ORIGINAL ARTICLE

Lebrikizumab Treatment in Adults with Asthma

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ABSTRACT

BACKGROUND

Many patients with asthma have uncontrolled disease despite treatment with inhaled glucocorticoids. One potential cause of the variability in response to treatment is heterogeneity in the role of interleukin-13 expression in the clinical asthma phenotype. We hypothesized that anti–interleukin-13 therapy would benefit patients with asthma who had a pretreatment profile consistent with interleukin-13 activity.

METHODS

We conducted a randomized, double-blind, placebo-controlled study of lebrikizumab, a monoclonal antibody to interleukin-13, in 219 adults who had asthma that was inadequately controlled despite inhaled glucocorticoid therapy. The primary efficacy outcome was the relative change in prebronchodilator forced expiratory volume in 1 second (FEV_1) from baseline to week 12. Among the secondary outcomes was the rate of asthma exacerbations through 24 weeks. Patient subgroups were prespecified according to baseline type 2 helper T-cell (Th2) status (assessed on the basis of total IgE level and blood eosinophil count) and serum periostin level.

RESULTS

At baseline, patients had a mean FEV_1 that was 65% of the predicted value and were taking a mean dose of inhaled glucocorticoids of 580 μg per day; 80% were also taking a long-acting beta-agonist. At week 12, the mean increase in FEV_1 was 5.5 percentage points higher in the lebrikizumab group than in the placebo group (P=0.02). Among patients in the high-periostin subgroup, the increase from baseline FEV_1 was 8.2 percentage points higher in the lebrikizumab group than in the placebo group (P=0.03). Among patients in the low-periostin subgroup, the increase from baseline FEV_1 was 1.6 percentage points higher in the lebrikizumab group than in the placebo group (P=0.61). Musculoskeletal side effects were more common with lebrikizumab than with placebo (13.2% vs. 5.4%, P=0.045).

CONCLUSIONS

Lebrikizumab treatment was associated with improved lung function. Patients with high pretreatment levels of serum periostin had greater improvement in lung function with lebrikizumab than did patients with low periostin levels. (Funded by Genentech; ClinicalTrials.gov number, NCT00930163.)

Asthma is a complex disease with marked heterogeneity in the clinical course and in the response to treatment.[1-9] Variability in the type of airway inflammation may underlie this heterogeneity.[2-5] Despite treatment with inhaled glucocorticoids, many patients continue to have uncontrolled asthma that requires more intensive therapy.[10]

Interleukin-13, a pleiotropic cytokine of type 2 helper T cells (Th2), has been thought to contribute to many key features of asthma.[11] Production of interleukin-13 is inhibited by inhaled glucocorticoids, but these agents also have many other effects on the airways. Some patients with uncontrolled asthma continue to have elevated levels of interleukin-13 in the sputum, despite the use of systemic and inhaled glucocorticoids,[12] a finding that is consistent with the hypothesis that interleukin-13 can contribute to resistance to glucocorticoids.[13-16]

Interleukin-13 induces bronchial epithelial cells to secrete periostin, a matricellular protein.[17,18] Activated airway epithelial cells secrete large quantities of periostin basally into the underlying matrix, where it has autocrine effects on epithelial-cell function and paracrine effects on fibroblasts.[18] Thus, periostin may contribute to the mechanisms of airway remodeling in asthma.[18,19]

To evaluate the biologic and clinical relevance of interleukin-13 in patients with uncontrolled asthma despite treatment with medium-dose to high-dose inhaled glucocorticoids, we used lebrikizumab, an IgG4 humanized monoclonal antibody that specifically binds to interleukin-13 and inhibits its function[20] (CAS number 953400-68-5; http://www.ama-assn.org/resources/doc/usan/lebrikizumab.pdf; see section on Functional Characterization, as well as Fig. S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Lebrikizumab has been altered by a single point mutation in the hinge region to increase the stability of the molecule.[21] We conducted a randomized, controlled trial to determine whether treatment with lebrikizumab would improve the control of asthma. We examined all enrolled patients as a group and then stratified the patients according to baseline serum periostin level. We used this marker as a surrogate for interleukin-13 activity because highly sensitive assays are required to quantify interleukin-13 in blood or airway samples.[22]

