Tezepelumab, an anti–thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial

Eric L. Simpson, MD,[a] Jane R. Parnes, MD,[b] Dewei She, PhD,[c] Sarah Crouch, BA (Hons),[d] William Rees, PhD,[c] May Mo, MS,[b] and René van der Merwe, MBChB[d]

Portland, Oregon; Thousand Oaks, California; Gaithersburg, Maryland; and Cambridge, United Kingdom

Background: Tezepelumab (AMG 157/MEDI9929), a first-in-class monoclonal antibody, targets thymic stromal lymphopoietin, a cytokine that is implicated in the pathogenesis of atopic dermatitis (AD).

Objective: We sought to evaluate the efficacy and safety of tezepelumab in adults with moderate to severe AD.

Methods: In this phase 2a study (NCT02525094), 113 patients were randomized 1:1 to subcutaneous tezepelumab 280 mg or placebo every 2 weeks, plus class 3 topical corticosteroids (TCS). The primary endpoint was the week 12 response rate for a ≥50% reduction in the Eczema Area and Severity Index (EASI50). Secondary endpoints including EASI75, Investigator's Global Assessment, SCORAD 50, SCORAD 75, pruritus numeric rating and 5-D itch scales, and exploratory endpoints (including EASI90) were assessed at weeks 12, and 16 (post hoc).

Results: A numerically greater percentage of tezepelumab plus TCS-treated patients achieved EASI50 (64.7%) versus placebo plus TCS (48.2%; P = .091). Numerical improvements over placebo were demonstrated for week 12 secondary and exploratory endpoints, with further improvements at week 16. Treatment-emergent adverse events were similar between treatment groups.

Limitations: Greater than expected response rates in placebo-treated patients were possibly attributable to TCS.

Conclusion: Although not statistically significant, numerical improvements over placebo for all week 12 endpoints were demonstrated, with greater week 16 responses. (J Am Acad Dermatol 2019;80:1013-21.)

Key words: biologics; biomarkers; EASI; IGA; pruritus; T_H2; topical corticosteroids.

From Oregon Health and Science University,[a] Portland; Amgen Inc,[b] Thousand Oaks; MedImmune,[c] Gaithersburg; and MedImmune,[d] Cambridge.

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Drs She and Rees were employees of MedImmune at the time the study was conducted and are currently affiliated with Viela Bio, Gaithersburg.

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Reprint requests: Eric L. Simpson, MD, Oregon and Science University, 3303 SW Bond Ave, CH16D, Portland, OR 397225. E-mail: simpsone@ohsu.edu.

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Atopic dermatitis (AD) is a chronic, complex inflammatory skin condition that is characterized by pruritic eczematous skin lesions, impacting patients' and their families' quality of life.[1-3] Patients with mild AD can usually control their condition by avoiding disease triggers and applying emollients and topical corticosteroids (TCS).[4] AD onset is often accompanied by other allergic disease manifestations[5] and, as recently identified, is associated with an increased risk of cardiovascular disease versus patients without AD,[6] suggesting that the condition is a complex systemic disorder. Patients with moderate to severe AD may benefit from systemic therapy[4,7,8]; however, more robust studies are required to evaluate their efficacy and long-term safety.[9]

CAPSULE SUMMARY

- Thymic stromal lymphopoietin may initiate inflammation and therefore be a key target for atopic dermatitis treatment.
- Thymic stromal lymphopoietin blockade shows limited efficacy after 12 weeks' treatment.
- Findings at later time points suggest that future clinical trials may require longer treatment periods to determine a significant treatment effect.

