

Efficacy and safety of mepolizumab administered subcutaneously for moderate to severe atopic dermatitis

To the Editor,

Mepolizumab is a humanized immunoglobulin G (IgG) monoclonal antibody (IgG1, kappa) with human heavy and light chain frameworks. It binds to Interleukin-5 (IL-5), which is responsible for the growth, differentiation, recruitment, activation, and survival of eosinophils.^{1,2} Neutralization of IL-5 is thought to reduce the production and survival of eosinophils which may be therapeutic in subjects with atopic dermatitis (AD).³⁻⁵

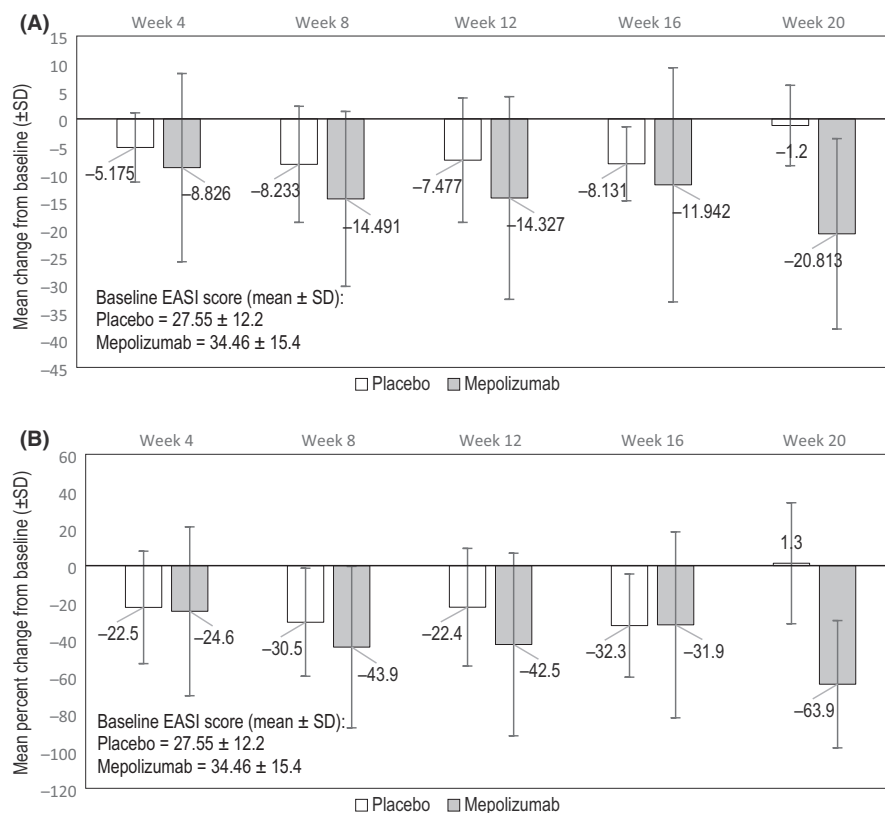
We conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase-2 clinical trial to investigate the efficacy and safety of 100 mg mepolizumab administered subcutaneously (SC). The study consisted of a prescreening period (≤ 4 weeks), a screening period (≤ 2 weeks), a 16-week treatment period, and a follow-up period (≤ 4 weeks). Adult patients, with moderate or severe AD, were randomized 1:1 to receive mepolizumab or placebo every 4 weeks on day 1, week 4, week 8, and week 12 of the 16-week treatment period. Mepolizumab 100 mg SC was determined as the dose producing 90% of maximum effect on blood

eosinophils (ID_{50}) in patients with moderate or severe asthma and blood eosinophils > 300 cells/microliter.⁶ The primary efficacy endpoint was the proportion of patients who achieve treatment success defined as an Investigator's Global Assessment (IGA) score of 0 or 1 and at least a 2-grade improvement at week 16. A secondary endpoint was the mean percentage change in Eczema Area and Severity Index (EASI) score from baseline to each study visit.

Key inclusion criteria required male or female patients to be 18- to 70-years old with AD by the Eichenfield⁷ revised criteria of Hanifin and Rajka at least 2 years prior to screening, have an IGA score of 3 or higher, an EASI score of 16 or higher at the screening and baseline visits, and an absolute blood eosinophil count of 350 cells/microliter or higher at screening. Key exclusion criteria prohibited other types of eczema, concomitant skin disorder and/or history of other diseases (eg, being immunocompromised), ongoing serious illness, known or suspected conditions that could lead to elevated eosinophils (eg, hypereosinophilic syndromes), or severe asthma. Treatment with concomitant medications (eg, topical

FIGURE 1 EASI Score (ITT Population).

