (nE/100 PYE)	<i>n</i> (adj % [†])	Adj rate [‡] (nE/100 PYE)	<i>n</i> (adj % [†])	Adj rate [‡] (nE/100 PYE)
Summary						
All AEs	844 (71.9)	237.8	1080 (65.7)	639.5	449 (67.2)	678.3
Severity						
Mild	695 (59.2)	158.2	881 (53.2)	429.8	326 (49.0)	391.0
Moderate	435 (37.1)	72.1	518 (31.5)	189.5	258 (39.0)	254.3
Severe	62 (5.3)	7.5	77 (4.6)	20.2	40 (6.3)	33.0
Serious AEs	55 (4.7)	4.8	37 (2.1)	7.4	18 (2.8)	11.9
Leading to withdrawal from trial	19 (1.6)	1.5	38 (2.3)	9.9	20 (2.8)	13.3
Outcome						
Not recovered/not resolved	280 (23.9)	32.9	232 (14.3)	65.4	90 (13.5)	65.2
Recovering/resolving	109 (9.3)	11.3	79 (4.9)	18.9	36 (5.4)	22.7
Recovered/resolved	757 (64.5)	190.3	997 (60.2)	544.5	416 (62.4)	585.4
Recovered/resolved with sequelae	9 (0.8)	1.0	18 (1.0)	3.5	2 (0.3)	1.7
Unknown	19 (1.6)	2.2	27 (1.7)	7.0	6 (0.9)	3.3
Most frequently reported AEs (≥2.0% of participants)						
Viral upper respiratory tract infection [§]	250 (21.3)	29.3	256 (15.7)	65.1	78 (12.2)	53.5
Dermatitis atopic	158 (13.5)	20.6	272 (15.4)	68.0	167 (26.2)	139.7
Upper respiratory tract infection	83 (7.1)	9.1	92 (5.6)	20.8	33 (4.8)	18.5
Headache	49 (4.2)	5.7	72 (4.6)	21.6	26 (3.9)	19.6
Conjunctivitis	45 (3.8)	4.5	90 (5.4)	21.0	13 (1.9)	6.9
Injection site reaction	28 (2.4)	3.9	58 (3.5)	22.9	2 (0.3)	4.0
Diarrhea	40 (3.4)	3.7	29 (1.8)	6.8	11 (1.6)	6.1
Influenza	43 (3.7)	3.6	24 (1.3)	4.5	11 (1.6)	6.1
Cough	37 (3.2)	3.3	NR	NR	NR	NR
Back pain	33 (2.8)	3.0	NR	NR	NR	NR
Herpes simplex	25 (2.1)	2.9	1 (0.1)	0.2	0	0
Rhinitis	26 (2.2)	2.7	NR	NR	NR	NR
Oral herpes	24 (2.0)	2.6	13 (0.8)	3.1	10 (1.6)	8.1
Gastroenteritis	30 (2.6)	2.5	1 (0.1)	0.2	0	0
Pruritus	28 (2.4)	2.4	47 (2.6)	10.6	19 (3.0)	13.1
Bronchitis	27 (2.3)	2.3	1 (0.1)	0.2	1 (0.2)	0.6
Sinusitis	27 (2.3)	2.3				
Conjunctivitis allergic	24 (2.0)	2.3	34 (2.0)	7.1	7 (1.1)	4.3
AEs of special interest						
Eye disorders [¶]	77 (6.6)	7.8	132 (7.9)	31.1	22 (3.4)	12.9
Skin infections requiring systemic treatment	21 (1.8)	2.2	42 (2.6)	9.7	35 (5.5)	22.8
Eczema herpeticum	10 (0.9)	0.8	6 (0.3)	1.2	10 (1.5)	5.2
Malignancies diagnosed after dosing [#]	9 (0.8)	0.7	1 (0.1)	0.2	0 (0)	0

Adj, Adjusted; AEs, adverse events; nE, number of events; NR, not reported; PYE, patient-years of exposure.