Thymic stromal lymphopoietin (TSLP), an epithelial cell-derived cytokine, is produced in response to proinflammatory stimuli. TSLP-activated dendritic cells induce production of T helper 2-type (T_H2) cytokines, interleukins (IL)-4, -5, and -13 and tumor necrosis factor−α.[10] Increasing evidence supports a role for T_H2 inflammation in AD pathogenesis[11-17]; recent studies of dupilumab (an IL-13/-4 inhibitor) demonstrated substantial responses in patients with AD. TSLP could be a key target to control AD-associated inflammation and skin barrier disruption, the pathogenesis of which is associated with these downstream T_H2 cytokines and immunomodulating proteins. Serum periostin and dipeptidyl peptidase-4 (DPP-4) are considered biomarkers of IL-13 axis activation[18,19] and may predict response to molecules targeting TSLP, which is upstream of IL-13.[10] Similarly, immunoglobulin E (IgE) and chemokine (C-C motif) ligand 17/thymus- and activation-regulated chemokine (CCL17/TARC) are upregulated by TSLP[10,20] and could reflect increased TSLP activity.

Tezepelumab (AMG 157/MEDI9929) is a first-in-class, fully human immunoglobulin G2λ monoclonal antibody that specifically binds TSLP and prevents interaction with its receptor complex. In the phase 2b PATHWAY study, tezepelumab demonstrated significant reductions in annual asthma exacerbation rate versus placebo in patients with uncontrolled asthma, irrespective of baseline biomarker status.

We evaluate the efficacy and safety of tezepelumab in patients with moderate to severe AD who were treated with continuous concomitant class 3[21] TCS. The effects of tezepelumab in patient-reported outcomes and impact of serum biomarkers on treatment response are also reported.

METHODS

Study design

This phase 2a, randomized, double-blind, placebo-controlled study (ALLEVIAD; NCT02525094) was conducted at 26 centers in Australia, Canada, Germany, Hungary, New Zealand, and the United States, in accordance with the Declaration of Helsinki, International Conference on Harmonization guidelines, and relevant laws and regulations. The protocol and amendments were approved by appropriate institutional review boards and independent ethics committees. Written informed consent was obtained from all patients.

Eligible patients received maintenance class 3 (high-strength) TCS at least once daily on lesional skin during the 2-week run-in period and throughout the 24-week study. Patients were stratified at randomization by their screening serum IgE concentration (<150 or ≥150 kU/L). Within each stratum, patients were randomized 1:1 (via central interactive voice/web response) to receive placebo or tezepelumab 280 mg subcutaneously every 2 weeks for 12 weeks; the last dose was at week 10. Patients completed a 10-week safety follow-up period. Randomization, treatment administration, blinding methodology, and study termination guidelines are provided in the supplement (available at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=22659).

Patients

Eligible patients were 18 to 75 years of age and had a diagnosis of AD (according to the criteria established by Hanifin and Rajka), an Eczema Area and Severity Index (EASI) score ≥12 and Investigator's Global Assessment (IGA) score ≥3 (screening and baseline), a Scoring of Atopic Dermatitis (SCORAD) ≥20, and total AD body surface area ≥10% as assessed by EASI (screening). Patients with dermatologic conditions that might confound a diagnosis of AD or a treatment

Abbreviations used:

AD:	atopic dermatitis
CCL17/TARC:	ligand 17/thymus- and activation-regulated chemokine
DPP-4:	dipeptidyl peptidase-4
EASI:	Eczema Area and Severity Index
IGA:	Investigator's Global Assessment
IgE:	immunoglobulin E
IL:	interleukin
ITT:	intention-to-treat
NRS:	numerical rating scale
OR:	odds ratio
SCORAD:	Scoring of Atopic Dermatitis
SE:	standard error
TCS:	topical corticosteroids
TEAE:	treatment-emergent adverse event
TESAE:	serious treatment-emergent adverse event
T_H2:	T helper 2-type
TSLP:	thymic stromal lymphopoietin

assessment were excluded. Detailed inclusion and exclusion criteria are provided in the supplement (available at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=22659).

Study endpoints

The primary efficacy endpoint was the percentage of patients achieving a ≥50% reduction in EASI score (EASI50) from baseline to week 12. Secondary endpoints (including patient-reported outcomes) and exploratory endpoints were measured at week 12; the full details are provided in the supplement (available at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=22659). A post hoc analysis of all endpoints was conducted at week 16.

