Early and sustained improvements in patient-reported outcomes with tralokinumab in combination with topical corticosteroids as needed in moderate-to-severe atopic dermatitis

Boni E. Elewski,[1] Sonja Ständer,[2] Matthew Zirwas,[3] Juan Francisco Silvestre,[4] Sunil Kalia,[5,6] Jan Gutermuth,[7] Thomas Mark,[8] Ann-Marie Tindberg,[8] Jonathan I. Silverberg[9]

[1]Department of Dermatology, University of Alabama, Birmingham, AL, USA; [2]Department of Dermatology and Interdisciplinary Competence Center Chronic Pruritus (KCP), University Hospital Münster, Münster, Germany; [3]Probity Medical Research, Columbus, OH, USA; [4]Dermatology Department, Hospital General Universitario de Alicante, Alicante, Spain; [5]Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada; [6]Vancouver Coastal Health Research Institute and BC Children's Hospital Research Institute, Vancouver, BC, Canada; [7]Department of Dermatology, Universitair Ziekenhuis Brussel and Vrije Universiteit Brussel, Brussels, Belgium; [8]LEO Pharma A/S, Ballerup, Denmark; [9]Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

Introduction

- Atopic dermatitis is a chronic, inflammatory skin disease[1] characterized by eczematous skin lesions associated with intense itch, sleep loss, impaired quality of life (QoL), anxiety, and depression[2,3]
- Interleukin 13 (IL-13) is a key driver of the underlying type 2 inflammation and skin barrier dysfunction in atopic dermatitis and is overexpressed in lesional and nonlesional skin[4,5]
- Tralokinumab is a fully human immunoglobulin G4 monoclonal antibody that specifically binds to the IL-13 cytokine with high affinity, preventing interaction with the IL-13 receptor and subsequent downstream IL-13 signaling[6]
- The pivotal Phase 3 ECZTRA 3 trial (NCT03363854) investigated the efficacy and safety of tralokinumab plus topical corticosteroids (TCS) as needed in adults with moderate-to-severe atopic dermatitis[7]

Objective

- To assess the effects of treatment with tralokinumab plus TCS as needed on patient-reported outcomes (PROs) over 32 weeks