METHODS

STUDY OVERSIGHT

The study protocol was designed, written, and edited, and the data were stored and analyzed, by employees of the sponsor (Genentech). The clinical investigators reviewed the protocol and collected the data. One clinical investigator and one industry author wrote the first draft of the manuscript; all the authors reviewed and approved all subsequent drafts and made the decision to submit the manuscript for publication. All authors vouch for the accuracy and completeness of the reported data and for the fidelity of this report to the study protocol and statistical analysis plan. A third party was hired by the sponsor to provide assistance with the writing of the manuscript. All the clinical investigators signed a confidentiality agreement with the sponsor. The study protocol and statistical analysis plan are available at NEJM.org. The protocol was reviewed and approved by the institutional review board for each participating center, and all participants provided written informed consent.

STUDY DESIGN

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study (Fig. 1). Before randomization, each patient's status with respect to an interleukin-13 signature surrogate (henceforth termed Th2 status) was characterized on the basis of a combination of the total serum IgE level and peripheral-blood eosinophil count[23]; high Th2 was defined as a total IgE level of more than 100 IU per milliliter and an eosinophil count of 0.14×10^9 cells per liter or more; low Th2 was defined as a total IgE level of 100 IU per milliliter or less or eosinophil count of less than 0.14×10^9 cells per liter (Fig. S3 and Table S2 in the Supplementary Appendix). Patients were randomly assigned, in a 1:1 ratio, to receive lebrikizumab or placebo on the basis of a dynamic randomization scheme. Randomization was balanced through stratification according to the following hierarchy: Th2 status (high vs. low), use or no use of long-acting beta-agonists, and study site.

PATIENTS

Eligible patients had asthma diagnosed by a physician, at least a 12% increase in the forced expiratory volume in 1 second (FEV_1) after inhalation of a short-acting bronchodilator, and prebronchodilator FEV_1 between 40% and 80% (inclusive) of the pre-

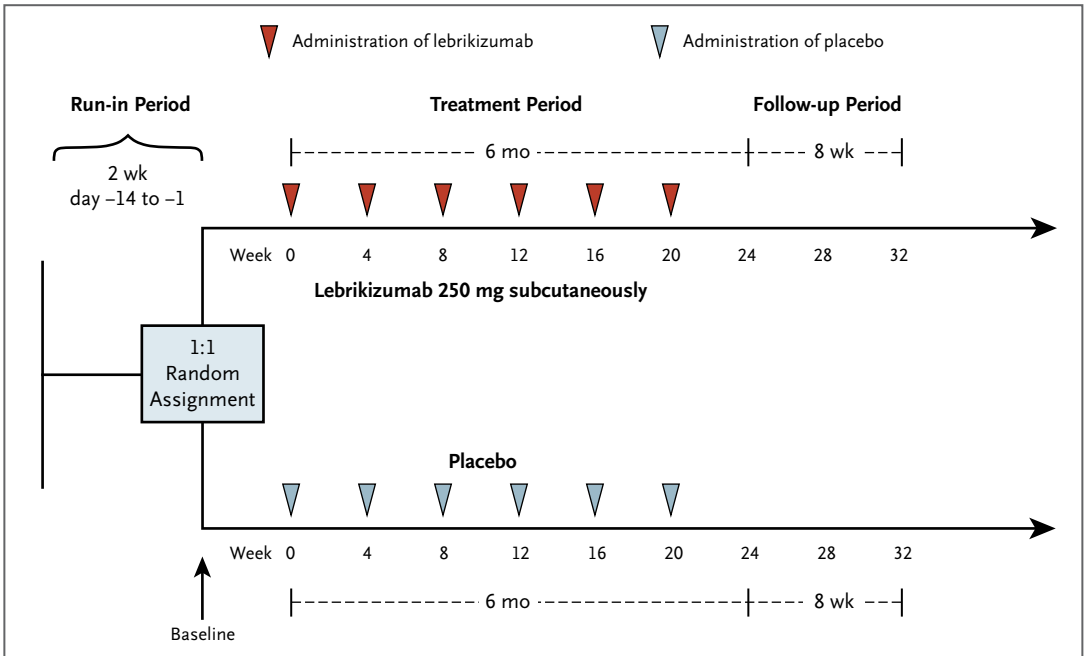

Figure 1. Schematic Representation of the Study Design.