A, Mean change from baseline in EASI score at each visit. B, Mean percent change from baseline in EASI score at each visit. Differences in percent change from baseline were seen between the placebo- and mepolizumab-treated groups in later assessments. At Week 8, the mean score for the placebo group demonstrated a modest improvement in EASI score (-30.5%) whereas the mepolizumab-treated group reflected a greater improvement (-43.9%) and this trend continued through Week 12 (-22.4% vs -42.5%). Similar mean scores between treatment groups were observed at Week 16 (-32.3% vs -31.9%), and while an increase in mean score was observed at Week 20 in the placebo group, there was a further decrease in the mepolizumab group (1.3% vs -63.9%)



corticosteroids, antibiotics, and antifungals) during the study were permitted if their use did not impact the study assessments.

A preplanned formal interim analysis was conducted after approximately 50% (N = 29) of the patients were randomized and had completed the week 8 visit for clinical assessments. A Bayesian predictive probability of success at the final analysis was conducted and found to be <10% which met the prespecified protocol futility criteria and led to the study termination. Results from the final analysis are presented for the Intent-to-Treat (ITT) population.

The study enrolled 34 patients and 8 patients completed the study. The distribution of the patients in the mepolizumab group was 18 enrolled, 4 (22%) completed, 14 (78%) withdrew, and in the placebo group 16 enrolled, 4 (25%) completed, 12 (75%) withdrew. The main reason reported by patients for withdrawing was a perceived lack of efficacy. The key demographic characteristics between the two patient groups were similar. In the mepolizumab group, median age was 28.5 years and 12 (67%) were male, and in the placebo group, median age was 28.0 years and 9 (56%) were male. A summary of the patients' baseline characteristics is presented in Table 1A.

For IGA at baseline, the proportion of patients in the "moderate" category was lower in the mepolizumab group (n = 7, 39%) than in the placebo group (n = 9, 56%), but higher in the mepolizumab group (n = 11, 61%) than in the placebo group (n = 7, 44%) in the "severe" category. For EASI at baseline, the median score in the mepolizumab group (32.4) was higher compared to the placebo group (25.2).

TABLE 1 (A) Summary of baseline characteristics (ITT Population). (B) Summary of proportion of patients with $\geq 50\%$ or $\geq 75\%$ improvement in EASI score from baseline at each visit (ITT Population). Week 20 was a follow-up visit that took place 8 wk after the last dose (administered at Week 12)

(A)		
Demographic characteristics	Placebo (N = 16)	Mepolizumab 100 mg SC (N = 18)
Age [years]		
Mean $\pm$ SD	30.8 $\pm$ 9.95	34.6 $\pm$ 13.99
Median	28.0	28.5
Min, max	18, 56	21, 69
Gender, n (%)		
Female	7 (44)	6 (33)
Male	9 (56)	12 (67)
Ethnicity, n (%)		
Hispanic or Latino	0	1 (6)
Not Hispanic or Latino	16 (100)	17 (94)
Height [cm]		
Mean $\pm$ SD	167.9 $\pm$ 9.64	168.9 $\pm$ 10.26
Median	167.0	168.0
Min, max	156, 185	152, 185

(Continues)

TABLE 1 (Continued)

(A)		
Demographic characteristics	Placebo (N = 16)	Mepolizumab 100 mg SC (N = 18)
Weight [kg]		
Mean $\pm$ SD	69.22 $\pm$ 12.23	79.10 $\pm$ 19.86
Median	65.90	80.70
Min, max	50.0, 94.4	52.7, 136.8
BMI [kg/m ²]		
Mean $\pm$ SD	24.46 $\pm$ 3.05	27.64 $\pm$ 6.43
Median	25.25	26.20
Min, max	19.00, 27.90	20.70, 48.50
Fitzpatrick skin type, n (%)		
I – Pale white skin, blue/hazel eyes, blond/red hair; always burns, does not tan	1 (6)	2 (11)
II – Fair skin, blue eyes; burns easily, tans poorly	2 (13)	4 (22)
III – Darker white skin; tans after initial burn	3 (19)	3 (17)
IV – Light brown skin; burns minimally, tans easily	6 (38)	3 (17)
V – Brown skin; rarely burns, tans darkly easily	3 (19)	5 (28)
VI – Dark brown or black skin; never burns, always tans darkly	1 (6)	1 (6)
IGA, n (%)		
Clear	0	0
Almost clear	0	0
Mild	0	0
Moderate	9 (56)	7 (39)
Severe	7 (44)	11 (61)
EASI		
Mean $\pm$ SD	27.55 $\pm$ 12.162	34.46 $\pm$ 15.387
Median	25.20	32.40
Min, max	16.2, 58.8	16.0, 67.8
Blood eosinophils [10 ⁹ /L]		
Mean $\pm$ SD	0.751 $\pm$ 0.5945	0.740 $\pm$ 0.3224
Median	0.515	0.745
Min, max	0.19, 2.54	0.14, 1.24
Itch/pruritus NRS (numeric rating scale) score		
n	15	17
Mean $\pm$ SD	6.27 $\pm$ 2.059	6.85 $\pm$ 2.091
Median	6.70	6.80
Min, max	1.0, 8.8	2.1, 10.0