Safety endpoints measured through week 22 included treatment-emergent adverse events (TEAEs) and serious TEAEs (TESAEs). In an exploratory analysis, selected endpoints were evaluated in subgroups, defined by inflammatory markers of pathways downstream of TSLP: serum periostin, DPP-4, and CCL17/TARC, and IgE. The clinical assessments performed and methods for serum biomarker determination are detailed in the supplement (available at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=22659).

Statistical methods

Based on a previous study, it was estimated that a sample size of 25 patients per treatment group would provide 80% power (2-sided significance of .05) to detect a treatment difference of 40% for the primary endpoint, assuming a placebo response rate of 45%. The biomarker subpopulation was assumed to be 50% of the total population, and sample size was adjusted by doubling the required number to 50 patients per treatment group.

Efficacy endpoints were analyzed in the intention-to-treat population, defined as all patients who were randomized to and received treatment; data were grouped by randomized treatment. Safety data were reported in the as-treated population, defined as all patients who received treatment, with data grouped by first treatment received.

Baseline demographics and safety data were summarized descriptively. Binary endpoints were analyzed at each visit using logistic regression with total serum IgE concentration and baseline value as covariates. The last nonmissing postbaseline value was carried forward when data were missing. For patients who received prohibited or discouraged AD treatment, the last response value from the day of or before receipt of the therapy was carried forward. Continuous endpoints were analyzed using a mixed-effect model repeated-measure analysis. No multiplicity adjustments were made for secondary or exploratory analyses. Exploratory analyses of biomarker data were not powered, but were prespecified and used similar statistical methods for the primary analysis.

RESULTS

Patients

The first patient was screened on August 15, 2015, and the first patient dosed on August 29, 2015. The last patient was evaluated on July 15, 2016. Of 155 patients screened, 113 were randomized and 111 received treatment (placebo plus TCS: N = 56; tezepelumab plus TCS: N = 55; Fig 1). Baseline demographics and clinical characteristics were similar between treatment groups (Table I). In both groups, 84.7% of patients had childhood AD, 43.2% had childhood asthma, and 39.6% had adult asthma. At the end of the treatment period, tezepelumab-treated patients had applied fewer TCSs versus placebo (mean [standard deviation], 323.4 [347.7] mg vs 429.3 [570.4] mg).

Efficacy outcomes

At week 12, a numerically greater percentage of tezepelumab plus TCS-treated patients achieved an EASI50 response (64.7%) compared with placebo plus TCS (48.2%); however, the treatment difference was not statistically significant (odds ratio [OR] [95% confidence interval {CI}]) 1.97 (0.90-4.33); P = .091; Fig 2, *A*). Comparable improvements were seen post hoc at week 16 (60.9% vs 51.9%; OR [95% CI] 1.45 [0.66-3.16]; P = .353; Fig 2, *A*). Similarly, a numerically greater percentage of tezepelumab plus TCS-treated patients achieved an