Rate calculated by the number of AEs divided by PYE, multiplied by 100. As ECZTEND is an ongoing trial, the percentage of AEs not recovered/not resolved is likely to change.

*Five placebo-controlled trials formed the AD pool: phase 3 (ECZTRA 1, ECZTRA 2, and ECZTRA 3), phase 2 (ECZTRA 5), and phase 2b.

[†]Adj % calculated using Cochran-Mantel-Haenszel weighting.

[‡]Adj rate calculated using Cochran-Mantel-Haenszel weighting.

[§]Most commonly reported as common cold.

^{||}Additional information was collected for AEs of special interest.

[¶]Including conjunctivitis, keratoconjunctivitis, and keratitis.

[#]Excluding basal cell carcinoma, localized squamous cell carcinoma of the skin, and carcinoma in situ of the cervix; the malignancies diagnosed after randomization in the ECZTEND safety analysis set included breast cancer, invasive ductal breast carcinoma, prostate cancer, Hodgkin disease, malignant melanoma, and squamous cell carcinoma of skin.

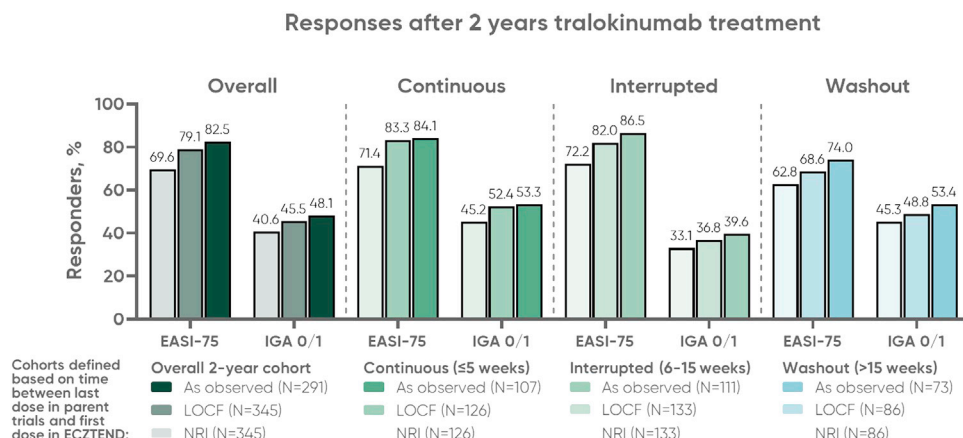


Fig 2. Proportion of participants with EASI-75 and IGA 0/1 at 2 years of tralokinumab treatment. The 2-year group was restricted to participants who received treatment with tralokinumab for 52 weeks in PT ECZTRA 1 and 2, followed by treatment with tralokinumab for 56 weeks in ECZTEND. LOCF and NRI analyses were utilized for participants within this group with missing data during the ECZTEND period. Dropouts during PT were not accounted for in the analyses. *EASI*, Eczema Area and Severity Index; *IGA*, Investigator's Global Assessment; *LOCF*, last observation carried forward; *NRI*, nonresponder imputation; *PT*, parent trial.