Eligibility of the patients was established during a 2-week run-in period. This period was followed by a double-blind, randomized, placebo-controlled treatment period (day 1 to week 24) during which patients recorded their peak expiratory flow twice a day, as well as symptoms of asthma once a day. At monthly study visits through week 24, assessments included spirometry, safety evaluation, blood testing, measurement of Fe_{NO}, and outcome questionnaires; at the visits through week 20, the study drug was also administered. Safety and efficacy continued to be monitored during the follow-up period (week 24 to week 32).

dicted value at the time of randomization (see the study protocol). Other eligibility criteria included the use for at least 6 months of inhaled glucocorticoids (≥200 and ≤1000 μg of inhaled fluticasone propionate daily, administered by means of a dry-powder inhaler, or a nominal equivalent) and evidence of uncontrolled asthma on the day of randomization. Uncontrolled asthma was defined as a score on the symptom-only version of the Asthma Control Questionnaire 5 (ACQ5) of 1.5 or higher, on a scale of 0 to 6, with higher scores indicating poorer control of asthma; the minimal clinically important difference on the ACQ5 is 0.50 points.[24,25] Patients taking long-acting beta-agonists and leukotriene modifiers were not excluded. Detailed descriptions of the inclusion and exclusion criteria are provided in the study protocol.

STUDY TREATMENTS

Lebrikizumab (at a dose of 250 mg) or placebo was given subcutaneously once a month for a total of 6 months. The placebo contained sterile water and the same excipients as the lebrikizumab formulation. The study drug was supplied in a kit, with a unique kit code number; vials of lebrikizumab and placebo were identical and contained the same volume of solution. Randomization codes were concealed from all staff members at the investigational sites and from staff members of the sponsor who had access to site information and patient data. Monitoring visits were conducted regularly to ensure the integrity of the blinded treatment given to the patients at randomization and to ensure that at subsequent visits the patients received the study drug assigned to them. The doses of inhaled glucocorticoids and any other asthma treatments (e.g., long-acting beta-agonists) were not altered during the run-in period to enable patients to meet the criteria for eligibility, nor were they altered throughout the 24-week treatment period.

ASSESSMENTS

Assessments included spirometry, measurement of the fraction of exhaled nitric oxide (Fe_{NO}), measurement of peak exploratory flow, and the score

on the Asthma Control Daily Diary (ACDD) questionnaire, which patients completed twice a day. The scores for asthma symptoms on the ACDD range from 1 to 5, with higher scores indicating worse symptoms. The scores for rescue medications range from 0 to 8, with higher scores representing a larger number of puffs of inhaler or nebulizer used; a score of 8 was assigned when the diary was scored as "more than 6." There is currently no established minimum clinically important difference for the ACDD. Details of these procedures are provided in the section on Assessment Procedures, as well as in Table S1, in the Supplementary Appendix.

OUTCOMES

The primary efficacy outcome was the relative change in prebronchodilator FEV_1 from baseline to week 12. This was calculated as the absolute change in FEV_1 (volume in liters) from baseline to week 12 divided by the FEV_1 at baseline. Secondary prespecified outcomes included the rates of protocol-defined exacerbations and severe exacerbations through week 24, morning prebronchodilator peak exploratory flow, change in ACQ5 score from baseline to week 12, asthma symptom score as assessed by means of the ACDD, and use of rescue medication (as assessed by means of the ACDD). Analyses of all these outcomes in the total cohort and in subgroups according to Th2 status and periostin level were prespecified in the statistical analysis plan. Post hoc exploratory outcomes included exhaled F_{ENO}; weekly frequency of nocturnal awakening due to asthma (as assessed by means of the ACDD); serum CCL13 (MCP-4), CCL17 (TARC), and IgE levels and peripheral-blood eosinophil counts at week 12; and postbronchodilator FEV_1 at week 20.