Methods

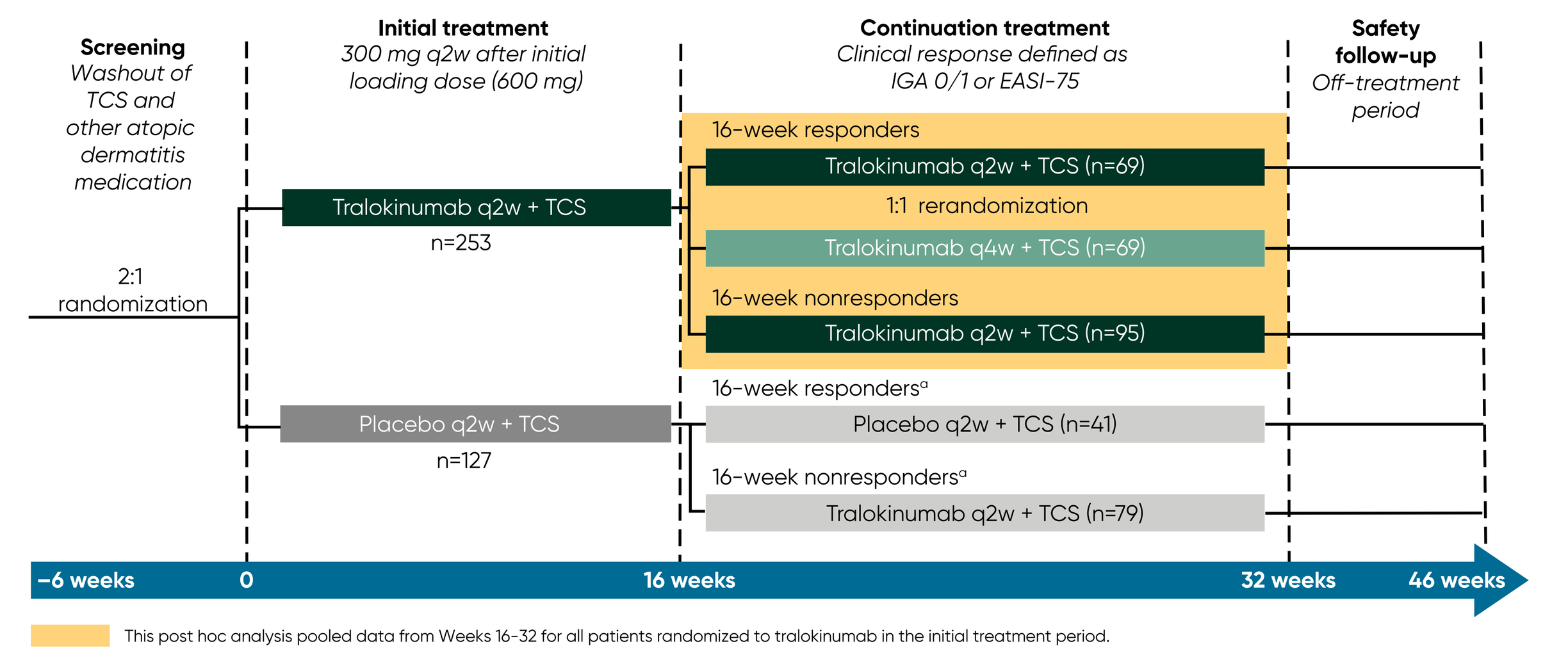
Patients

- Eligible patients were ⩾18 years of age with a confirmed diagnosis of atopic dermatitis for ⩾1 year, atopic dermatitis body surface area involvement of ⩾10%, an Eczema Area and Severity Index (EASI) score of ⩾12 at screening and ⩾16 at baseline, an Investigator's Global Assessment (IGA) score of ⩾3, and worst daily pruritus Numeric Rating Scale (NRS) of ⩾4 prior to baseline

Study design

- Patients were randomized 2:1 to subcutaneous tralokinumab 300 mg every 2 weeks (q2w) plus TCS as needed or placebo plus TCS as needed for an initial treatment period of 16 weeks **(Figure 1)**
- TCS (180–200 g mometasone furoate 0.1% cream; Europe, Class 3 [potent]; USA, Class 4 [midstrength]) was supplied free of charge by the sponsor from randomization to the end of treatment
- Patients were instructed to apply a thin film of the TCS once daily to active lesions as needed and discontinue when control was achieved
- Lower potency TCS or topical calcineurin inhibitors could be prescribed if needed on areas where the supplied TCS was not advisable or considered unsafe

Figure 1. Study design



[a]To maintain blinding of the study, patients who achieved the clinical response criteria with placebo continued to receive placebo (q2w) and patients not achieving the clinical response criteria with placebo were assigned tralokinumab q2w plus TCS as needed. These patients were not included in analyses after Week 16.

EASI-75, at least 75% improvement in the Eczema Area and Severity Index; IGA 0/1, Investigator's Global Assessment score of 0 or 1; q2w, every 2 weeks; q4w, every 4 weeks; TCS, topical corticosteroids.

- At 16 weeks, patients who achieved clinical response with tralokinumab (IGA score of 0 or 1 and/or 75% improvement in EASI) were rerandomized 1:1 to tralokinumab q2w plus TCS or every 4 weeks (q4w) plus TCS for an additional 16 weeks
- Patients not achieving the clinical response criteria with tralokinumab received tralokinumab q2w plus TCS from Week 16
- The three treatment arms during the continuation period were combined in this analysis

Endpoints

- Patients completed the worst daily pruritus NRS and eczema-related sleep interference NRS daily via eDiary
- Patients completed the Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), and Hospital Anxiety and Depression Scale (HADS) during scheduled visits
- Adverse events (AEs) were assessed at baseline and at each visit

Statistical analysis

- Post hoc analyses of Weeks 16–32 data were conducted by pooling all patients who were randomized to tralokinumab in the initial treatment period, irrespective of tralokinumab dosing regimen beyond Week 16
- Statistical analyses followed prespecifications, ie, mixed model for repeated measures with fixed effects of planned treatment, region, and baseline IGA score, as well as interactions between treatment and visit and baseline value and visit for continuous endpoints
- Data after rescue medication or permanent discontinuation of trial product was set to missing and an unstructured (compound symmetric when needed for convergence) covariance matrix was assumed for repeated measures of a patient

Results

Patient characteristics

- 380 patients were randomized in ECZTRA 3 to receive either tralokinumab q2w plus TCS (n=253) or placebo q2w plus TCS (n=127) in the initial treatment period. Two patients did not receive a treatment dose and were not included in the analyses
- Baseline demographics and disease characteristics were similar across both treatment groups **(Table 1)**