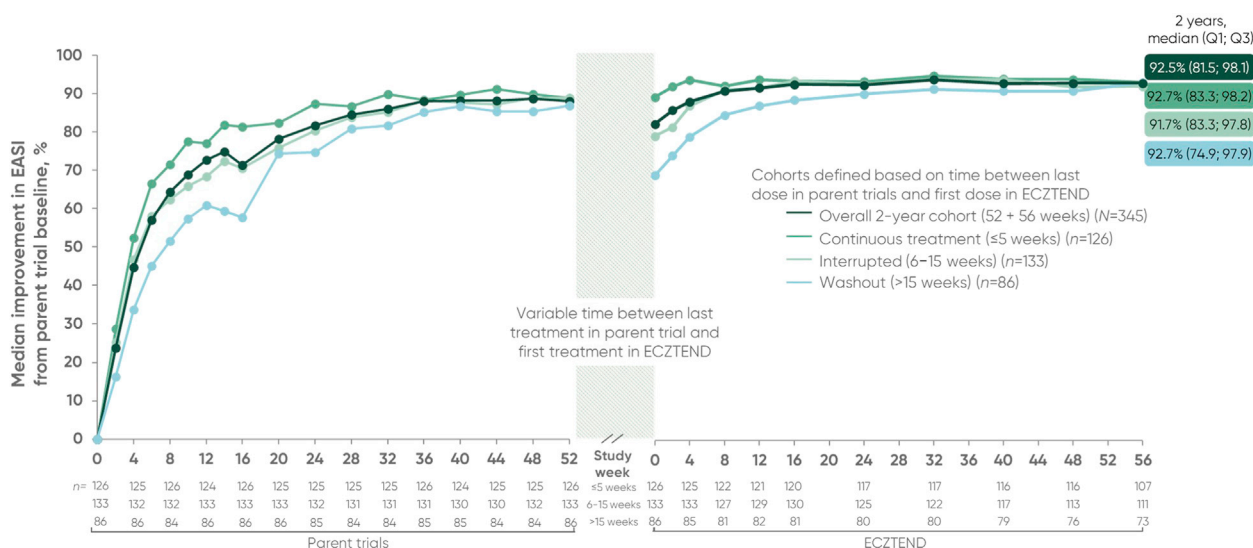


Fig 3. Median percentage improvement in EASI from PT baseline through 2 years of tralokinumab treatment (week 56 in ECZTEND). Variable intervals between week 52 of PTs and the first dose of ECZTEND are denoted as continuous (≤ 5 weeks interval), interrupted (6-15 weeks interval), or washout (>15 weeks interval) groups. Parent trial data shown here include only participants who elected to enter the ECZTEND trial. Data are as observed. *EASI*, Eczema Area and Severity Index; *PT*, parent trial.

Clinically meaningful improvements in worst weekly pruritus NRS and eczema-related weekly sleep interference NRS scores were sustained over time in ECZTEND (Supplementary Fig 5, available via Mendeley at <https://doi.org/10.17632/ms9xg8cb9g.1>). Itch improved from severe to mild itch [overall: median worst weekly pruritus NRS, 3.0 (IQR 1.0;5.0), $n = 291$], and sleep improved from

severe to mild interference with sleep [overall: median eczema-related weekly sleep NRS, 1.0 (IQR 0.0;3.0), $n = 291$] at 2 years of tralokinumab treatment (Supplementary Fig 5). Impact on quality of life improved from a very large effect [overall: Dermatology Life Quality Index of 17 (IQR 11.0, 23.0; $n = 341$)] to a small effect on life quality [overall group: Dermatology Life Quality Index of 2.0 (IQR

1.0, 5.0; $n = 274$)] at 2 years of tralokinumab treatment (Supplementary Fig 6, available via Mendeley at <https://doi.org/10.17632/ms9xg8cb9g.1>).

DISCUSSION

Tralokinumab was well tolerated and maintained substantial clinical improvements over 2 years in participants with moderate-to-severe AD. The exposure-adjusted incidence rate of AEs per 100 PYE in ECZTEND was numerically lower than that in the 16 week initial treatment period in a pooled analysis of 5 randomized, double-blinded, placebo-controlled phase 3 and phase 2 trials.¹⁵ The overall safety profile in ECZTEND was comparable to that in the PTs, with viral upper respiratory tract infection (most commonly reported as common cold) occurring as the most common AE, although at a numerically lower rate than observed with tralokinumab or placebo in the initial treatment periods of the PTs.⁹⁻¹¹ The rate of AEs leading to withdrawal was at least the same or lower in ECZTEND relative to the PTs.¹⁵ Conjunctivitis is an AE of special interest given it is commonly comorbid with AD,¹⁶ and it has been associated with dupilumab treatment for AD, which inhibits IL-4 and IL-13 signaling.¹⁷ The 4.5 conjunctivitis events/100 PYE in this trial appears lower than that reported in an open-label extension trial of dupilumab, albeit utilizing indirect comparisons.¹⁸ No new safety signals emerged with cumulative exposure.

