A Phase 2b Dose-Ranging Efficacy and Safety Study of Tralokinumab in Adult Patients with Moderate to Severe Atopic Dermatitis (AD)

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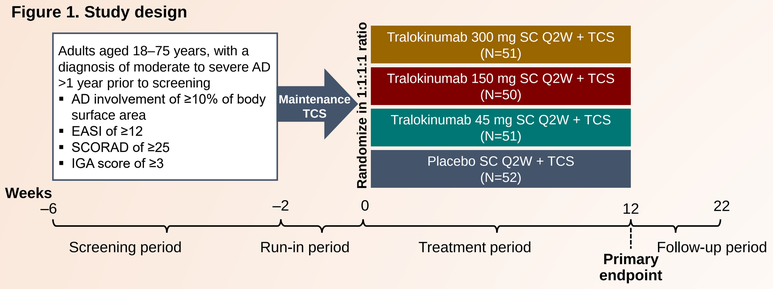
Introduction

- Novel, well-tolerated treatments that target the molecular pathways underlying atopic dermatitis (AD), rather than symptomatic relief, are needed
- Interleukin (IL)-13, a type 2 T helper cytokine, has been implicated in the pathophysiology of AD[1–4] and is reportedly upregulated in acute and chronic lesions[5]
- Tralokinumab is an immunoglobulin G_4 human monoclonal antibody that potently and specifically neutralizes IL-13.[6] We report the findings from a Phase 2b study of tralokinumab in patients with moderate to severe AD
- Serum dipeptidyl peptidase 4 (DPP-4) has been reported as a predictive biomarker for tralokinumab efficacy in patients with severe asthma[7]

Figure 1. Study design



EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; SC, subcutaneous; SCORED, Scoring of Atopic Dermatitis; TCS, topical corticosteroids

Methods

Study design

- This was a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study (NCT02347176) with a 12-week treatment period (Figure 1)
- Patients were randomized to receive tralokinumab (45, 150, or 300 mg) following a 2-week run-in period with Class 3 (mid-strength) topical corticosteroids (TCS, administered throughout the study) (Figure 1)

Assessments

Co-primary efficacy analyses (ITT [intention-to-treat] population)

- Change from baseline in total Eczema Area and Severity Index (EASI) at Week 12
- Percentage of Investigator's Global Assessment (IGA) responders (patients achieving an IGA score of 0 or 1, and at least a 2-grade reduction from baseline at Week 12)

Secondary analyses (ITT population)

- Change from baseline in Scoring of Atopic Dermatitis (SCORAD)
- Change from baseline in pruritus numerical rating scale (NRS) (7-day mean score)
- Change from baseline in Dermatology Life Quality Index (DLQI)
- Percentage of patients achieving ≥50% reduction from baseline in EASI (EASI 50)
- Percentage of patients achieving ≥50% reduction from baseline in SCORAD (SCORAD 50)
- *Staphylococcus aureus* (*S. aureus*) colonization and infection were measured on lesional and non-lesional skin

Exploratory analysis (DPP-4 subpopulations)

- Primary endpoints were assessed in a subpopulation of patients with concentrations of DPP-4 equal to or above (DPP-4-high) or below (DPP-4-low) the total population median at baseline

Safety (As-treated population)

- Most frequent treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs)

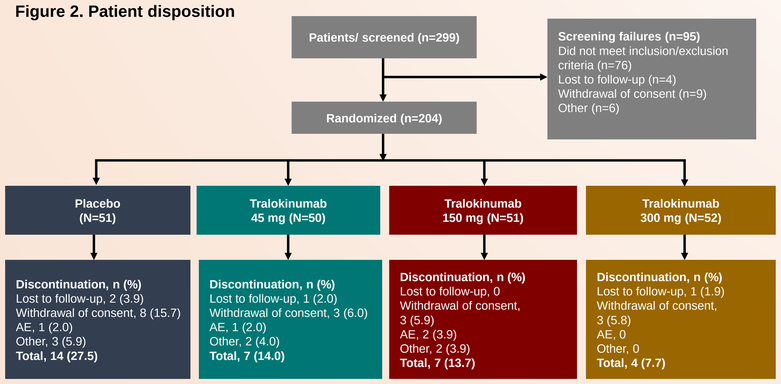
Statistical analysis

- Continuous endpoints (change from baseline in EASI, SCORAD, pruritus NRS, and DLQI) were analyzed using repeated measures analysis, adjusting for baseline
- Binary endpoints (IGA, EASI 50, and SCORAD 50 responders, and *S. aureus* status) were analyzed using logistic regression, adjusting for each baseline endpoint value
- Other endpoints were summarized descriptively