Table 1. Patient demographics and disease characteristics at baseline

	Tralokinumab q2w + TCS (n=253)	Placebo q2w + TCS (n=127)
Mean age, years	39.8	37.7
Male, n (%)	125 (49)	84 (66)
Mean duration of atopic dermatitis, years (SD)	28.0 (16.5)	28.7 (15.0)
Mean BSA involvement with atopic dermatitis, % (SD)	47.6 (23.3)	49.0 (25.9)
Severe disease (IGA 4), %	45.8	47.2
Mean weekly average worst daily pruritus NRS score (SD)	7.7 (1.5)	7.9 (1.5)
Mean weekly average of eczema-related sleep NRS (SD)	6.9 (2.1)	7.1 (2.2)
Mean POEM score (SD)	22.3 (5.1)	22.4 (5.6)
Mean DLQI score (SD)	17.6 (7.1)	17.2 (7.2)
Mean HADS anxiety score (SD)	6.7 (4.2)	6.7 (4.3)
Mean HADS depression score (SD)	5.0 (3.9)	5.2 (4.1)

BSA, body surface area; DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measure; q2w, every 2 weeks; SD, standard deviation; TCS, topical corticosteroids.

PROs at Weeks 16 and 32

- Improvements in PROs were observed from baseline to Week 16 and were maintained at Week 32 **(Table 2)**

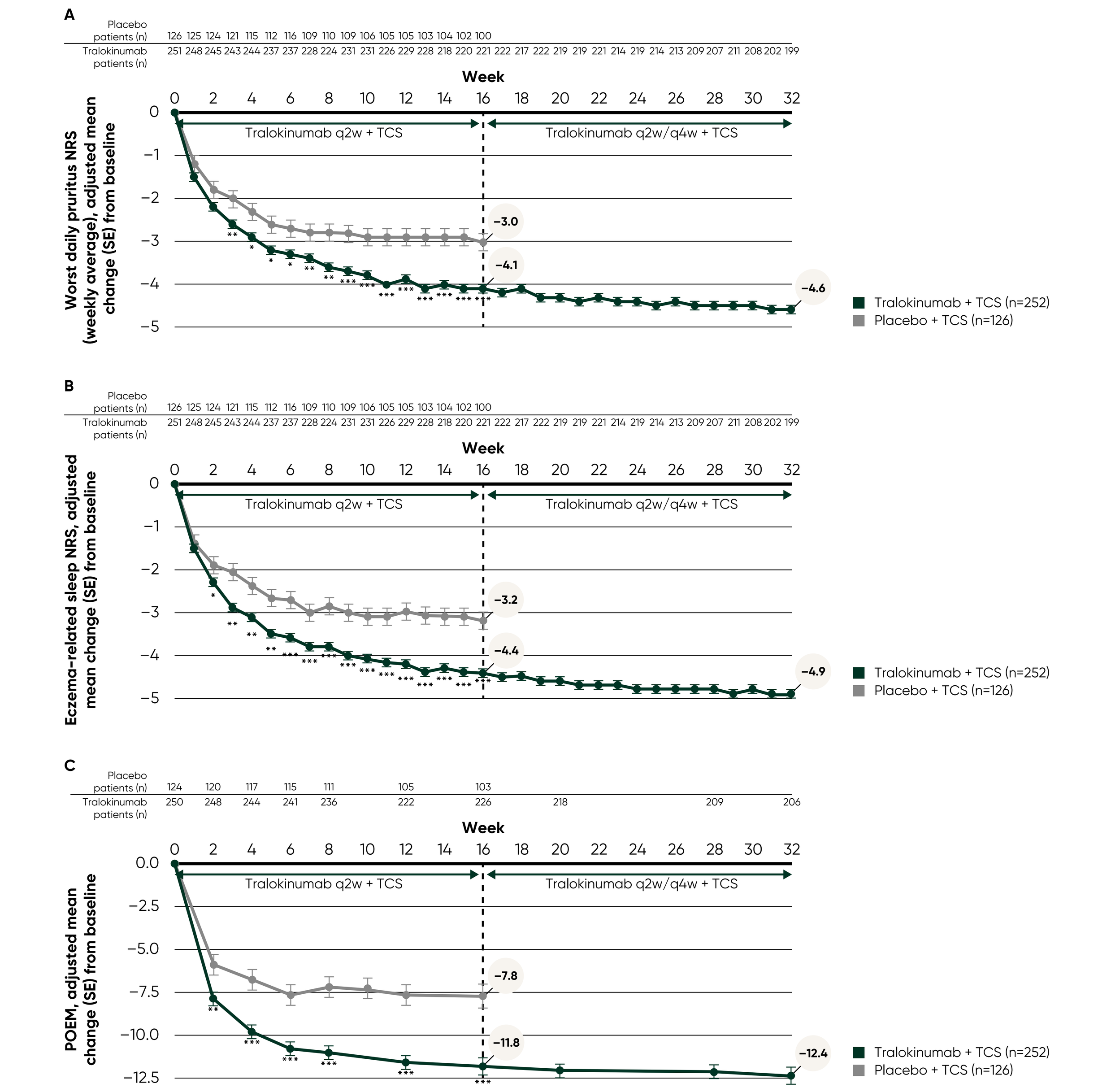
Table 2. Change in PROs at Weeks 16 and 32