Tralokinumab showed substantial and sustained improvements in AD signs and symptoms from the baseline of PTs for both the 1-year efficacy analysis set (a heterogeneous population of tralokinumab-naïve and tralokinumab-experienced participants with varying treatment duration before entering ECZTEND) and the 2-year subgroup (those treated with tralokinumab for 52 weeks before entering ECZTEND). More than 8 of 10 participants in the 2-year subgroup achieved EASI-75, and approximately 6 of 10 achieved EASI-90 in this population. The proportion of participants with the treat-to-target goal of EASI ≤ 7 (recently suggested target threshold for long-term treatment of AD¹⁹) was also sustained over 2 years. Tralokinumab led to long-term improvements in patient-reported outcomes with scores sustained at a level of mild symptoms and a small effect of AD on quality of life. Efficacy data are supported by the consistency of sensitivity analyses with as-observed analyses, demonstrating that participant withdrawals during ECZTEND did not substantially influence the results. There were few participants with missing data in the overall efficacy analysis set (291 participants in as-observed population, 345 in last observation carried forward and

nonresponder imputation populations). Additionally, this interim ECZTEND population was approximately 30% non-White; while this suggests that the results may be generalizable across racial/ethnic subgroups, the present analysis did not assess this.

There were varying intervals between the PTs and ECZTEND due to the initial safety follow-up in the PT protocols. We categorized results by length of this between-trials interval to clarify the impact of treatment interruptions. Treatment interruption/washout was reflected by higher ECZTEND baseline values of AD severity, and resumption of tralokinumab led to similar magnitude of improvements to continuous treatment within a few weeks. Importantly, the efficacy achieved with tralokinumab appears sustained, even after >15-weeks interruption, as the median percentage improvement in EASI from PT baseline was 68.6% for the washout group at ECZTEND baseline (Fig 3).

This trial is strengthened by the inclusion of participants regardless of prior treatment regimen or level of response, with the goal of avoiding selection bias. However, selection biases may persist, as not all PT sites were offered the option to enroll in ECZTEND, and 54% of participants initially enrolled in ECZTRA 1, 2, 3, and 5 were eligible and chose to enroll in ECZTEND. Participants with a good response to PT treatment may be more likely to enroll in ECZTEND. The consistency of results between the 1-year efficacy analysis set and the subgroup of participants treated with tralokinumab over 2 years supports the sustained efficacy of tralokinumab over time. These analyses do not take dropouts during the PTs into account. Additional limitations include the open-label, single-arm design, and possible influence of transient topical rescue therapy. Influence of transient TCS use is possible, however expected to be limited, as 29.4% to 35.4% of participants reported use of TCS in the last week throughout the trial.

In conclusion, this interim analysis of ECZTEND demonstrates a well-tolerated long-term safety profile and sustained efficacy in participants with up to 2 years of tralokinumab treatment. These data support specific inhibition of IL-13 with tralokinumab as a safe and efficacious option for the long-term treatment of moderate-to-severe AD.

The authors wish to thank the ECZTEND investigators and the individuals who participated in the studies. Medical writing support, including assisting authors with the development of the manuscript drafts and incorporation of comments, was provided by Meredith Whitaker, PhD, and Clair Geary, PhD, of Alphabet Health (New York, NY), supported by LEO Pharma A/S, according to Good

Publication Practice guidelines (<https://www.ismpp.org/gpp3>).

