

Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids

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Background: Asthma is a disease with marked heterogeneity in its clinical course and response to treatment. IL-13 is central to type 2 inflammation, which contributes to many key features of asthma. Lebrikizumab is an anti-IL-13 mAb previously reported to significantly improve lung function in patients with inadequately controlled asthma despite inhaled corticosteroid therapy, especially in periostin-high patients.

Objective: This phase II study investigated the efficacy and safety of IL-13 blockade with different doses of lebrikizumab in asthmatic patients not receiving inhaled corticosteroids.

Methods: Patients were randomized to receive 125, 250, or 500 mg of lebrikizumab or placebo subcutaneously monthly for 12 weeks with an 8-week follow-up period. The primary efficacy end point was the relative change in prebronchodilator FEV₁ from baseline to week 12.

Results: A total of 212 patients were randomized. The mean relative change in FEV₁ was numerically higher in all lebrikizumab dose groups versus the placebo group, although the difference was neither statistically nor clinically significant.

There were no meaningful differences in changes in FEV₁ between the dose groups and the placebo group by the periostin subgroup. Lebrikizumab treatment was associated with a reduced risk of treatment failure at all doses versus placebo ($P < .001$), and results were similar by the periostin subgroup, with no apparent differences between doses of lebrikizumab. Lebrikizumab was generally well tolerated.

Conclusion: Blocking IL-13, a single cytokine, in this population of asthmatic patients is insufficient to improve lung function. There is evidence that IL-13 blockade may improve disease control, as measured by prevention of protocol-defined treatment failure in these patients. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Asthma, lebrikizumab, IL-13, type 2 inflammation, periostin, uncontrolled, antibody, FEV₁

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Asthma is a complex disease with marked heterogeneity in its clinical course and response to treatment.^{1–3} Inhaled corticosteroids (ICSs), along with β_2 -agonist therapy, are the cornerstones of asthma treatment and provide effective control in the majority of patients. Yet because of poor response or potential side effects in some patients, additional therapies are still required.

IL-13 is believed to be central to type 2 inflammation, which contributes to many key features of asthma, including mucus production, IgE synthesis, bronchial fibrosis, and airway hyper-responsiveness.^{4–7} Lebrikizumab is a novel, humanized, stabilized IgG₄ mAb with high binding affinity to human IL-13, neutralizing its functional activities with high potency.^{8–10} Periostin is a matricellular protein the expression of which is inducible in bronchial epithelial cells by IL-13 and that is detectable in peripheral blood. Periostin was shown to be the best independent predictor of airway eosinophilia among multiple T_H2-associated biomarkers (IgE levels, blood eosinophil numbers, and fraction of exhaled nitric oxide [FENO] levels).¹¹ Furthermore, lebrikizumab has been demonstrated to result in a greater improvement in FEV₁ in symptomatic asthmatic patients despite ICS treatment and who had periostin levels greater than the median compared with patients with periostin levels of less than the median.⁸

Corticosteroids have been noted to inhibit IL-13 activity¹² and therefore could affect interpretation of data when investigating IL-13 blockade on a background of ICS therapy. The effects of IL-13 blockade in patients with mild asthma not taking ICSs have been demonstrated in allergen challenge studies.¹³ In addition, a recent study with a novel IL-13 mAb described dose-dependent reductions in FENO levels,¹⁴ but the effects of IL-13 blockade on airway function (FEV₁) in this population have not been evaluated. Other asthma therapies have been investigated in patients not receiving ICSs.^{15,16}

Abbreviations used

AE:	Adverse event
FENO:	Fraction of exhaled nitric oxide
HR:	Hazard ratio
ICS:	Inhaled corticosteroid
mITT:	Modified intent-to-treat
PEF:	Peak expiratory flow
SABA:	Short-acting β_2 -agonist

The current dose-response study investigated the efficacy and safety of IL-13 blockade with different doses of lebrikizumab in asthmatic patients not receiving ICSs.

METHODS**Study design/patients**

This phase II, randomized (1:1:1:1), double-blind, placebo-controlled, dose-ranging study (NCT00971035) evaluated the efficacy and safety of lebrikizumab. The study consisted of a 2-week screening period, a 12-week treatment period, and an 8-week safety follow-up period. During the 12-week treatment period, patients received 125, 250, or 500 mg of lebrikizumab or placebo subcutaneously every 28 days on days 1, 29, and 58 (plus an additional loading dose at day 8) for a total of 4 doses. At randomization patients were classified with available blood tests, serum IgE and eosinophil count into IL-13 signature surrogate status and stratified across the treatment arms; patients were designated IL-13-signature-surrogate-positive with IgE levels of greater than 100 IU/mL and a peripheral blood eosinophil count of 0.14×10^9 cells/L or greater, and IL-13-signature-surrogate-negative for the remaining combinations (IgE low or eosinophil count low).^{8,17} IgE and eosinophil levels were used because the periostin assay was unavailable at the start of the trial. Periostin status was ascertained before unblinding and prospectively assessed by using the baseline samples (day 1 before treatment).

All patients provided written informed consent, and the protocol was approved by applicable independent review committees or institutional review boards.

Inclusion criteria

Asthmatic adults (18-65 years old) not receiving ICSs were enrolled (Fig 1). Patients had to have a bronchodilator response of 15% or greater and a prebronchodilator FEV₁ of 60% to 85% of predicted value, with protocol-defined disease stability demonstrated during the run-in period. Stable asthma was defined as diagnosis of asthma 12 or more months before enrollment, a bronchodilator response, and relative change in prebronchodilator FEV₁ the week before treatment of less than 15%. Prebronchodilator peak expiratory flow (PEF) also had to be stable before treatment, and daily use of short-acting β_2 -agonist (SABA) therapy had to be less than 10 inhalations or 2 or fewer nonscheduled administrations of nebulized SABA therapy. ICSs or oral or parenteral corticosteroids were not permitted (see the **Methods** section in this article's Online Repository at www.jacionline.org for more detail on the definition of stable asthma and exclusion criteria).

End points and analyses

Objectives and end points. The primary objective was to evaluate the efficacy, safety, and tolerability of different doses of lebrikizumab compared with placebo. The primary efficacy end point was the relative change in prebronchodilator FEV₁ from baseline to week 12. Secondary and exploratory end points included relative change in FEV₁ from baseline to week 12 in subjects who were periostin high and periostin low at baseline, time to treatment failure, change in morning PEF, PEF variability, and reliever medication use.

Periostin-high and periostin-low patients were defined as patients with measured predose baseline serum periostin levels of greater than and less than

the median value, respectively. Serum periostin concentrations were obtained by using an Elecsys periostin immunoassay (investigational use only, currently in development).

Treatment failure was predefined as worsening of asthma symptoms in association with 1 or more of the following: relative decrease in prebronchodilator FEV₁ (volume) of 20% or greater compared with the baseline value; 20% decrease in morning prebronchodilator PEF on 2 consecutive days compared with baseline values; use of 10 or more inhalations of albuterol metered-dose inhaler (or equivalent) or 2 or more additional administrations (or any new use) of nebulized SABA therapy in a single day; or need for any ICS or oral or parenteral corticosteroids.