PRO	Week 16		Week 32
Least square mean change (SE)	Tralokinumab q2w + TCS	Placebo q2w + TCS	Tralokinumab q2w/q4w + TCS
Weekly average of worst daily pruritus NRS	−4.1 (0.1)	−3.1 (0.2)	−4.6 (0.1)
Difference vs placebo (95% CI); *P* value	−1.1 (−1.6, −0.7); *P*<0.001		
Eczema-related sleep NRS	−4.4 (0.1)	−3.2 (0.2)	−4.9 (0.1)
Difference vs placebo (95% CI); *P* value	1.2 (−1.7, −0.7); *P*<0.001		
POEM total score	−11.8 (0.5)	−7.8 (0.7)	−12.4 (0.5)
Difference vs placebo (95% CI); *P* value	−4.0 (−5.6, −2.4); *P*<0.001		
DLQI total score	−11.7 (0.4)	−8.8 (0.6)	−12.2 (0.4)
Difference vs placebo (95% CI); *P* value	−3.0 (−4.3 , −1.6); *P*<0.001		
HADS total score	−4.3 (0.4)	−2.2 (0.5)	−5.2 (0.3)
Difference vs placebo (95% CI); *P* value	−2.0 (−3.1, −1.0); *P*=0.001		
HADS anxiety score	−2.3 (0.2)	−1.0 (0.3)	−2.8 (0.2)
Difference vs placebo (95% CI); *P* value	−1.3 (−2.0, −0.6); *P*<0.001		
HADS depression score	−2.0 (0.2)	−1.2 (0.3)	−2.4 (0.2)
Difference vs placebo (95% CI); *P* value	−0.8 (−1.5, −0.1); *P*=0.017		

CI, confidence interval; DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measure; PRO, patient-reported outcome; q2w, every 2 weeks; q4w, every 4 weeks; SE, standard error; TCS, topical corticosteroids.