Conflicts of interest

Blauvelt has served as a scientific adviser and/or clinical study investigator for AbbVie, Abcentra, Aligos, Almirall, Amgen, Arcutis, Arena, Aslan, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, EcoR1, Eli Lilly, Evomune, Forte, Galderma, Incyte, Janssen, Landos, LEO Pharma, Novartis, Pfizer, Rapt, Regeneron, Sanofi Genzyme, Sun Pharma, UCB Pharma, and Vibliome. Langley has served and received compensation in the form of grants and/or honoraria as principal investigator for and is on the scientific advisory board or has served as a speaker for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Merck, Novartis, Pfizer, and UCB. Lacour has received grants or honoraria as an investigator, advisory board member, or speaker from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Janssen, Lilly, LEO Pharma, Novartis, Pfizer, Regeneron, and Sanofi. Toth has served as an investigator for AbbVie, Amgen, Arcutis, Boehringer Ingelheim, Bond Avillion, Bristol-Myers Squibb, Celgene, Centocor, Dermira, Eli Lilly, Galderma, GSK, Incyte, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Regeneron, UCB, and Valeant. Laquer has received grants from AbbVie, Eli Lilly, Galderma, LEO Pharma, and Novartis. Beissert has served an advisory board member or received speaker honoraria from AbbVie Deutschland & Co, Actelion Pharmaceuticals, Almirall-Hermal, Amgen, BMS, Celgene, Galderma, GSK, Hexal-Sandoz, Janssen-Cilag, LEO Pharma, Lilly Deutschland, Menlo Therapeutics, MSD Sharp & Dohme, Novartis, Pfizer, Roche-Posay, Sanofi-Aventis Deutschland, and UCB Pharma. Wollenberg has received grants, personal fees, or nonfinancial support from AbbVie, Almirall, Beiersdorf, Bioderma, Chugai, Galapagos, Galderma, Hans Karrer, LEO Pharma, Lilly, L'Oreal, Maruho, MedImmune, Novartis, Pfizer, Pierre Fabre, Regeneron, Santen, and Sanofi-Aventis. Herranz has served as a consultant, speaker, or investigator for Amgen, Janssen, LEO Pharma, Lilly, Novartis, Parexel, Pfizer, and Sanofi. Pink reports personal fees and nonfinancial support from LEO Pharma, Novartis, and UCB and personal fees from AbbVie, Almirall, Amgen, BMS, Boehringer, Janssen, La Roche-Posay, Lilly, Pfizer, and Sanofi. Peris reports grants or personal fees for participation in advisory boards from AbbVie, Almirall, Galderma, Lilly, LEO Pharma, Novartis, Pierre Fabre, Sanofi, Sun Pharma, and Janssen. Fangel, Gjerum, and Coriveau are employees of LEO Pharma. Saeki has received lecture fees from Kyorin, Kyowa Kirin, LEO Pharma, Mitsubishi Tanabe, Maruho, Sanofi, Tokiwa, and Taiho and scholarship donations from Esai, Mitsubishi Tanabe, Maruho, and Torii. Warren has received research grants or consulting fees from AbbVie, Almirall, Amgen, Arena, Astellas, Avillion, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, DiCE, Eli Lilly, GSK, Janssen, LEO Pharma, Medac, Novartis, Pfizer, Sanofi, Sun Pharma, UCB, and UNION. He is supported by the Manchester NIHR Biomedical Research Centre. Simpson reports grants and/or personal fees from AbbVie,

Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, FortéBio, Galderma, Incyte, Kyowa Kirin, LEO Pharma, MedImmune, Menlo Therapeutics, Merck, Novartis, Ortho Dermatologics, Pfizer, Pierre Fabre Dermo Cosmetique, Regeneron, Sanofi, Tioga, and Valeant. Reich has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by Abbvie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Forward Pharma, Gilead, Galderma, Janssen-Cilag, Kyowa Kirin, LEO, Lilly, Medac, Novartis, Ocean Pharma, Pfizer, Sanofi, and UCB. Professor Reich is cofounder of Moonlake Immunotherapeutics.

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