Exacerbations were defined in the protocol as worsening asthma symptoms and at least one of the following: an increase in the use of short-acting $beta_2$-agonists to eight or more puffs of an albuterol metered-dose inhaler (or equivalent) over a 24-hour period, initiation of nebulizer therapy or an increase in current nebulizer therapy by one or more treatments over a 24-hour period as compared with baseline, an unscheduled outpatient visit for asthma, or a 20% decline from baseline in the peak exploratory flow that persisted for 2 or more consecutive days. Severe exacerbations were defined as asthma symptoms requiring hospitalization, overnight or for a longer period, for the treatment of asthma or requiring high-dose inhaled glucocorticoid therapy (at least a quadrupling of the total daily dose for ≥3 consecutive days) or oral or parenteral glucocorticoid therapy.

STATISTICAL ANALYSIS

The primary analysis was conducted with data from the intention-to-treat population, which included all patients who received at least one dose of the study drug. Assuming a standard deviation of 19%, a two-sided alpha level of 0.15, and a 5% dropout rate at week 12, we estimated that approximately 200 patients would need to be enrolled for the study to have 95% power to detect a between-group difference of 10% in the change in FEV_1 from baseline in the total cohort. With this sample size, we estimated that the study would also have 70% power to detect a between-group difference of 10% in the relative change in FEV_1 in a subset of patients with high Th2 that could include as few as 30% of all patients. Because the serum periostin assay was not yet available when this study was initiated, Th2 status was used as a surrogate measure of interleukin-13 activity and was defined on the basis of a combination of two clinically available assays (serum IgE level and peripheral-blood eosinophil count)[23] (Table S2 and Fig. S3 in the Supplementary Appendix). Before the treatment codes were broken, the statistical analysis plan prespecified an assessment of outcomes, to be performed on the basis of the patients' status with respect to the periostin level, with the use of the median value for all patients to define the cutoff point between the high-periostin subgroup (median value or higher) and the low-periostin subgroup (less than the median value).

The means (±SD) of all values for relative change were calculated according to study group at weeks 1, 4, 8, 12, 16, 20, 21, and 24 and at the follow-up visits (weeks 28 and 32); the week-12 analysis was prespecified as the primary analysis. The mean relative changes from baseline were compared between the study groups by a calculation of the differences between the means for each group, with the associated two-sided 95% confidence intervals. Missing values for the change in FEV_1 were imputed with the use of the last-observation-carried-forward approach, as prespecified in the statistical analysis plan. An analysis-of-covariance model with factors for treatment, periostin level, and the interaction of treatment with periostin level was fit to assess the heterogeneity of treatment effects across baseline periostin levels[26]

Table 1. Baseline Demographic and Clinical Characteristics of All Patients Who Underwent Randomization.*

Characteristic	Total Cohort (N=219)	Placebo Group (N=112)	Lebrikizumab Group (N=107)	P Value
Age (yr)	44±12	44±13	45±12	0.48
Sex (%)				0.81
Female	66	67	65	
Male	34	33	35	
Race (%)†				1.00
White	85	85	85	
Black	14	14	14	
Asian	0.9	0.9	0.9	
Weight (kg)	86±19	85±19	87±19	0.59
IgE (IU/ml)‡	182	232	166	0.09
High periostin level (%)§	52	54	51	0.60
FEV_1 (% of predicted value)	65±11	66±10	64±12	0.21
Use of LABAs (%)	81	80	81	0.86
Use of leukotriene modifiers (%)	25	21	29	0.35
Glucocorticoids (μg/day)				
Median	500	500	500	
Mean	580±272	621±276	537±262	0.02
High-dose: ≥500 μg of fluticasone propionate–equivalent (%)	60	66	53	0.05
FE_{NO} (ppb)¶	30.7±26.2	30.4±27.7	31.0±24.6	0.87
FEV_1 (% reversibility)‖	25.6±14.2	24±10.7	27.3±17.1	0.09
ACQ5 score**	2.5±0.9	2.5±0.9	2.5±0.9	0.97
Positive skin test (%)††	83	82	84	0.74