Pharmacodynamic analyses. Several pharmacodynamic biomarkers, including FENO levels, serum IgE levels, peripheral blood eosinophil numbers, and serum CCL13 and CCL17 levels, were measured at different time points throughout the study to provide evidence for the mechanism of action of the drug, as well as to assess the response to treatment in patient subgroups. Further details and results are available in the **Methods and Results** sections in this article's Online Repository.

Pharmacokinetic analysis. Serum lebrikizumab concentrations were measured at multiple time points throughout the study up to 12 weeks after the last dose for all subjects. Noncompartmental pharmacokinetic analysis with WinNonlin Enterprise 5.2.1 software (Pharsight, Sunnyvale, Calif) was performed to estimate the terminal elimination half-life.

Dose selection

The doses (125, 250, or 500 mg every 4 weeks) were selected to maintain steady-state trough concentrations of at least 50-fold higher than a theoretic target concentration of approximately 0.25 μ g/mL that would neutralize IL-13 and block IL-13 activity in the lung. These doses were expected to provide a wide distribution of data to develop a dose-response curve. The dosing frequency of once every 4 weeks was selected based on the half-life of lebrikizumab (approximately 25 days). A loading dose of study drug was administered 1 week after the first dose to achieve steady-state drug levels safely and rapidly.

Statistical analysis

A total of 212 patients were equally randomized to 1 of the 4 treatment groups. This sample size (52-54 patients per group) provided greater than 90% power to detect a treatment difference of 10% in the primary end point of FEV₁ in the highest dose group compared with the placebo group. This sample size also provided approximately 70% power to detect a treatment difference of 10% in the primary end point of relative change from baseline in prebronchodilator FEV₁ in diagnostic-positive patients, assuming the prevalence of patients with a positive diagnosis is at least 50%.

All efficacy analyses were based on the modified intent-to-treat (mITT) population, including all patients who were randomized and received 1 or more doses of study drug. All safety analyses included all randomized patients who received 1 or more doses of study drug. On the basis of previous data,⁸ periostin was prioritized over IL-13 signature surrogate as the subgroup of interest. All analyses were performed for periostin-high and periostin-low patients, along with a limited analysis of FEV₁ for IL-13 signature surrogate-positive and IL-13 signature surrogate-negative patients (see **Tables E1 and E2** in this article's Online Repository at www.jacionline.org). Further statistical methods are detailed in the **Methods** section in this article's Online Repository.

RESULTS**Disposition and demographics**

A total of 212 patients were randomized, and 210 received 1 or more doses of study drug. Among the 210 patients who received 1 or more doses of study drug, 26 (12.4%) discontinued the study before week 20 ($n = 16$ [10.1%] in the lebrikizumab group and $n = 10$ [19.2%] in the placebo group, Fig 1; reasons for discontinuation are detailed in **Tables E3 and E4** in this article's Online

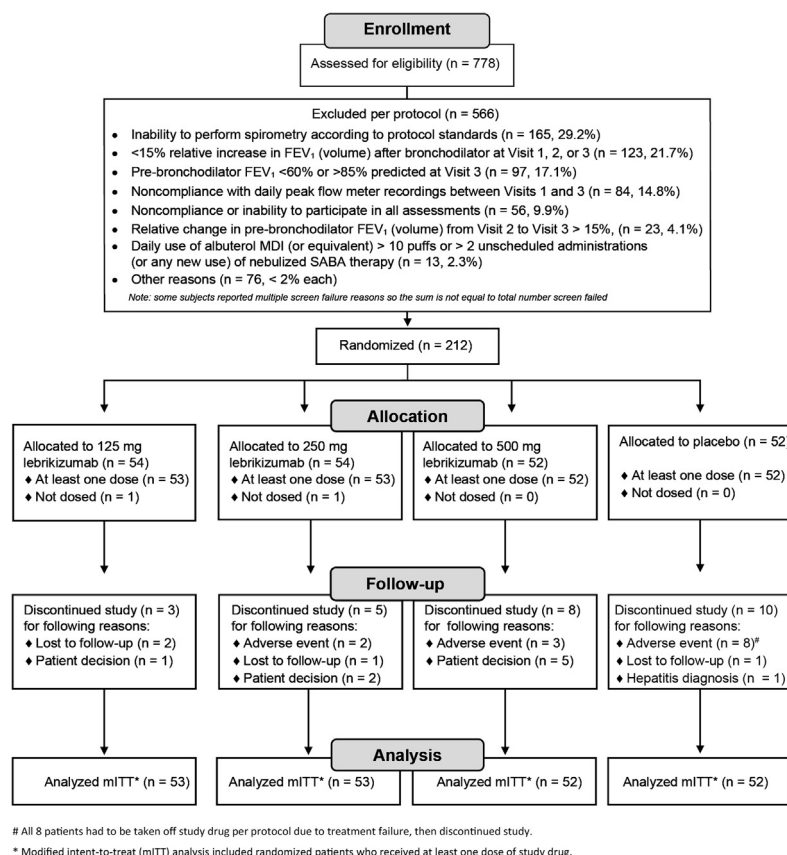


FIG 1. Patient disposition.

Repository at www.jacionline.org). Baseline characteristics were mostly balanced between the treatment groups, with the exception of periostin status (Table I).

Periostin status

Baseline periostin concentrations were available for all patients in the mITT population and were similar to those measured in the previous phase II study.⁸ Among the mITT population, 117 (56%) were periostin high and 93 (44%) were periostin low by using the prespecified threshold of the median value from the previous study in patients receiving ICS (50 ng/mL)⁸ to define the 2 groups. In the lebrizumab group the proportion of periostin-high and periostin-low patients was similar (53% and 47%, respectively). However, in the placebo group the proportions were not well balanced, with 65% of patients defined as periostin high and 35% of patients defined as periostin low. Confidence in the estimates of the differences in effects between lebrizumab- and placebo-treated patients on the basis of periostin status is limited because of the discrepancy in group sizes.

The IL-13 signature surrogate used to initially stratify the patients at baseline did not correlate well with subsequently measured baseline periostin status. Data suggest no agreement between the 2 categorization approaches (Cohen κ coefficient = -0.06 , 48% observed agreement, $P = .8$).

Efficacy

FEV₁. The mean relative change in FEV₁ was numerically higher in all lebrizumab dose groups than in the placebo group,

although the difference was not statistically or clinically significant (Fig 2). There was no evidence of a relationship between dose and response, as measured by change in FEV₁ (125-mg dose group, 3.5% [95% CI, -1.1% to 8.1%] difference from placebo at week 12 ($P = .13$); 250-mg dose group, 4.8% [95% CI, -0.1% to 9.7%] difference from placebo at week 12 ($P = .05$); and 500-mg dose group, 2.3% [95% CI, -2.6% to 7.3%] difference from placebo at week 12 ($P = .35$); Fig 2).