- Weekly average of worst daily pruritus NRS improved throughout the initial treatment period, with separation between tralokinumab plus TCS and placebo plus TCS from Week 3 (*P*<0.05) onward **(Figure 2A)**
  - At Week 16, least square (LS) mean weekly average of worst daily pruritus NRS improved by -4.1 from baseline with tralokinumab plus TCS and by -3.0 with placebo plus TCS (*P*<0.001) **[Table 2** and **Figure 2A]**
  - The reduction in worst daily pruritus was sustained with continued tralokinumab treatment, with a LS mean (standard error [SE]) change from baseline of -4.6 (0.1) at Week 32 **(Table 2** and **Figure 2A)**
- Eczema-related sleep interference NRS improved throughout the initial treatment period, with separation between tralokinumab plus TCS and placebo plus TCS from Week 2 (*P*<0.05) onward **(Figure 2B)**
  - LS mean eczema-related sleep interference NRS improved by -4.4 with tralokinumab q2w plus TCS versus -3.2 with placebo plus TCS (*P*<0.001) at Week 16 **(Table 2** and **Figure 2B)**
  - The improvement in eczema-related sleep interference was maintained with continued tralokinumab treatment, with a LS mean (SE) change from baseline of -4.9 (0.1) at Week 32 **(Table 2** and **Figure 2B)**
- POEM improved throughout the initial treatment period, with separation between tralokinumab plus TCS and placebo plus TCS from Week 2 onward (*P*<0.01) **[Figure 2C]**
  - At Week 16, LS mean POEM improved by -11.8 with tralokinumab q2w plus TCS versus -7.8 with placebo plus TCS (*P*<0.001) **[Table 2]**
  - The improvement in POEM was maintained with continued tralokinumab treatment, with a LS mean (SE) change from baseline of -12.4 (0.5) at Week 32 **(Table 2** and **Figure 2C)**
- Improvements in DLQI and HADS total scores were observed throughout the initial treatment period, with separation between tralokinumab plus TCS and placebo plus TCS from Week 2 onward for DLQI (*P*<0.01) and from Week 4 onward for HADS (*P*<0.05) **[Figure 3]**
- LS mean total score (SE) was reduced from 17.4 (0.3) at baseline to 5.6 (0.3) at Week 16 with tralokinumab q2w plus TCS versus 8.3 (0.5) with placebo plus TCS (*P*<0.001). The improvement with tralokinumab was maintained at Week 32 (estimated total score [SE], 5.1 [0.3]) **[Figure 3A]**
  - LS mean DLQI scores at Weeks 16 and 32 were equivalent to atopic dermatitis having a small impact on QoL (DLQI total score <6) from a large impact at baseline (DLQI total score ⩾11)[7]
- LS mean (SE) HADS total score improved from 11.6 (0.3) at baseline to 7.2 (0.3) at Week 16 with tralokinumab q2w versus 9.2 (0.4) with placebo plus TCS (*P*<0.001). The improvement with tralokinumab was maintained at Week 32 (estimated total score [SE], 6.4 [0.3]) **[Figure 3B]**
  - At Week 16, the proportion of patients with baseline HADS anxiety and HADS depression subscale scores of ⩾8 that improved to <8 (normal)[3] was higher in the tralokinumab q2w plus TCS group (53.9%) versus the placebo plus TCS group (26.9%; difference, 24.8% [95% confidence interval 9.3, 40.4; *P*=0.003])

Figure 2. Change in (A) mean worst daily pruritus NRS (weekly average), (B) mean eczema-related sleep interference NRS, and (C) mean POEM total score from baseline to Week 32