* Plus–minus values are means ±SD, except as otherwise noted. FE_{NO} denotes fraction of exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, and LABA long-acting beta-agonist.
† Race was self-reported.
‡ The median level is shown. Data were missing for one patient in the lebrikizumab group.
§ High periostin levels were defined as values above the median for the 212 patients with nonmissing values. Data were missing for three patients in the placebo group and four in the lebrikizumab group.
¶ Data were missing for two patients in the placebo group and four in the lebrikizumab group.
‖ Percent reversibility refers to the increase in FEV_1 in response to 400 μg of albuterol (or salbutamol or other short-acting beta-agonist) in divided doses relative to prebronchodilator FEV_1 at least 15 minutes after, and no more than 30 minutes after, the last bronchodilator administration.
** Scores on the Asthma Control Questionnaire 5 (ACQ5) range from 0 to 6, with higher scores indicating poorer control of asthma. The minimal clinically important difference is 0.50 points.[25] Data were missing for one patient in each group.
†† Skin tests were performed in 74 patients in the placebo group and 71 in the lebrikizumab group.

(Table 1, and Table S3 in the Supplementary Appendix).

The rates of protocol-defined exacerbations of asthma during the 24-week treatment period were estimated by dividing the total number of such exacerbations in each group over the course of the treatment period by the total patient-weeks at risk for the group. The first dose of study drug had to be given within 24 hours after randomization. For each patient, the weeks at risk were computed by calculating the number of days between the first administration of the study drug and the date of completion or termination of treatment (whichever came first) and dividing that number by 7 days. In the case of patients who discontinued the study prematurely, there was no imputation of additional exacerbations. The rates of asthma exacerbations were compared between study groups with the use of a Poisson regression model with overdispersion. Reductions in the rate of exacerbations of asthma

were calculated by exponentiation of the coefficient for the treatment group, and corresponding two-sided 95% confidence intervals are reported. Safety events were monitored for up to 32 weeks after randomization, and the rates of adverse events through week 32 were compared between patients who received placebo and those who received lebrikizumab.

RESULTS

PATIENTS

A total of 219 patients underwent randomization, of whom 218 received at least one dose of a study drug (1 patient in the lebrikizumab group received no study drug) (Fig. S4 in the Supplementary Appendix). The baseline characteristics of the study groups are shown in Table 1. The median dose of inhaled glucocorticoids and the types of inhaled glucocorticoids that were used were similar in the two groups; however, the percentage of patients receiving a high dose of inhaled glucocorticoids (≥500 μg of fluticasone propionate–equivalent) was greater in the placebo group than in the lebrikizumab group (66% vs. 53%, P=0.05), leading to a higher mean dose of glucocorticoids in the placebo group than in the lebrikizumab group (621 μg vs. 532 μg, P=0.02) (Table 1, and Fig. S5 in the Supplementary Appendix). Approximately 80% of the patients were also treated with a long-acting beta-agonist.

PRIMARY EFFICACY OUTCOME

At week 12, the mean (±SE) increase from baseline in prebronchodilator FEV_1 was greater by 5.5 percentage points (95% confidence interval [CI], 0.8 to 10.2) in the lebrikizumab group than in the placebo group (9.8±1.9% vs. 4.3±1.5%, P=0.02) (Fig. 2 and Table 2). An interaction test indicated that there was a significant interaction between treatment and baseline periostin level (P=0.03). In the high-periostin subgroup, the relative increase from baseline FEV_1 was higher by 8.2 percentage points (95% CI, 1.0 to 15.4) among patients receiving lebrikizumab than among those receiving placebo (14.0±3.1% vs. 5.8±2.1%, P=0.03). In the low-periostin subgroup, the relative increase from baseline FEV_1 was higher by 1.6 percentage points (95% CI, −4.5 to 7.7) among patients receiving lebrikizumab than among those receiving placebo (5.1±2.4% vs. 3.5±2.0%, P=0.61) (Fig. 2 and Table 2, and Table S4 in the Supplementary Appendix). Relative changes in FEV_1 were evident after 1 week of treatment and were sustained throughout the study; the last measurement was performed 32 weeks after randomization (Fig. 2).