(Continues)

TABLE 1 (Continued)

(B)					
Analysis visit	Improvement	Placebo (N = 16)	Mepolizumab 100 mg SC (N = 18)	Proportions difference	90% CI for the proportions difference
Week 4	n	16	17		
	≥50%	2 (13%)	4 (24%)	11%	(-10.7%, 32.7%)
	≥75%	2 (13%)	2 (12%)	-1%	(-19.4%, 18.0%)
Week 8	n	15	16		
	≥50%	4 (27%)	8 (50%)	23%	(-4.5%, 51.2%)
	≥75%	1 (7%)	6 (38%)	31%	(8.3%, 53.4%)
Week 12	n	11	11		
	≥50%	2 (18%)	5 (45%)	27%	(-4.0%, 58.5%)
	≥75%	1 (9%)	4 (36%)	27%	(-0.5%, 55.1%)
Week 16	n	8	6		
	≥50%	2 (25%)	2 (33%)	8%	(-32.1%, 48.8%)
	≥75%	1 (13%)	2 (33%)	21%	(-16.2%, 57.9%)
Week 20	n	4	4		
	≥50%	0	3 (75%)	75%	(39.4%, 110.6%)
	≥75%	0	2 (50%)	50%	(8.9%, 91.1%)

For the IGA endpoint, only 2 of 18 (11%) patients receiving mepolizumab and none of the 16 patients receiving placebo achieved treatment success at Week 16.

The proportion of patients with ≥50% or ≥75% improvement in EASI score from baseline is presented in Table 1B. A greater proportion of patients achieved ≥50% and ≥75% improvement in score from baseline starting at week 4 and 8, respectively, of the treatment period in the mepolizumab group. However, no meaningful differences were observed. Figure 1 shows changes from baseline in EASI score at each study visit.

Geometric mean blood eosinophil counts were comparable between the placebo (611 cells/μL) and mepolizumab (634 cells/μL) groups at baseline. In the mepolizumab group, a marked decrease in blood eosinophil count from baseline was observed by the first post-baseline measurement at week 4 and maintained throughout Week 8-16 (78%-86% vs 2%-44% in the placebo group).

Mepolizumab was studied over a short treatment period in patients with AD and did not show clinical efficacy.⁸ This study evaluated a longer treatment duration with mepolizumab. This study did not show clinical improvement in patients with moderate/severe AD while receiving mepolizumab despite the observed blood eosinophils reduction and mepolizumab concentrations being consistent with that observed in patients with severe asthma. The lack of an observed clinical effect could indicate that the decrease in the number of blood eosinophils may have a negligible impact on resident tissue-bound eosinophils or their activation status, or that mepolizumab concentration in the skin was not optimal. Alternatively, patients with moderate or severe AD may have been an inappropriate population for this study design. Mepolizumab may be effective in preventing flares in stabilized AD rather than controlling an active disease as was the case in asthma. Mepolizumab is indicated to reduce the risk

of exacerbations in severe asthma but is not indicated to treat acute asthma flares.⁹

In this study, mepolizumab was generally well tolerated and no safety concerns were identified. Seven patients receiving placebo and one patient receiving mepolizumab reported nonserious adverse events. The only event that was reported by more than one patient was diarrhea (two patients in the placebo group). The only AE reported for the mepolizumab group was for one patient with impetigo. All events were of mild or moderate intensity and none were considered related to study treatment by the investigators. No patient discontinued study treatment or withdrew from the study due to an AE or had treatment-emergent anti-mepolizumab antibody.

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CONFLICTS OF INTEREST

All authors are GlaxoSmithKline employees and shareholders. Studies cited in references 6 (Pouliquen IJ, et al), 8 (Oldhoff JM, et al), and 9 (Ortega HG, et al) were sponsored by GlaxoSmithKline.

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individual participant data and associated documents can be found at www.clinicalstudydatarequest.com.

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