Results

- 204 patients were randomized to treatment and 172 (84.3%) completed the study (Figure 2)
- Demographics and baseline disease characteristics were similar between treatment groups (Table 1)

Figure 2. Patient disposition



AE, adverse event

Table 1. Demographics and baseline disease characteristics (ITT population)

		Tralokinumab + TCS		
	Placebo Q2W (N=51)	45 mg Q2W (N=50)	150 mg Q2W (N=51)	300 mg Q2W (N=52)
Age, years, mean (SD)	39.4 (14.5)	39.1 (15.1)	37.1 (14.0)	35.7 (14.6)
Male, n (%)	22 (43.1)	29 (58.0)	26 (51.0)	33 (63.5)
Race[a], n (%)				
Asian	10 (19.6)	11 (22.0)	8 (15.7)	16 (30.8)
Black or African-American	8 (15.7)	4 (8.0)	10 (19.6)	7 (13.5)
White	31 (60.8)	33 (66.0)	33 (64.7)	28 (53.8)
Other	1 (2.0)	1 (2.0)	0	0
Total EASI, mean (SD)	26.4 (12.6)	24.8 (8.3)	27.1 (11.2)	27.3 (10.9)
Baseline IGA[b], n (%)				
Moderate	31 (60.8)	32 (64.0)	31 (60.8)	29 (55.8)
Severe	20 (39.2)	18 (36.0)	16 (31.4)	20 (38.5)
Very severe	0	0	4 (7.8)	3 (5.8)
Total SCORAD, mean (SD)	58.5 (12.9)	57.5 (12.6)	60.8 (11.9)	60.8 (12.3)

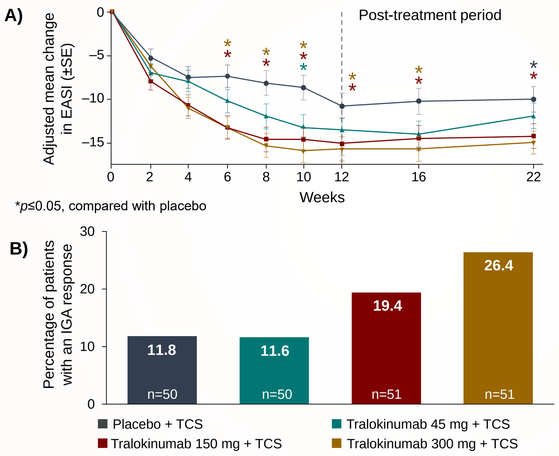
[a]Each race category contains patients who only selected this category
[b]Per the inclusion/exclusion criteria, no patient had a baseline IGA of clear, almost clear or mild EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; ITT, intention-to-treat; Q2W, every 2 weeks; SCORAD, Scoring of Atopic Dermatitis; SD, standard deviation; TCS, topical corticosteroids

Efficacy

Primary analyses

- At Week 12, tralokinumab 150 mg and 300 mg significantly reduced total EASI from baseline (adjusted mean difference [standard error; SE]: –4.4 [2.0] p=0.027 and –4.9 [1.9] p=0.011, respectively), compared with placebo (Figure 3A)
- A greater number of patients treated with tralokinumab 150 mg and 300 mg had an IGA response of 0 or 1 at Week 12, compared with placebo (Figure 3B)

Figure 3. Adjusted mean change from baseline in EASI (A) and the percentage of patients with an IGA response at Week 12 (B) (ITT population)