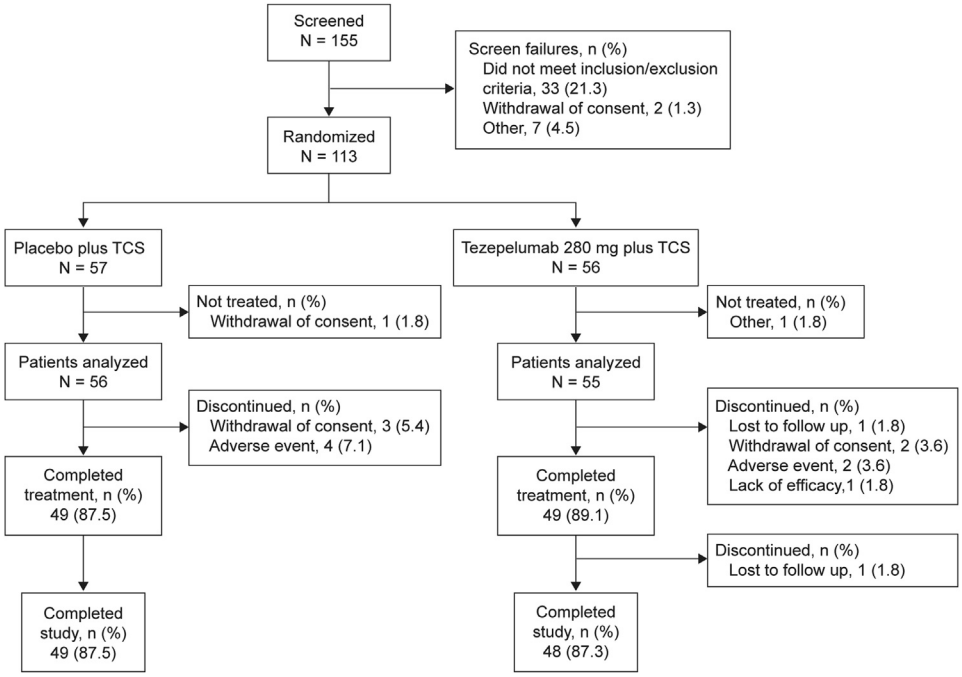

Fig 1. Patient disposition. *TCS*, Topical corticosteroids.

EASI75 response at week 12 (24.4% vs 19.8%; OR [95% CI] 1.31 [0.51-3.31]; P = .574), with greater improvements seen at week 16: 36.9% vs 21.9%; OR [95% CI] 2.09 [0.88-5.00]; P = .096; Fig 2, *A*). In exploratory analyses, tezepelumab plus TCS-treated patients had numerical improvements over placebo in EASI90 response rates at week 12 (11.8% vs 5.6%; OR [95% CI] 2.27 [0.45-14.70]; P = .283) and week 16 (20.8% vs 10.6%; OR [95% CI] 2.20 [0.74-6.60]; P = .158; Fig 2, *A*). A post hoc analysis of change in lichenification (measured through EASI and SCORAD scoring) found no significant difference between treatment groups at any time point (Supplemental Table S1, available at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=22659). Improvements in adjusted mean percentage improvement from baseline in EASI (total score) relative to placebo plus TCS were observed from week 4 and maintained until week 16 in tezepelumab plus TCS-treated patients (Fig 2, *B*). The adjusted mean percentage difference for the improvement from baseline in EASI (95% CI) at week 12 was 6.28 (−7.92-20.49; P = .382).

A numerical difference between treatment groups in IGA response rate was observed at week 12 (19.3% vs 12.8%; OR [95% CI] 1.64 [0.57-4.71]; P = .361). By week 16, the improvement in IGA response rate in tezepelumab plus TCS-treated patients versus placebo plus TCS had reached a nominal P value of <.05 (29.4% vs 12.9%; OR [95% CI] 2.81 [1.04-7.63]; P = .042; Fig 2, *C*).

Numerical improvements in SCORAD versus placebo were observed throughout the analysis period (Fig 2, *D*); the adjusted mean percentage difference (95% CI) between treatment groups for improvement from baseline at week 12 was 8.46 (−2.95-19.87; P = .144). Furthermore, numerical improvements versus placebo were observed in SCORAD50 or SCORAD75 response rates at week 12 (41.0% vs 29.4%; OR [95% CI] 1.67 (0.74-3.80); P = .219 for SCORAD50 and 9.8% vs 7.4%; OR [95% CI] 1.36 (0.27-7.26); P = .762 for SCORAD75). Similarly, at week 16, there was no substantial difference between treatment groups (data not shown).

Patient-reported outcomes

Patients receiving tezepelumab plus TCS demonstrated nominally significant improvements from baseline to week 12 in pruritus NRS versus placebo plus TCS (adjusted mean percentage improvement [standard error {SE}] 35.53 [5.89] vs 21.05 [5.91]; P = .050; Fig 3). Peak pruritus NRS scores were numerically lower for tezepelumab plus TCS-treated patients at week 12 but did not reach nominal significance (adjusted mean percentage improvement [SE] 33.54 [6.02] vs 25.41 [6.06]; P = .258). Little improvement in pruritus 5-D itch scale score was observed in tezepelumab plus TCS-treated patients versus placebo plus TCS at week 12 (−3.79 vs −3.85; adjusted mean difference [95% CI] 0.07 [−1.55-1.69]; P = .934) or other time points analyzed (data not shown).