There was no meaningful increase in FEV₁ in response to lebrizumab in periostin-high patients compared with all patients, although a slight improvement was noticed in periostin-low patients. By dose, these changes in FEV₁ at week 12 for periostin-high patients were as follows: 125 mg, 3.1% (95% CI, -3.8% to 9.9%) difference from placebo ($P = .37$); 250 mg, 3.6% (95% CI, -3.2% to 10.5%) difference from placebo ($P = .29$); and 500 mg, 2.0% (95% CI, -5.2% to 9.1%) difference from placebo ($P = .58$). For periostin-low patients, the values were as follows: 125 mg, 4.9% (95% CI, 0.4% to 9.5% ; $P = .03$); 250 mg, 7.1% (95% CI, 1.2% to 13.1% ; $P = .02$); and 500 mg, 4.0% (95% CI, -1.6% to 9.6% ; $P = .16$; Fig 2). There was also no meaningful increase in FEV₁ in response to lebrizumab when analyzed by IL-13 surrogate signature status (see Table E2).

Treatment failures. Lebrizumab treatment was associated with a reduced risk of treatment failure in all dose groups compared with the placebo group (hazard ratio [HR], 0.21; 95% CI, 0.09-0.47; $P < .001$). Approximately 27% (14/52) of placebo-treated patients experienced treatment failure compared with 6% (10/158) of lebrizumab-treated patients (Fig 3). The most common reason for treatment failure was the need for ICSs or oral or

TABLE I. Demographics and baseline characteristics

	Placebo (n = 52)	Lebrikizumab				mITT (n = 210)
		125 mg (n = 53)	250 mg (n = 53)	500 mg (n = 52)	All doses (n = 158)	
Age (y)	40.8 (13.1)	37.6 (12.4)	40.0 (12.4)	40.6 (11.4)	39.4 (12.1)	39.7 (12.3)
Male sex, no. (%)	19 (36.5)	23 (43.4)	17 (32.1)	17 (32.7)	57 (36.1)	76 (36.2)
Weight (kg)	83.6 (19.2)	83.5 (20.1)	83.9 (16.0)	81.4 (16.1)	82.9 (17.5)	83.1 (17.9)
White race, no. (%)	34 (65.4)	40 (75.5)	38 (71.7)	36 (69.2)	114 (72.2)	148 (70.5)
FEV ₁ (L)	2.4 (0.6)	2.5 (0.6)	2.3 (0.5)	2.4 (0.6)	2.4 (0.6)	2.4 (0.6)
FEV ₁ (% predicted)	n = 51	n = 53	n = 51	n = 50	n = 154	n = 205
	73.7 (7.3)	72.1 (7.0)	71.7 (7.2)	74.0 (6.2)	72.6 (6.8)	72.8 (7.0)
FEV ₁ (% reversibility) [†]	n = 51	n = 51	n = 49	n = 48	n = 148	n = 199
	22.2 (6.4)	24.5 (12.2)	23.3 (9.4)	22.6 (9.5)	23.5 (10.4)	23.2 (9.5)
Eosinophils ($\times 10^3/\mu\text{L}$)	0.2 (0.2)	0.2 (0.2)	0.2 (0.3)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)
Median IgE (IU/mL)	144.8	180.2	115.1	117.4	124.5	138.3
Periostin high,* no. (%)	34 (65.4)	30 (56.6)	28 (52.8)	25 (48.1)	83 (52.5)	117 (55.7)
IL-13 signature surrogate positive, no. (%)	22 (42.3)	22 (41.5)	21 (39.6)	21 (40.4)	64 (40.5)	86 (41.0)
FENO (ppb)	45.5 (35.7)	48.7 (53.0)	41.9 (35.2)	34.5 (34.3)	41.8 (41.9)	42.7 (40.4)
ACQ	2.0 (0.9)	1.7 (0.8)	1.7 (0.7)	1.7 (0.7)	1.7 (0.7)	1.8 (0.8)
PEF (L/min)	n = 52	n = 52	n = 52	n = 52	n = 156	n = 208
	349 (109)	377 (108)	370 (98)	377 (131)	375 (112)	368 (112)
PEF variability	n = 45	n = 46	n = 45	n = 40	n = 131	n = 176
	50.7 (31.3)	50.9 (33.8)	43.0 (24.8)	48.2 (21.5)	47.3 (27.5)	48.2 (28.5)
Reliever medication (inhalations/wk)	2.3 (2.0)	2.0 (1.9)	2.1 (1.6)	2.1 (2.0)	2.1 (1.8)	2.1 (1.9)

Values are means (SDs) unless otherwise stated.

ACQ, Asthma Control Questionnaire.

*Baseline periostin level of the median or greater.

[†]Relative change in FEV₁ after (compared with before) bronchodilator.

parenteral corticosteroids (17/24 [70%] patients). The majority of patients had multiple reasons for treatment failures, with a decrease in PEF being common (14/24 patients or a 58% prevalence) but generally coinciding with at least 1 other factor (see Table E5 in this article's Online Repository at www.jacionline.org). There was no dose response for any of the doses (see Table E6 in this article's Online Repository at www.jacionline.org). Results were similar for the periostin-high group (HR, 0.24; 95% CI, 0.09-0.63; $P < .001$) and the periostin-low group (HR, 0.17; 95% CI, 0.04-0.77; $P = .02$). In the periostin-high group approximately 29% (10/34) of placebo-treated patients experienced treatment failure compared with 8% (7/83) of all lebrikizumab-treated patients. In the periostin-low group approximately 22% (4/18) of placebo-treated patients experienced treatment failure compared with 4% (3/75) of all lebrikizumab-treated patients (Fig 3). When IL-13 signature status was included as a covariate in the Cox proportional hazard model used to analyze time to treatment failure, IL-13 signature status did not contribute to benefit for this end point ($P = .67$).

Other secondary end points. Increases among lebrikizumab-treated patients were seen for change in morning prebronchodilator PEF (6.3% for lebrikizumab vs -0.1% for placebo, $P = .03$), but this did not differentiate doses. Furthermore, analysis by periostin status showed a trend toward improved response in periostin-high patients compared with periostin-low patients (see Fig E1 in this article's Online Repository at www.jacionline.org). The reductions in reliever medication use and Asthma Control Questionnaire scores (indicating improved asthma control) were similar among lebrikizumab- and placebo-treated patients (Table II).

Pharmacokinetic analysis

Pharmacokinetic analyses were conducted with data from 144 evaluable patients who received all 4 doses of lebrikizumab. The

mean trough concentrations at weeks 4 and 8 were very similar at each dose level, suggesting that steady-state conditions were reached before the last dose. The observed concentrations at week 12 were dose proportional, with mean $\pm$ SE values of 15.4 ± 6.9 , 27.0 ± 10.2 , and 51.1 ± 19.4 $\mu\text{g/mL}$ in the 125-, 250-, and 500-mg dose groups, respectively. The mean terminal elimination half-life was approximately 25 days.

Pharmacodynamic analyses can be found in Table E7 and Figs E2 and E3 in this article's Online Repository at www.jacionline.org.

Safety

Lebrikizumab was generally well tolerated, with a similar proportion of patients having 1 or more adverse events (AEs) compared with those receiving placebo (67.7% in the combined lebrikizumab groups vs 67.3% in the placebo group, Table III). A greater proportion of lebrikizumab-treated patients in the 500-mg dose group (75.0%) had 1 or more AEs compared with the 2 lower dose groups (64.2% in both the 125- and 250-mg dose groups). Most AEs were moderate in severity, and of AEs of the highest severity, most were considered not related to the study drug.