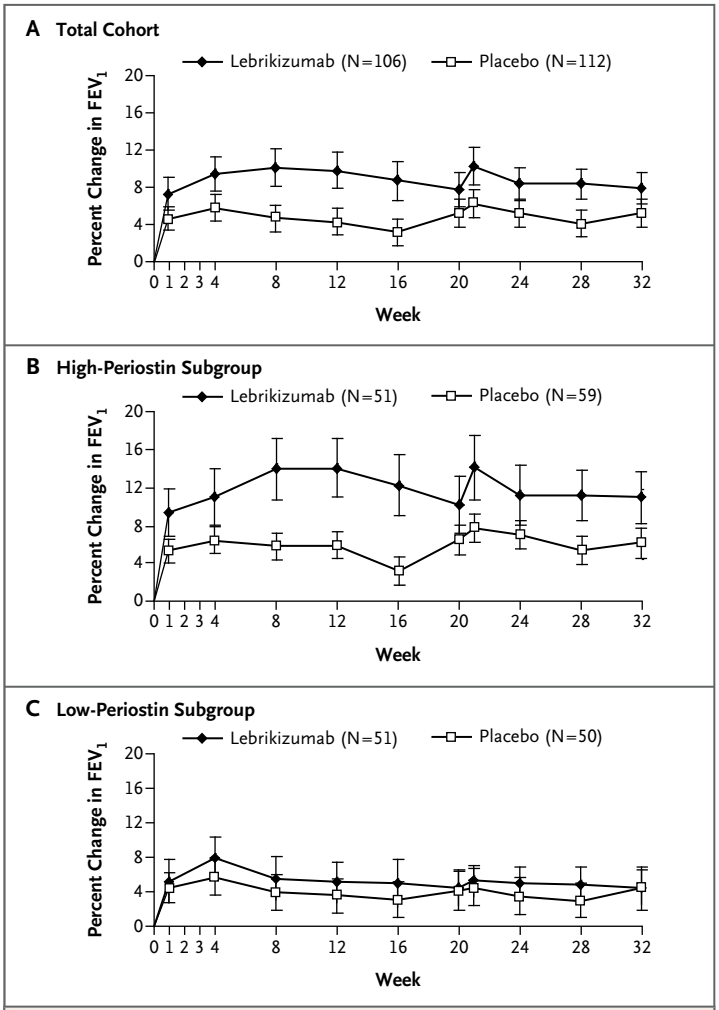

Figure 2. Relative Change in Forced Expiratory Volume in 1 Second (FEV_1) in the Intention-to-Treat Population.

At week 12, the increase from baseline in FEV_1 was higher by 5.5 percentage points (95% CI, 0.8 to 10.2) in the lebrikizumab group than in the placebo group (mean [±SE] change, 9.8±1.9% vs. 4.3±1.5%; P=0.02) (Panel A). In the subgroup of patients with high periostin levels, the relative increase from baseline FEV_1 was higher by 8.2 percentage points (95% CI, 1.0 to 15.4) in the lebrikizumab group than in the placebo group (mean change, 14.0±3.1% vs. 5.8±2.1%; P=0.03) (Panel B). Among patients in the low-periostin subgroup, the relative increase from baseline FEV_1 was higher by 1.6 percentage points (95% CI, −4.5 to 7.7) in the lebrikizumab group than in the placebo group (mean change, 5.1±2.4% vs. 3.5±2.1%; P=0.61) (Panel C).