Table I. Patient demographics and baseline disease characteristics

	Placebo plus TCS (N = 56)	Tezepelumab 280 mg plus TCS (N = 55)
Age, y, mean (SD)	38.82 (15.28)	38.55 (14.92)
Male, n (%)	30 (53.6)	32 (58.2)
Race, n (%)		
White	42 (75.0)	49 (89.1)
Asian	5 (8.9)	2 (3.6)
Black or African American	3 (5.4)	2 (3.6)
Native Hawaiian or other Pacific Islander	1 (1.8)	0
Other	2 (3.6)	1 (1.8)
Multiple categories checked	3 (5.4)	1 (1.8)
EASI score, mean (SD)	24.48 (11.21)	24.05 (12.38)
IGA classification, n (%)*		
Mild	0	1 (1.8)
Moderate	46 (82.1)	44 (80.0)
Severe	10 (17.9)	10 (18.2)
SCORAD, mean (SD)	58.66 (13.32)	57.68 (14.80)
Pruritus NRS, mean (SD)	5.2 (2.1)	5.3 (2.0)
Peak pruritus, mean (SD)	6.2 (2.2)	6.4 (2.1)
Total serum IgE, kU/L, mean (SD)	9930.4 (16,583.5)	7550.3 (9334.1)
≥150 kU/L, n (%)	52 (92.9)	48 (87.3)
Positive *Staphylococcus aureus*, n (%)		
Lesional skin	28 (57.1)	32 (66.7)
Nonlesional skin	18 (36.7)	18 (38.3)
Peripheral eosinophil count, cells/μL, mean (SD)	496.61 (381.42)	408.36 (256.39)
≥300 cells/μL, n (%)	33 (58.9)	35 (63.6)
TCS use at screening, n (%)		
Low potency	2 (4.3)	2 (4.3)
Medium to high potency	45 (95.7)	44 (95.7)
Childhood AD, n (%)	46 (82.1)	48 (87.3)
Childhood asthma, n (%)	27 (48.2)	21 (38.2)
Adult asthma, n (%)	21 (38.2)	23 (44.2)

EASI, Eczema Area Severity Index; *IGA*, Investigator's Global Assessment; *IgE*, immunoglobulin E; *NRS*, numeric rating scale; *SCORAD*, Scoring of Atopic Dermatitis; *SD*, standard deviation; *TCS*, topical corticosteroids.
*IGA severity categories are 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), 4 (severe), and 5 (very severe).

Safety assessments

The safety analysis was performed on the as-treated population (N = 111). One patient randomized to placebo received an incorrect first dose of tezepelumab and was included in the tezepelumab group; all subsequent doses were placebo.

The incidence of TEAEs was similar between treatment groups (Table II). Most were mild or moderate in severity (grade 1/2), while 5 (8.9%) tezepelumab plus TCS-treated and 7 (12.7%) placebo plus TCS-treated patients experienced a TESAE (≥grade 3). No deaths were reported. The most frequent TEAE that was considered by the investigators to be possibly treatment-related was injection-site erythema, which was reported in 3 (5.4%) patients receiving tezepelumab and no placebo plus TCS-treated patients. One placebo plus TCS-treated patient experienced a treatment-related TESAE of cellulitis.

Six patients discontinued treatment because of TEAEs; all events were unrelated to study treatment. Placebo plus TCS-treated patients experienced AD worsening (n = 3) and eczema flare (n = 1), while tezepelumab plus TCS-treated patients reported AD worsening (n = 1) and vasovagal syncope (n = 1).