Four (2.5%) lebrikizumab-treated patients experienced a total of 6 serious AEs, only 1 of which was considered related to study drug by the investigators; this patient (in the 125-mg dose group) experienced Lofgren syndrome (sarcoidosis). No serious AEs were reported among placebo-treated patients.

Among the 15 patients who discontinued treatment because of an AE, a greater proportion were in the placebo group than in the combined lebrikizumab groups (17.3% vs 3.8%, respectively), noting that patients who met the protocol-defined criteria for treatment failure were required to discontinue treatment. Injection-site reactions were reported in a greater proportion of

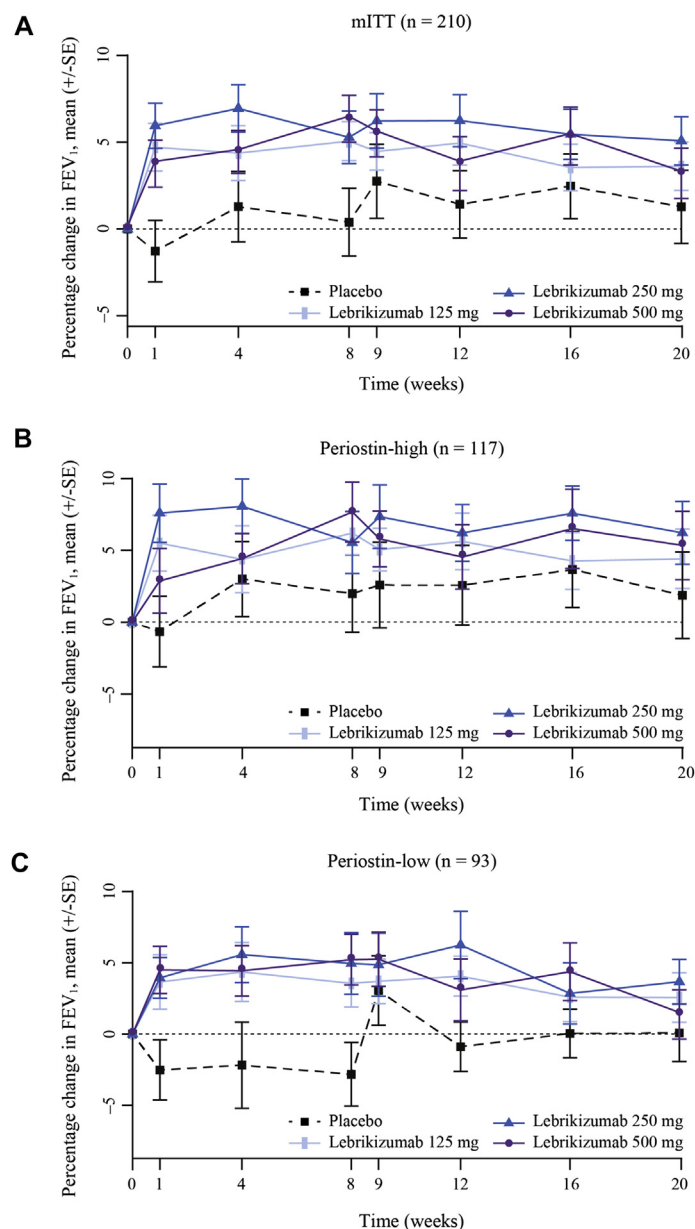


FIG 2. Percentage change in FEV₁ from baseline to week 20: **(A)** mITT; **(B)** periostin-high patients; and **(C)** periostin-low patients.

all lebrikizumab-treated patients than placebo-treated patients (23.4% vs 5.8%). There were no deaths reported in this study.

DISCUSSION

The study demonstrated that 12 weeks of lebrikizumab treatment (125, 250, or 500 mg) was associated with a small increase in FEV₁ in adults with asthma who were not receiving ICS therapy. The improvement in FEV₁ was similar in all lebrikizumab dose groups. The magnitude of treatment effect was lower than expected and was not considered clinically meaningful in comparison with reported improvements after ICSs (approximately 10% placebo-corrected change) or leukotriene receptor antagonists (approximately 7% placebo-corrected change) in a population not previously receiving ICS treatment.^{15,16} Overall, efficacy data did not demonstrate meaningful effects on FEV₁

based on treatment group, dose, or diagnostic subpopulation (serum periostin or IL-13 signature surrogate status).

Lebrikizumab treatment was associated with a significant reduction in the rate of protocol-defined treatment failure compared with placebo, as well as a reduction in FENO levels, indicating a positive effect on some clinical aspects in these patients. Yet there was no differential response in treatment failure by periostin subgroup. There was a small and statistically significant increase in PEF (6.3% placebo-corrected improvement in combined lebrikizumab-treated subjects, $P = .03$), and there appeared a trend toward an increased treatment effect in periostin-high patients. However, these small differences did not translate into improved asthma control, as assessed based on Asthma Control Questionnaire scores or reliever use.

Lebrikizumab inhibited both systemic (IgE, CCL13, and CCL17) and local (FENO) biomarkers of T_H2 inflammation,

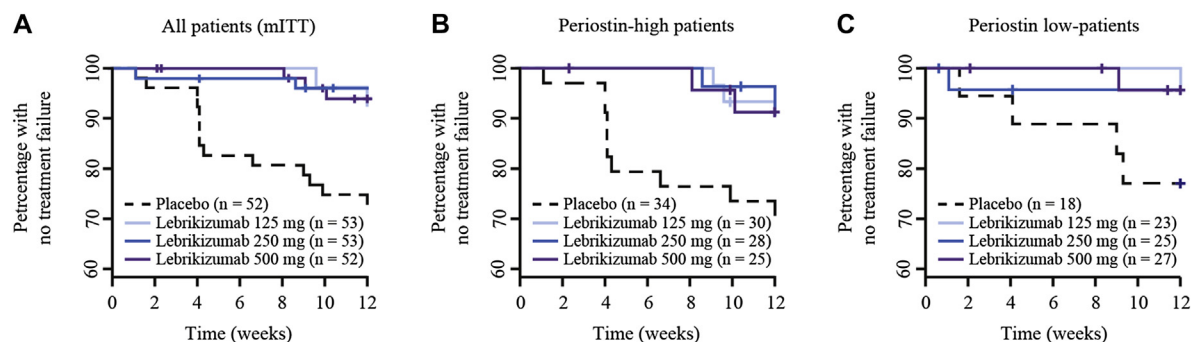


FIG 3. Kaplan-Meier plots of time to treatment failure: (A) mITT; (B) perioestin-high patients; and (C) perioestin-low patients.