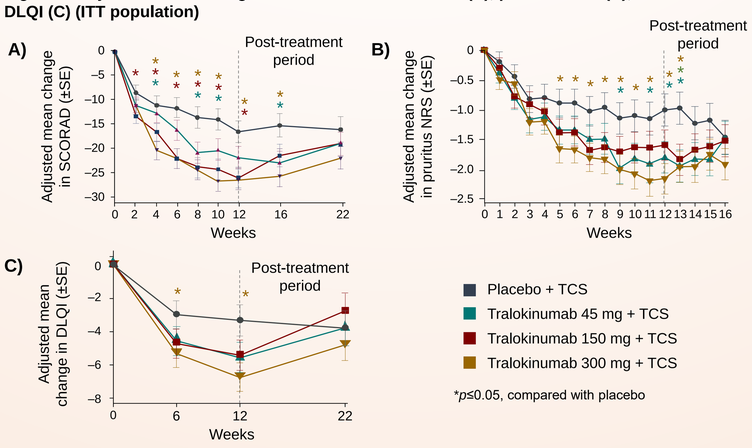
*p≤0.05, compared with placebo

EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; ITT, intention-to-treat; SE, standard error; TCS, topical corticosteroids

Secondary analyses

- A significant decrease in SCORAD from baseline to Week 12 was demonstrated for tralokinumab 150 mg (p=0.003) and 300 mg (p=0.002), compared with placebo (Figure 4A)
- Patients treated with tralokinumab had lower pruritus scores at Week 12, compared with placebo (Figure 4B)
- Treatment with tralokinumab 300 mg was associated with a significant decrease in DLQI score at Week 12 (p=0.006), compared with placebo (Figure 4C)
- At Week 12, tralokinumab 300 mg significantly reduced *S. aureus* colonization on lesional and non-lesional skin, compared with placebo (p<0.001)

Figure 4. Adjusted mean change from baseline in SCORAD (A), pruritus NRS (B), and DLQI (C) (ITT population)

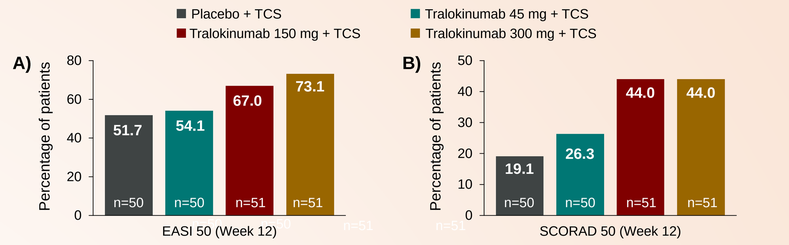


*p≤0.05, compared with placebo

DLQI, Dermatology Life Quality Index; ITT, intention-to-treat; NRS, numerical rating scale; SCORAD, Scoring of Atopic Dermatitis; SE, standard error; TCS, topical corticosteroids

- 37 (73.1%) patients treated with tralokinumab 300 mg reached EASI 50, demonstrating a significant increase of 21.4% (p=0.025) in response rates, compared with placebo (Figure 5A)
- Significantly more patients treated with tralokinumab 150 mg (p=0.007) and tralokinumab 300 mg (p=0.007) achieved SCORAD 50 at Week 12, compared with placebo (Figure 5B)

Figure 5. Percentage of patients achieving EASI 50 (A) and SCORAD 50 (B) at Week 12 (ITT population)

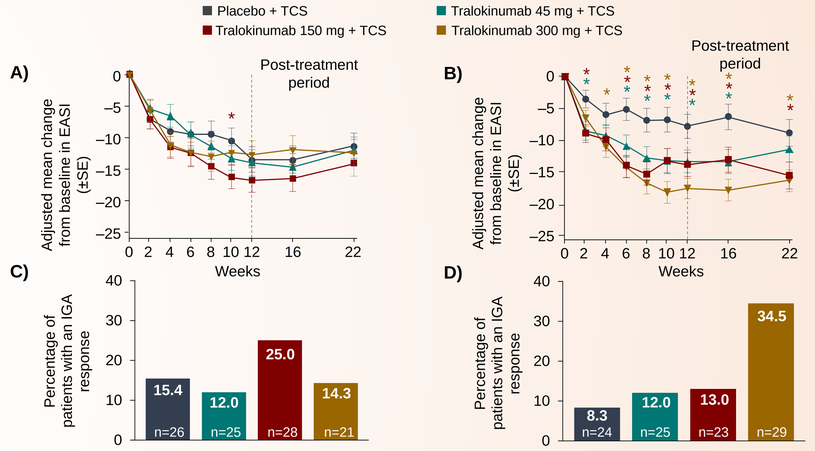


EASI, Eczema Area and Severity Index; ITT, intention-to-treat; SCORAD, Scoring of Atopic Dermatitis; TCS, topical corticosteroids