Exploratory biomarker subgroup analyses

Tezepelumab plus TCS-treated patients who were DPP-4—high, periostin-low, CCL17/TARC-low, or IgE-high had numerically greater week 12 responses compared with opposing biomarker subgroups. The percentage (adjusted) of tezepelumab plus TCS versus placebo plus TCS-treated patients with an EASI50 response was 72.4% versus 56.5% (OR [95% CI] 2.03 [0.63-6.51]) for DPP-4—high patients, 76.0% versus 46.4% (OR [95% CI] 3.62 [1.11-11.88]) for periostin-low patients, 79.2% versus 50.0% (OR [95% CI] 3.98 [1.14-13.95]) for CCL17/TARC-low

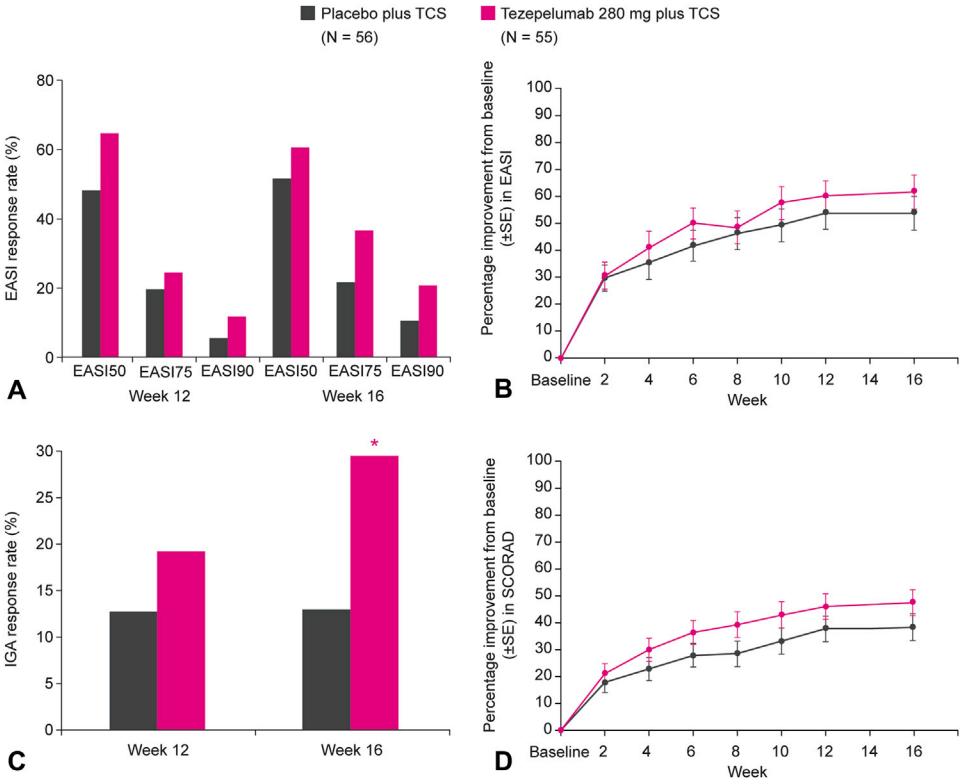

Fig 2. **A**, Percentage of patients who achieved EASI50, EASI75, and EASI90 responses at weeks 12 and 16. **B**, Percentage improvement from baseline in EASI (total score) over time. **C**, Percentage of patients with an IGA response at weeks 12 and 16. **D**, Percentage improvement from baseline in SCORAD (total score) over time. Analyses conducted in the ITT population. Patients were considered to be IGA responders if they had an IGA response of 0 or 1 and a reduction of ≥2 grades from baseline to week 12. IGA severity categories are 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), 4 (severe), and 5 (very severe). *Nominal $P < .05$ for the comparison with placebo. *EASI50*, A ≥50% reduction in Eczema Area and Severity Index score; *EASI75*, a ≥75% reduction in Eczema Area and Severity Index score; *EASI90*, a ≥90% reduction in Eczema Area and Severity Index score; *IGA*, Investigator's Global Assessment; *ITT*, intention-to-treat; *SCORAD*, Scoring of Atopic Dermatitis; *SE*, standard error; *TCS*, topical corticosteroids.