TABLE II. Change over 12 weeks in exploratory end points: mITT population

End point	Placebo (n = 52)	Lebrikizumab placebo-corrected changes			
		125 mg (n = 53)	250 mg (n = 53)	500 mg (n = 52)	All doses (n = 158)
Mean percentage change from baseline in morning PEF	-0.1	5.7 (<i>P</i> = .09)	9.5 (<i>P</i> = .09)	3.6 (<i>P</i> = .31)	6.3 (<i>P</i> = .03)
Mean percentage change from baseline in PEF variability	-2.1	-2.5 (<i>P</i> = .85)	10.9 (<i>P</i> = .42)	-2.5 (<i>P</i> = .89)	1.8 (<i>P</i> = .87)
Mean percentage change from baseline in FENO level	11	-48 (<i>P</i> < .001)	-56 (<i>P</i> < .001)	-41 (<i>P</i> = .02)	-49 (<i>P</i> < .001)
Mean change in reliever medication use (inhalations/d)	-0.6	-0.3 (<i>P</i> = .40)	0 (<i>P</i> = .99)	-0.7 (<i>P</i> = .09)	-0.3 (<i>P</i> = .29)
Mean change in ACQ score	-0.4	-0.2 (<i>P</i> = .34)	-0.1 (<i>P</i> = .64)	-0.4 (<i>P</i> = .06)	-0.2 (<i>P</i> = .21)

ACQ, Asthma Control Questionnaire.

TABLE III. Summary of AEs

	Placebo (n = 52)	Lebrikizumab			
		125 mg (n = 53)	250 mg (n = 53)	500 mg (n = 52)	All doses (n = 158)
Any AE	35 (67.3)	34 (64.2)	34 (64.2)	39 (75.0)	107 (67.7)
SAEs	0	3 (5.7)	0	1 (1.9)	4 (2.5)
SAEs related to study drug	0	1 (1.9)	0	0	1 (0.6)
Discontinuation of treatment caused by AEs*	9 (17.3)	0	2 (3.8)	4 (7.7)	6 (3.8)
Mild AEs	13 (25.0)	15 (28.3)	12 (22.6)	15 (28.8)	42 (26.6)
Mild related AEs	6 (11.5)	5 (9.4)	11 (20.8)	8 (15.4)	24 (15.2)
Moderate AEs	20 (38.5)	17 (32.1)	22 (41.5)	22 (42.3)	61 (38.6)
Moderate related AEs	2 (3.8)	4 (7.5)	10 (18.9)	6 (11.5)	20 (12.7)
Severe AEs	2 (3.8)	2 (3.8)	0	2 (3.8)	4 (2.5)
Severe related AEs	0	1 (1.9)	0	2 (3.8)	3 (1.9)
Deaths	0	0	0	0	0

Values are presented as numbers (percentages). Multiple occurrences of a specific AE for a patient were counted once at the highest severity. The table includes AEs that started on or after the first treatment with study drug.

SAE, Serious adverse event.

*Number of patients with AEs as the primary reason for discontinuation.

demonstrating IL-13 pathway modulation, with all 3 dose levels achieving similar effects, suggesting maximal biomarker responses were achieved in these patients. Concordant with the primary efficacy result, there was no evidence of a dose-response relationship in the analyses of secondary and exploratory end points, indicating that the maximum effect of IL-13 blockade was achieved with the lowest dose (125 mg) in these patients.

Although the trough concentrations achieved with the 125-mg dose are at least 50-fold higher than a theoretic target concentration that would neutralize IL-13 and block IL-13 activity in the lung, given the uncertainties in the IL-13 levels in lung tissue of asthmatic patients and the serum-to-lung partitioning of the injected lebrikizumab, the true target lebrikizumab exposure is yet to be established. On the basis of limited pharmacodynamic data in phase I studies, we expected that the low dose, 125 mg, would show a minimal clinical effect, whereas the 2 higher doses, 250 and 500

mg, would allow us to evaluate whether the plateau of the dose response had been reached.

The lack of a dose response in this study suggests that in the non-ICS-treated asthmatic patient population, these responses were likely to be saturated at the exposure levels achieved by 125 mg of lebrikizumab and greater every 4 weeks (>30 µg/mL). Interestingly, the effects of lebrikizumab on serum IgE, CCL13, CCL17, and FENO levels and blood eosinophil numbers were very similar in the current study in patients not taking ICSs and in the study investigating lebrikizumab in patients whose symptoms were uncontrolled despite ICSs.⁸ These data suggest that the IL-13 activity present in both patient populations is similarly blocked by lebrikizumab. However, the differential responses of lebrikizumab observed on FEV₁ in the 2 studies suggest that IL-13 or the interaction of ICSs and IL-13 might play a different role in driving FEV₁ responses in these 2 different patient populations. It is important to recognize

that the dose response of lebrikizumab could also be different in patients taking ICSs compared with the current patient population.

In the phase II placebo-controlled study of lebrikizumab in patients whose symptoms were inadequately controlled despite ICSs, a significant improvement in FEV₁ after lebrikizumab treatment was seen, particularly in the periostin-high patients.⁸ One hypothesis for the difference in response seen in that study is that the patients enrolled likely had residual IL-13 activity that ICSs were not able to fully suppress. Thus the patients might have had a relative steroid insensitivity. Blocking IL-13 in those steroid-insensitive patients, particularly in the periostin-high patients, might be associated with a more pronounced effect on FEV₁. In asthmatic patients who are not receiving ICSs, this study suggests that IL-13 is not a dominant driver of lung function, but in a proportion of these patients, treatment failure is more likely to be prevented by IL-13 inhibition. The majority of the patients enrolled in this study would be expected to be steroid sensitive, as evidenced by the proportion who typically respond to ICSs.¹⁸ In these steroid-sensitive patients, the contribution of IL-13 to disease activity might be relatively small, as measured by FEV₁, because steroids affect multiple genes in the airway, either directly or indirectly.^{19,20}

Additionally, this study was powered at 70% to detect a 10% increase in FEV₁ in the IL-13 signature surrogate-positive group. Given the small effect size, this study had insufficient power to detect differences between periostin-high and periostin-low groups. However, on the basis of the ability to neutralize IL-13 and block IL-13 activity in the lung, the study was expected to show an improvement in FEV₁ and to elucidate whether the 125-mg dose was less effective than the 250- and 500-mg doses. It was also expected that the IL-13 signature surrogate-positive group would show a greater FEV₁ improvement. The results reported here do not provide clear insight as to why the effects of lebrikizumab on FEV₁ were not greater in this study or why the response could not be predicted by serum biomarkers of IL-13 activity in the lung in this group of patients.

The placebo-corrected increase in FEV₁ was numerically higher in the periostin-low group than in the periostin-high group (5.3% vs 2.9%, respectively), but CIs around both estimates were wide and overlapping. It is notable that lebrikizumab-treated patients had a similar effect size in the periostin-high and periostin-low groups (5.5% vs 4.4%, respectively), whereas placebo-treated patients had a greater difference between groups (2.6% for the periostin-high group and -0.9% for the periostin-low group). The limited number of placebo-treated patients in the periostin-low group (n = 18) contributed uncertainty to the estimates in that group. The imbalance in periostin-high and periostin-low patients, particularly in the placebo group, was likely a consequence of having to use the combination of IgE levels and peripheral blood eosinophil numbers at randomization as a surrogate for IL-13 activity because the periostin assay was not ready for use at trial initiation. Taken together, these limitations preclude reliable conclusions from this study about the predictive value of periostin for clinically meaningful benefit from lebrikizumab in patients not taking ICSs, as measured by changes in lung function (FEV₁).