Exploratory analysis

- At Week 12, all doses of tralokinumab demonstrated a significant reduction in EASI from baseline compared with placebo (p<0.05) for patients in the DPP-4-high subpopulation
- Tralokinumab 300 mg demonstrated a significant increase in IGA response at Week 12 compared with placebo (p=0.025) for patients in the DPP-4-high subpopulation. Numerical improvements were observed for all treatment groups, compared with placebo
- Significant differences in either primary endpoint were not observed for the DPP-4-low subpopulation at Week 12 (Figure 6)

Figure 6. Adjusted mean change from baseline in EASI (DPP-4-low [A] and -high [B] subpopulations) and the percentage of patients with an IGA response at Week 12 (DPP-4-low [C] and -high [D] subpopulations)



*p≤0.05, compared with placebo

DPP-4, dipeptidyl peptidase 4; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; SE, standard error; TCS, topical corticosteroids

Safety

- TEAEs and TESAEs are shown in Table 2

Table 2. TEAEs and TESAEs (As-treated population)

		Tralokinumab + TCS			
	Placebo Q2W (N=51)	45 mg Q2W (N=50)	150 mg Q2W (N=51)	300 mg Q2W (N=52)	Total (N=204)
At least one TEAE, n (%)	31 (60.8)	36 (72.0)	35 (68.6)	30 (57.7)	132 (64.7)
At least one TEAE leading to discontinuation[a], n (%)	5 (9.8)	2 (4.0)	3 (5.9)	0	10 (4.9)
Most common TEAEs, occurring in ≥5% of patients, n (%)					
Nasopharyngitis	5 (9.8)	11 (22.0)	6 (11.8)	12 (23.1)	34 (16.7)
Upper respiratory tract infection	5 (9.8)	5 (10.0)	5 (9.8)	4 (7.7)	19 (9.3)
Headache	2 (3.9)	3 (6.0)	4 (7.8)	4 (7.7)	13 (6.4)
AD	4 (7.8)	3 (6.0)	3 (5.9)	3 (5.8)	13 (6.4)
At least one TESAE, n (%)	1 (2.0)	3 (6.0)	2 (3.9)	0	6 (2.9)

[a]One patient treated with tralokinumab 45 mg withdrew consent for further participation in the study and began treatment with cyclosporine A and clobegalen cream for AD. The patient later died from a cardiac event that was not considered related to treatment with tralokinumab
AD, atopic dermatitis; Q2W, every 2 weeks; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

- 6/204 (2.9%) patients had a TEAE of conjunctivitis during the study (2 [3.9%],1 [2.0%], and 3 [5.9%] were treated with placebo, and tralokinumab 45 and 150 mg, respectively)
- Injection-site reactions of incidence ≥1% were bruising (1.0%), pain (1.5%), and reaction (1.0%). Of these, all patients were treated with tralokinumab except for 1 patient in the placebo group who experienced some injection-site pain

Conclusions

- In this Phase 2b study of patients with moderate to severe AD symptoms (despite daily treatment with Class 3 TCS), tralokinumab demonstrated efficacy in the primary and key secondary endpoints, and an acceptable safety and tolerability profile, compared with placebo
- Furthermore, tralokinumab demonstrated significant improvements in quality of life (as shown by reduction in DLQI) and pruritus, compared with placebo
- Patients treated with tralokinumab 300 mg in the DPP-4-high subgroup demonstrated significant efficacy in both primary endpoints compared with placebo; the observed effect sizes were greater than in the ITT population, suggesting that DPP-4 may serve as a predictive biomarker for patients who may benefit from tralokinumab treatment
- However, treatment with Class 3 TCS may have impacted on efficacy effect sizes observed, providing a limitation to the study design
- These data suggest that targeting IL-13 is a promising approach for AD treatment. Clinical efficacy and dose response across a range of relevant endpoints supports the further evaluation of tralokinumab in this disease

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Disclosures

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