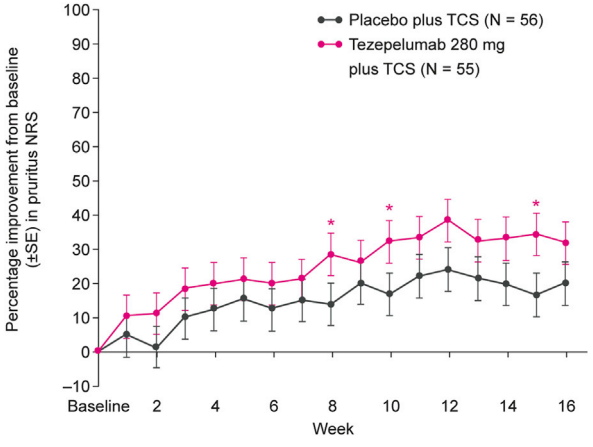

Fig 3. Percentage improvement from baseline in pruritus NRS for the ITT population. *Nominal $P < .05$ for the comparison with placebo. *ITT*, Intention-to-treat; *NRS*, numerical rating scale; *SE*, standard error; *TCS*, topical corticosteroids.

patients, and 65.9% versus 46.0% (OR [95% CI] 2.28 [0.98-5.33]) for IgE-high patients. Similar results were demonstrated for EASI75, EASI90, and IGA analyses (data not shown).

DISCUSSION

Subcutaneous tezepelumab 280 mg every 2 weeks plus TCS did not demonstrate statistically significant improvements in patients with moderate to severe AD versus placebo plus TCS, as assessed by EASI50 at week 12. A trend toward improvement for tezepelumab plus TCS-treated patients versus placebo plus TCS was observed for almost all endpoints. At week 16, a trend toward a superior EASI75 response and stronger improvement in IGA response in tezepelumab plus TCS-treated patients versus placebo plus TCS was observed.

Table II. Summary of treatment-emergent adverse events

	Placebo plus TCS (N = 55)	Tezepelumab 280 mg plus TCS (N = 56)
At least 1 TEAE, n (%)	40 (72.7)	38 (67.9)
At least 1 treatment-related TEAE, n (%)	3 (5.5)	9 (16.1)
At least 1 TEAE leading to discontinuation, n (%)	4 (7.3)	2 (3.6)
At least 1 TESAE, n (%)	3 (5.5)	2 (3.6)
At least 1 treatment-related TESAE, n (%)	1 (1.8)	0
Death, n (%)	0	0
Most common TEAEs, occurring in ≥5% of either treatment group, n (%)		
Nasopharyngitis	11 (20.0)	13 (23.2)
Atopic dermatitis	7 (12.7)	6 (10.7)
Upper respiratory tract infection	7 (12.7)	1 (1.8)
Diarrhea	3 (5.5)	5 (8.9)
Cellulitis	3 (5.5)	0
Headache	1 (1.8)	3 (5.4)
Injection-site erythema	0	3 (5.4)
Most common TESAEs, occurring in ≥1% of either treatment group, n (%)		
Atopic dermatitis	1 (1.8)	1 (1.8)
Cellulitis	1 (1.8)	0
Chest pain	1 (1.8)	0
Infected dermal cyst	0	1 (1.8)
Syncope	1 (1.8)	0

TCS, Topical corticosteroids; *TEAE*, treatment-emergent adverse event; *TESAE*, treatment-emergent serious adverse event.

The limited efficacy demonstrated on inflammatory signs and itch via TSLP blockade is surprising because preclinical studies implicate a role for TSLP in AD. In AD mouse models, TSLP directly stimulates T_H2 cytokine production leading to inflammation[22] and collagen production leading to skin fibrosis.[23] Genetic studies have identified associations between *TSLP* polymorphisms and patient susceptibility to AD development, and TSLP protein is overexpressed in the keratinocytes of patients with chronic or acute AD.[10] There is also evidence that TSLP causes pruritus in mice via neurostimulatory effects.[24,25] In this study, little improvement in pruritus was seen in tezepelumab plus TCS-treated patients. Conversely, dupilumab improved pruritus in a phase 3 study of patients with moderate to severe AD,[14] indicating that IL-4 may play a more fundamental role than TSLP in blocking signals within itch neurons. However, it should be noted that TSLP is upstream of IL-4[10] and therefore should diminish this cytokine, thereby affecting pruritus. It is possible that this inhibition may not be as complete as for IL-4 receptor α blockade by dupilumab. The effect of tezepelumab on pruritus here could have been masked by concomitant high-strength TCS use.