Overall, lebrikizumab was largely well tolerated and did not reveal a specific safety concern. There was an increase in the number of injection-site reactions in lebrikizumab-treated patients, but these were not persistent and in most cases did not require treatment.

In conclusion, in this study lebrikizumab did not significantly increase FEV₁, and the study did not meet the objectives for demonstrating a dose response. The patients included in this study were not receiving ICSs, and it appears that blocking IL-13, a single cytokine, in this population is insufficient to improve FEV₁ compared with existing treatments. Lebrikizumab provided a notable protection against treatment failure. Thus although lebrikizumab did not significantly affect the primary end point of FEV₁, there was an indication of a positive effect on the clinical course of these patients. It is likely that these effects overall would not be superior to ICS treatment in this patient population. The study did demonstrate pharmacodynamic effects similar to those seen in patients who were symptomatic despite ICS treatment. The study emphasizes the heterogeneous nature of asthma and the need for predictive biomarkers that are relevant and specific for a treatment targeting an asthma subgroup.

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Clinical implications: Lebrikizumab did not improve lung function in patients with asthma not receiving ICSs in this study. Lebrikizumab is currently being developed for patients with severe asthma with a companion diagnostic (serum periostin).

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METHODS

Definition of stable asthma

Stable asthma was defined as diagnosis of asthma at least 12 months before day -14; bronchodilator response at days -14, -7, and 1 (before treatment); and relative change in prebronchodilator FEV₁ from day -7 to day 1 (before treatment) had to be less than 15%. Relative change in mean morning prebronchodilator PEF between days -14 and -7 had to be less than 20% of the mean prebronchodilator PEF between day -7 and day 1 (before treatment), daily use of SABA therapy had to be less than 10 inhalations or 2 or less nonscheduled administrations of nebulized SABA therapy, and there could have been no required ICSs or oral or parenteral corticosteroids.

These criteria have been established as useful to investigate novel asthma therapeutics where there is a reasonable expectation that FEV₁ will be improved. Patients are selected with a deficit in lung function, but reversibility is selected for at least 15%. The asthma stability for FEV₁ and SABA use were defined to help ensure that the study could be reasonably powered for a change from baseline of 10% in FEV₁ as the primary end point.

Exclusion criteria

Patients previously managed with ICS therapy could not have received ICSs for 30 or more days before the first study visit. The study did not mandate ICS withdrawal; patients were not to be taken off ICSs for the sole purpose of becoming eligible for the study. Further exclusion criteria included no respiratory tract infections during screening, known malignancy or immunodeficiency, pre-existing lung disease other than asthma, uncontrolled clinically significant medical disease, current or former smoking status with a greater than 10 pack year history, use of prohibited concomitant medications, pregnancy, or unwillingness to use highly effective contraception.

Pharmacodynamic analyses

Serum total IgE levels were measured by using a standard *in vitro* diagnostic ImmunoCAP assay (Phadia, Portage, Mich). Serum CCL17 and CCL13 levels were determined by means of ELISA (R&D Systems, Minneapolis, Minn). Peripheral blood eosinophil counts were obtained from standard complete blood counts. FENO measurements were performed with a hand-held portable device (NIOX MiNO; Aerocrine, Solna, Sweden). For each marker, mean change from baseline and corresponding SEs were calculated and plotted by treatment group at each visit.

Statistical analysis

Demographic and baseline characteristics were summarized for all randomized patients by treatment group by using descriptive statistics.

The primary end point was analyzed by reporting the mean relative changes from baseline to week 12 by treatment group, along with the treatment effect size, *P* value, and corresponding 2-sided 95% CIs.

The proportion of subjects with treatment failure was estimated by using Kaplan-Meier methodology. HRs were estimated with a Cox regression model with IL-13 signature surrogate as the stratification factor. *P* values and 95% CIs were estimated by using a stratified log-rank test.

RESULTS

Pharmacodynamic responses

Lebrikizumab administration resulted in an immediate reduction in FENO and serum CCL17 and CCL13 levels (10% to 40% median reduction compared with predose levels, [Table E7](#)). Serum IgE levels were reduced more gradually after lebrikizumab administration, reaching a median reduction from baseline of 12% at week 12 in all lebrikizumab-treated patients.

The magnitude of response to lebrikizumab treatment for these pharmacodynamic biomarkers was similar across all doses, and the effects were sustained through week 20 ([Figs E2 and E3](#)), with the exception of CCL17; serum CCL17 levels appeared to return toward baseline values at the end of the study (week 20).

Baseline FENO levels were higher in the periostin-high group (35 and 48 ppb in the all lebrikizumab dose and placebo groups, respectively) than in the periostin-low group (23 and 19 ppb, respectively). The median relative change from baseline in FENO levels among lebrikizumab-treated patients was also greater in the periostin-high group than in the periostin-low group (53% vs 42% reductions at week 12, respectively). There was a slight increase but no dose response of lebrikizumab on peripheral blood eosinophil numbers ([Figs E2 and E3](#)).

Dose response

There were no statistically significant differences observed in any of the efficacy and pharmacodynamic measurements between the lebrikizumab-treated dose groups.

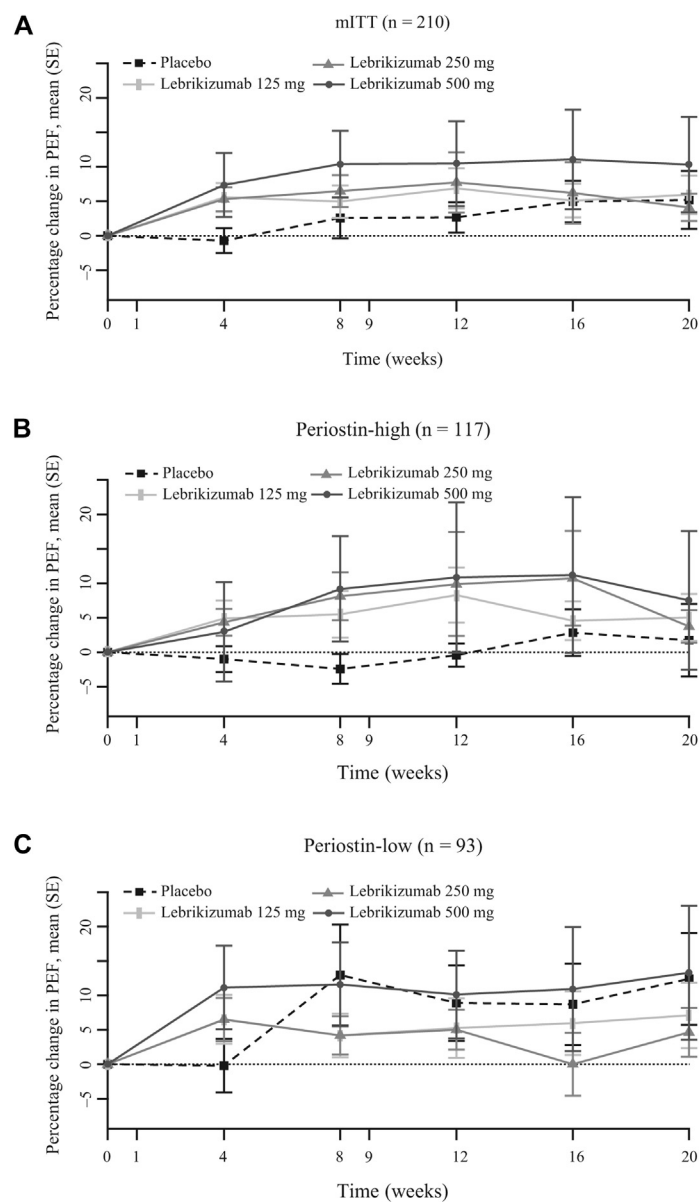


FIG E1. Percentage change in PEF from baseline to week 20: **(A)** mITT; **(B)** periostin-high patients; and **(C)** periostin-low patients.