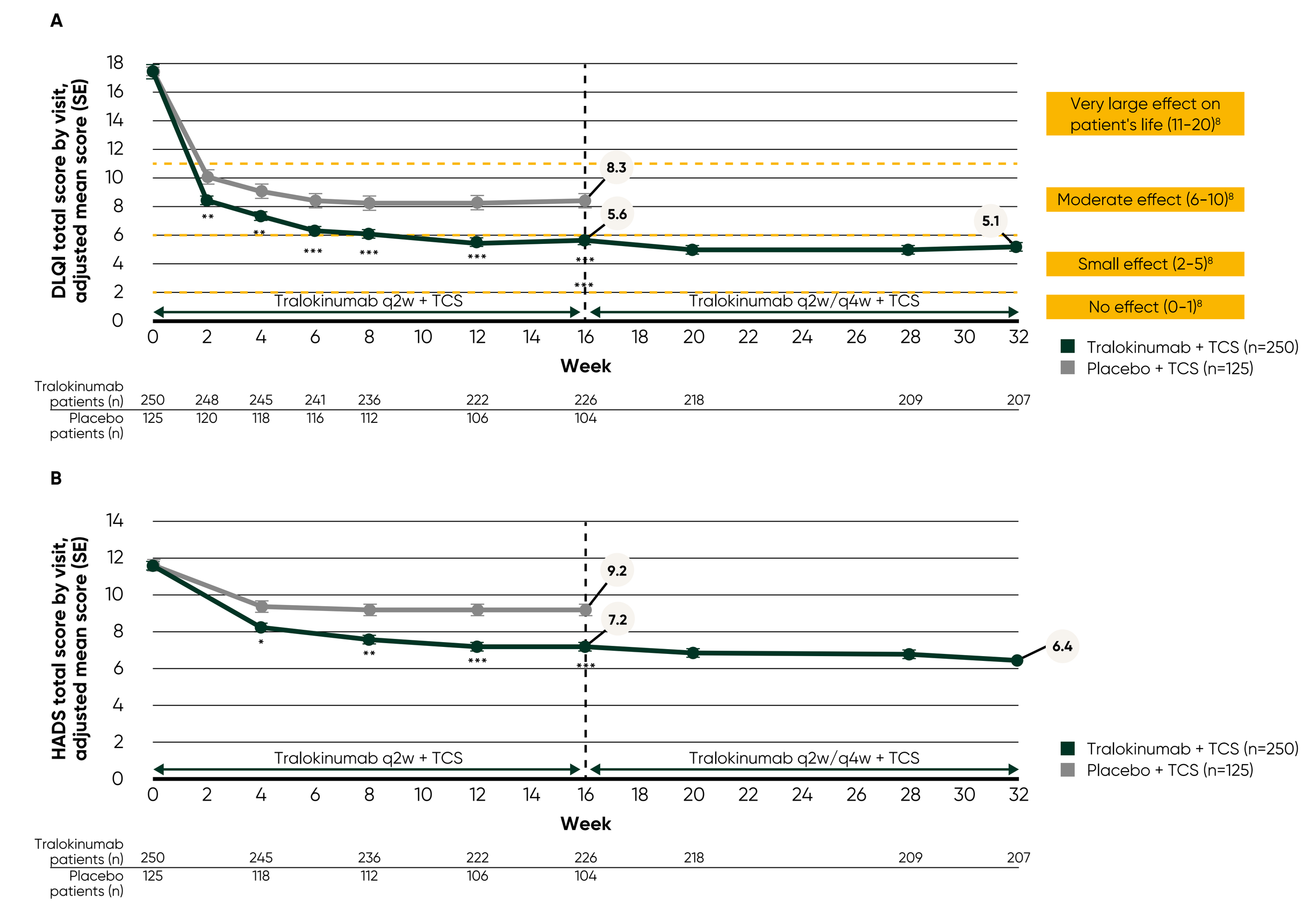


Hypothetical estimand: Treatments were reassigned at Week 16 and the placebo arm was only followed up to Week 16. The tralokinumab arm was followed beyond Week 16 and the different dosing (q2w or q4w) was ignored. Rescue medication was reset at Week 16. Data collected after permanent discontinuation of IMP or initiation of rescue medication was not included. In case of no postbaseline assessments before initiation of rescue medication, the Week 2 change was imputed as 0. Repeated measurements mode: Endpoint = Treatment*Week + Baseline*Week + Region + Baseline IGA. For change in worst daily pruritus NRS (weekly average) and mean change in eczema-related sleep interference NRS, compound symmetry was assumed for the covariance matrix. For change in mean POEM total score an unstructured covariance matrix was assumed.

*P<0.05 vs placebo + TCS; **P<0.01 vs placebo + TCS; ***P<0.001 vs placebo + TCS.

IGA, Investigator's Global Assessment; IMP, investigational medicinal product; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measure; q2w, every 2 weeks; q4w, every 4 weeks; SE, standard error; TCS, topical corticosteroids.

Figure 3. Total scores by visit from baseline to Week 32 for (A) DLQI and (B) HADS



Hypothetical estimand: Treatments were reassigned at Week 16; therefore, the placebo arm was only followed up to Week 16 and the tralokinumab arm was followed beyond Week 16 as the different dosing (q2w or q4w) was ignored. Rescue medication was reset at week 16. Data collected after permanent discontinuation of IMP or initiation of rescue medication was not included. In case of no postbaseline assessments before initiation of rescue medication, the Week 2 change was imputed as 0. Repeated measurements mode: Endpoint = Treatment*Week + Baseline*Week + Region + Baseline IGA. Compound symmetry was assumed for the covariance matrix.

*P<0.05 vs placebo + TCS; **P<0.01 vs placebo + TCS; ***P<0.001 vs placebo + TCS.

DLQI, Dermatology Life Quality Index; IGA, Investigator's Global Assessment; IMP, investigational medicinal product; HADS, Hospital Anxiety and Depression Scale; q2w, every 2 weeks; q4w, every 4 weeks; SE, standard error; TCS, topical corticosteroids.