Limitations of this study that may have confounded results included the patient population selected, TCS use, and duration of treatment. Patients were not required to be refractory to TCS at baseline and they received TCS during the run-in and treatment periods. This may have contributed to the placebo effect. A recent AD study revealed that continued TCS use yields substantial responses in placebo-treated patients.[26] In our study, placebo-treated patients applied greater TCS amounts during treatment versus tezepelumab-treated patients. All patients applied high-strength TCS during the 2-week run-in period, further blunting any differential effect related to study treatment. It is possible that a tezepelumab monotherapy study might uncover a more definitive efficacy signal. Alternatively, an adjunctive TCS study designed to exclude TCS responders by usng a longer run-in period or a lower potency TCS might demonstrate improved results. Furthermore, only a small number of enrolled patients had severe disease (20%), while most had moderate AD (as determined by IGA score). Given the upstream mechanism of action of TSLP, a longer treatment period may reveal greater improvements in AD symptoms beyond week 12. Finally, the dose used in this study (tezepelumab 280 mg) was selected after the phase 1 study (NCT00757042); we are unsure if complete inhibition of TSLP was demonstrated from our results.

AD is a heterogeneous disease, and understanding this may allow for the identification of patient subgroups that respond better to immune-modifying therapies. We found that DPP-4—high, periostin-low, or IgE-high patients demonstrated greater treatment

differences in clinical response at weeks 12 and 16 versus opposing biomarkers. Similar results were seen in the CCL17/TARC-low subgroup; given the role of IL-13 in enhancing CCL17/TARC expression,[27] these findings are somewhat unexpected and possibly attributed to confounding concomitant TCS treatment. CCL17/TARC concentration has been reported to decrease after TCS therapy. Therefore, the run-in period where patients received TCS may have led to reported baseline CCL17/TARC concentrations being lower than unreported screening values, identifying a potential responder population. Analyses of biomarker subgroups in this study were not powered, but were prespecified.

The incidence of TEAEs was similar between treatment groups, and the safety profile reported was comparable to that described in the phase 2b PATHWAY trial in patients with uncontrolled asthma.

In conclusion, patients with moderate to severe AD achieved numerical improvements over placebo in week 12 EASI50 responses when treated with the anti-TSLP monoclonal antibody tezepelumab plus TCS; however, these improvements were not statistically significant. Numerical improvements were seen across several clinical and patient-reported endpoints, and greater efficacy in biomarker-defined subgroups suggest potential benefits in TSLP blockade. Given the preclinical evidence establishing the role of TSLP in AD, additional clinical studies are required to validate these findings.

Dr Simpson contributed to study design, data gathering, generation and analysis, manuscript preparation and review, and approved the final version of the manuscript for publication. Dr Parnes contributed to study design, data gathering and analysis, manuscript preparation and review, and approved the final version of the manuscript for publication. Dr She contributed to data gathering, generation and analysis, manuscript preparation and review, and approved the final version of the manuscript for publication. Ms Crouch contributed to study design, data gathering, manuscript preparation and review, and approved the final version of the manuscript for publication. Dr Rees contributed to data gathering, generation and analysis, manuscript preparation and review, and approved the final version of the manuscript for publication. Ms Mo contributed to data analysis, manuscript preparation and review, and approved the final version of the manuscript for publication. Dr van der Merwe contributed to data analysis, manuscript preparation and review, and approved the final version of the manuscript for publication. We thank Rebecca Plant, MSc, of QXV Comms, Macclesfield, an Ashfield Company, part of UDG Healthcare plc, for medical writing support that was funded by MedImmune, Cambridge, United Kingdom, in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3). We also thank the patients and their families, as well as the staff members at all trial sites.

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