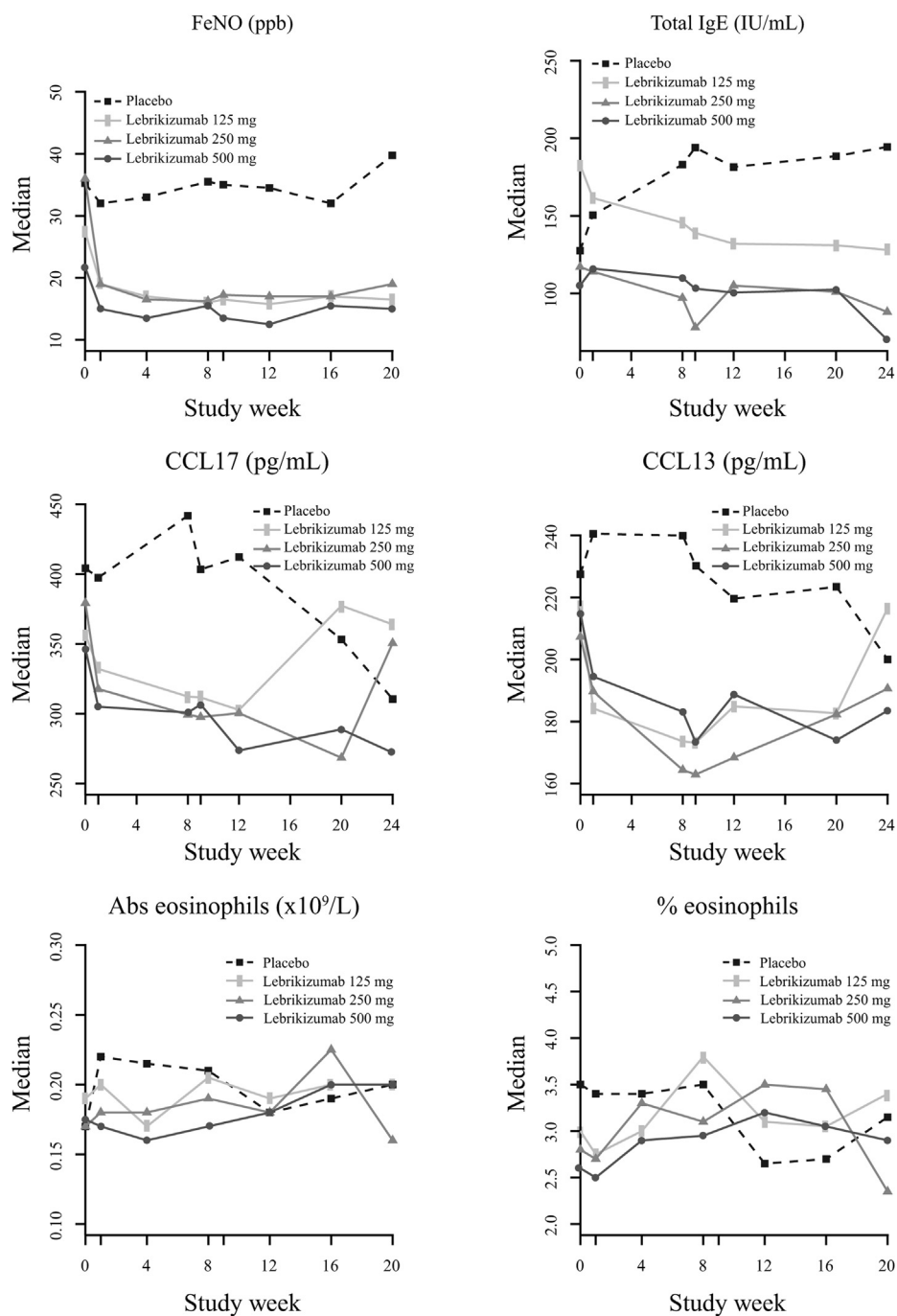


FIG E2. Median values of pharmacodynamic biomarkers during the study.