TCS use

- The cumulative use of TCS at the end of the initial treatment period (Week 16) was lower in the tralokinumab group versus the placebo group (mean [SE], 134.9 g [11.7] vs 193.5 g [16.7]; *P*=0.004)
- At Weeks 15–16, patients treated with tralokinumab used less TCS versus patients treated with placebo (mean [SE], 11.6 g [1.57] vs 20.2 g [2.27]; *P*=0.002)
- Mean (SE) TCS use during Weeks 16–32 ranged from 9.2–13.6 g (1.2–2.0) every 2 weeks

Safety

- Tralokinumab in combination with TCS was well tolerated in patients with moderate-to-severe atopic dermatitis **(Table 3)**
- During the initial treatment period, the number of AEs was similar across treatment groups **(Table 3)** and the safety profile at Week 32 was comparable with the initial 16-week treatment period
- Tralokinumab plus TCS was associated with lower rates of severe and serious infections and eczema herpeticum compared with placebo plus TCS
- All conjunctivitis cases in patients treated with tralokinumab plus TCS were mild or moderate, with only one case leading to treatment discontinuation

Table 3. Summary of AEs in the initial 16-week treatment period

Week 16, N (%)	Tralokinumab q2w + TCS (n=252)	Placebo q2w + TCS (n=126)
At least one AE	180 (71.4)	84 (66.7)
At least one serious AE	2 (0.8)	4 (3.2)
AE leading to withdrawal from the trial	5 (0.2)	1 (0.8)
Frequent AEs (⩾5% in any treatment group)[a]		
Viral upper respiratory tract infection	49 (19.4)	14 (11.1)
Conjunctivitis	28 (11.1)	4 (3.2)
Upper respiratory tract infection	19 (7.5)	6 (4.8)
Injection site reaction	17 (6.7)	0
Atopic dermatitis	6 (2.4)	10 (7.9)
Headache	22 (8.7)	6 (4.8)

[a]Preferred terms according to Medical Dictionary for Regulatory Activities, version 20.0.

AE, adverse event; q2w, every 2 weeks; TCS, topical corticosteroids.

Conclusions

- At Week 16, tralokinumab provided significant improvements in patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related QoL, and patients used approximately 50% less of the supplied TCS compared to placebo
- Early improvements versus placebo plus TCS were seen from Weeks 2–3 onward
- The impact of atopic dermatitis on patients' QoL was significantly lessened from a very large effect at baseline to a small effect at Week 32
- Tralokinumab plus TCS as needed provided early and sustained improvements in PROs and was well tolerated in patients with moderate-to-severe atopic dermatitis over 32 weeks

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Disclosures

- Boni E. Elewski reports receiving honoraria as a consultant for Boehringer Ingelheim, Bristol Myers Squibb, Celgene, LEO Pharma, Lilly, Menlo Therapeutics, Novartis, Pfizer, Sun, Valeant (Ortho Dermatologics), and Verrica and receiving research funding from AbbVie, AnaptysBio, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Incyte, LEO Pharma, Lilly, Menlo Therapeutics, Merck, Novartis, Pfizer, Regeneron, Sun, Valeant (Ortho Dermatologics), and Vanda
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- Matthew Zirwas has acted as a consultant for AbbVie, Aclaris, Arcutis, Asana, Aseptic MD, Avillion, DS Biopharma, Fitbit, Foamix, Genentech, Incyte, Janssen, LEO Pharma, Lilly, L'Oreal, Menlo, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi, and UCB
- Juan Francisco Silvestre serves as the president of the Dermatology Society of British Columbia. He is the current chair of the Sun Awareness Working Group, Canadian Dermatology Association. He has acted as an advisor/consultant for, and has received honorarium from, AbbVie, Amgen, Aralez, Celgene, Galderma, Johnson & Johnson, La Bausch, La Roche-Posay, Lilly, Novartis, Pfizer, Sanofi-Genzyme, and UCB
- Sunil Kalia has conducted clinical trials that have received funding from AbbVie, Amgen, Corbus, Janssen, La Bausch, LEO Pharma, Lilly, Merck, Novartis, Pfizer, and UCB. He is the co-director of the Clinical Trials Unit, Skin Care Centre, Vancouver General Hospital. Intellectual property includes Raman Clinical Skin Database, with a commercial interest by Vita Imaging Inc. He has received grant funding and honoraria for educational lectures from the Eczema Society of Canada. He also has received honoraria for education lectures by SPH CME and BC Cancer Skin Tumour Group. He has acted as a consultant for BC PharmaCare and the Canadian Agency for Drugs and Technologies in Health. He is an advisor for the Drug Benefit Adjudication Advisory Committee, PharmaCare Benefits Branch, Ministry of Health, British Columbia. His salary is funded by the Photomedicine Institute and the UBC Hospital Foundation and the Michael Smith Foundation for Health Research
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