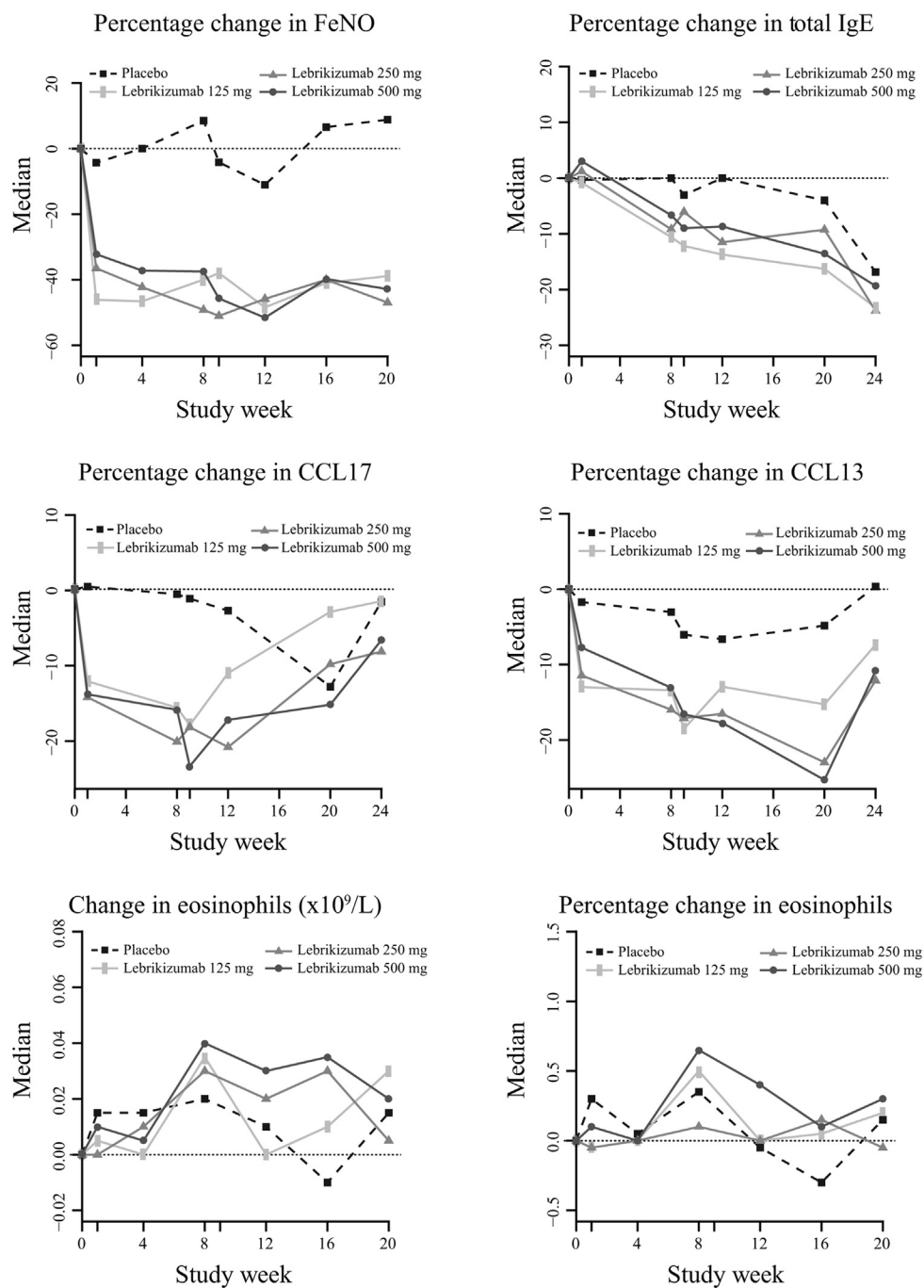


FIG E3. Median change from baseline of pharmacodynamic biomarkers after treatment.

TABLE E1. Patient stratification by IL-13 signature surrogate and periostin status

	Placebo (n = 52)	Lebrikizumab				All patients (mITT [n = 210])
		125 mg (n = 53)	250 mg (n = 53)	500 mg (n = 52)	All doses (n = 158)	
IL-13 signature surrogate positive, no. (%)	22 (42.3)	22 (41.5)	21 (39.6)	21 (40.4)	64 (40.5)	86 (41.0)
Periostin high,* no. (%)	34 (65.4)	30 (56.6)	28 (52.8)	25 (48.1)	83 (52.5)	117 (55.7)

*Baseline periostin level of the median or greater.

TABLE E2. Relative change from baseline in FEV₁ (in liters) by IL-13 surrogate signature (mITT population) at week 12

	Placebo (n = 52)	Lebrikizumab, 125 mg (n = 53)	Difference vs placebo	Lebrikizumab, 250 mg (n = 53)	Difference vs placebo	Lebrikizumab, 500 mg (n = 52)	Difference vs placebo	All lebrikizumab doses (n = 158)	Difference vs placebo
All subjects	1.4 (13.9)	4.9 (9.2)	3.5 (−1.1 to 8.1), <i>P</i> = .132	6.2 (10.7)	4.8 (−0.1 to 9.7), <i>P</i> = .053	3.8 (11.0)	2.3 (−2.6 to 7.3), <i>P</i> = .348	5.0 (10.3)	3.6 (−0.6 to 7.8), <i>P</i> = .095
IL-13 surrogate signature positive	1.6 (17.4)	6.4 (8.3)	4.9 (−3.5 to 13.3), <i>P</i> = .245	8.5 (9.7)	7.0 (−1.8 to 15.7), <i>P</i> = .114	4.7 (9.0)	3.1 (−5.5 to 11.7), <i>P</i> = .470	6.6 (9.0)	5.0 (−3.0 to 13.0), <i>P</i> = .210
IL-13 surrogate signature negative	1.3 (10.7)	3.9 (9.8)	2.6 (−2.7 to 7.9), <i>P</i> = .337	4.6 (11.3)	3.3 (−2.4 to 9.1), <i>P</i> = .251	3.2 (12.2)	1.9 (−4.1 to 7.8), <i>P</i> = .537	3.9 (11.0)	2.6 (−2.0 to 7.2), <i>P</i> = .267

TABLE E3. Study completion status and reasons for patient termination from the study: mITT population

	Placebo (n = 52)	Lebrikizumab				mITT* (n = 210)
		125 mg (n = 53)	250 mg (n = 53)	500 mg (n = 52)	All doses (n = 158)	
Patients who completed the study, no. (%)	42 (80.8)	50 (94.3)	48 (90.6)	44 (84.6)	142 (89.9)	184 (87.6)
Patients who discontinued from the study, no. (%)	10 (19.2)	3 (5.7)	5 (9.4)	8 (15.4)	16 (10.1)	26 (12.4)
Reason for discontinuation, no. (%)						
AE	8 (15.4)	0	2 (3.8)	3 (5.8)	5 (3.2)	13 (6.2)
Lost to follow-up	1 (1.9)	2 (3.8)	1 (1.9)	0	3 (1.9)	4 (1.9)
Patient decision	1 (1.9)	1 (1.9)	2 (3.8)	5 (9.6)	8 (5.1)	9 (4.3)

*Patients receiving at least 1 dose of study drug.

TABLE E4. AEs leading to study discontinuation

AE resulting in discontinuation	Placebo	Lebrikizumab
Asthma	7	1 (and sinusitis)
Hepatitis, alcoholic	1	—
Diabetes mellitus	—	1
Upper respiratory tract infection	—	1
Injection-site erythema	—	1
Injection-site pruritus	—	1

TABLE E5. Reasons for treatment failure

	Lebrikizumab (n = 10)	Placebo (n = 14)	Total (n = 24)
Systemic steroid use	7 (70%)	10 (71%)	17 (70%)
Decrease in FEV ₁	0	6 (43%)	6 (25%)
Decrease in PEF	5 (50%)	9 (64%)	14 (58%)
SABA use	2 (20%)	5 (36%)	7 (29%)

TABLE E6. Analysis of treatment failures by dose

Treatment group	All patients		Periostin-high patients		Periostin-low patients	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Lebrikizumab, 125 mg (n = 53)	0.24 (0.08-0.72)	.01	0.27 (0.07-1.00)	.05	0.13 (0.01-1.23)	.08
Lebrikizumab, 250 mg (n = 53)	0.20 (0.06-0.69)	.01	0.21 (0.05-0.94)	.04	0.24 (0.03-2.18)	.21
Lebrikizumab, 500 mg (n = 52)	0.19 (0.06-0.68)	.01	0.24 (0.05-1.09)	.06	0.17 (0.02-1.55)	.12
All lebrikizumab doses (n = 158)	0.21 (0.09-0.47)	<.001	0.24 (0.09-0.63)	<.001	0.17 (0.04-0.77)	.02

TABLE E7. Median percentage change in IL-13-associated biomarkers from baseline to week 12: mITT population

Pharmacodynamic biomarker	Placebo (n = 36)	Lebrikizumab			
		125 mg (n = 48)	250 mg (n = 46)	500 mg (n = 44)	All doses (n = 138)
IgE	0	−14	−12	−9	−12
Eosinophils, absolute	8	0	12	17	13
Eosinophils (%)	−1	0	0	11	6
CCL13	−7	−13	−17	−18	−16
CCL17	−3	−11	−21	−17	−17
FENO	−11	−48	−46	−52	−48

All values are median percentage changes. Note: *n* is the number of patients with at least 1 nonmissing biomarker value at week 12.