Findings from the mixed-effects model were consistent with findings from the prespecified analysis. The mean increase from baseline in prebronchodilator FEV_1 was greater by 4 percentage

Table 2. Primary and Secondary Efficacy Outcomes, According to Treatment Assignment and Periostin Status.*

Outcome	Placebo			Lebrikizumab			Difference between Lebrikizumab and Placebo (95% CI)†					
	All Patients (N=112)	High Periostin (N=59)	Low Periostin (N=50)	All Patients (N=106)	High Periostin (N=51)	Low Periostin (N=51)	All Patients		High Periostin		Low Periostin	
							Difference	*P Value*	*Difference*	*P Value*	*Difference*	*P Value*
Primary efficacy outcome												
Change in FEV_1, baseline to week 12 (%)	4.3	5.8	3.5	9.8	14.0	5.1	5.5 (0.8 to 10.2)	0.02	8.2 (1.0 to 15.4)	0.03	1.6 (−4.5 to 7.7)	0.61
Secondary efficacy outcomes												
Change in FEV_1, baseline to week 24 (%)	5.2	6.9	3.5	8.4	11.1	5.0	3.1 (1.4 to 7.6)	0.17	4.2 (−3.1 to 11.5)	0.26	1.5 (−4.1 to 7.2)	0.60
Absolute change in FEV_1, baseline to week 12 (liters)	0.09	0.11	0.09	0.20	0.28	0.11	0.11 (0.02 to 0.21)	0.02	0.18 (0.04 to 0.31)	0.01	0.03 (−0.11 to 0.16)	0.72
Rate of protocol-defined exacerbations through week 24	0.65	0.55	0.73	0.44	0.40	0.47	32 (−16 to 60)	0.16	26 (−50 to 64)	0.40	36 (−38 to 70)	0.26
Rate of severe exacerbations through week 24	0.27	0.25	0.33	0.15	0.08	0.24	43 (−10 to 71)	0.10	67 (−15 to 90)	0.08	29 (−69 to 70)	0.44
Absolute change in peak expiratory flow, baseline to week 12 (liters/min)	−3.73	−4.43	−2.06	−0.49	4.66	−7.22	3.24 (−11.34 to 17.81)	0.66	9.08 (−13.87 to 32.04)	0.44	−5.16 (−24.45 to 14.13)	0.60
Change in ACQ5 score, baseline to week 12	−0.88	−0.98	−0.75	−0.93	−1.02	−0.79	−0.05 (−0.32 to 0.22)	0.72	−0.03 (−0.42 to 0.36)	0.87	−0.04 (−0.45 to 0.37)	0.85
Change in asthma symptom score, baseline to week 12‡	−0.62	−0.66	−0.57	−0.60	−0.68	−0.50	0.02 (−0.24 to 0.28)	0.87	−0.03 (−0.43 to 0.37)	0.89	0.07 (−0.27 to 0.42)	0.68
Change in rescue medication use, baseline to week 12§	−0.89	−0.95	−0.87	−1.08	−1.04	−1.18	−0.19 (−0.72 to 0.34)	0.48	−0.09 (−0.87 to 0.70)	0.83	−0.32 (−1.09 to 0.46)	0.43

* All measurements were performed in the intention-to-treat population, which included all patients who received at least one dose of the study drug. ACQ5 denotes Asthma Control Questionnaire 5, and FEV_1 forced expiratory volume in 1 second.

† For rates of exacerbations, differences represent the percentage reduction in the rates between the lebrikizumab and placebo groups; for all other outcomes, the differences are absolute differences (the mean value in the lebrikizumab group minus the mean value in the placebo group).

‡ Asthma symptoms were measured with the use of the Asthma Control Daily Diary; scores range from 1 to 5, with higher scores indicating worse symptoms.

§ Use of rescue medications was assessed with the Asthma Control Daily Diary. The scores range from 0 to 8, with higher scores representing a larger number of puffs of inhaler or nebulizer used; a score of 8 was assigned when the diary was scored as "more than 6."

points (95% CI, 0 to 7.9) in the lebrikizumab group than in the placebo group at week 12 (P=0.05). In the high-periostin and low-periostin subgroups, the corresponding estimates were 6.3 percentage points (95% CI, −0.1 to 12.6; P=0.05) and 1 percentage point (95% CI, −3.9 to 5.8; P=0.69). In a post hoc analysis, high FE_{NO}, but not high Th2, also identified patients who had greater improvements in FEV_1 (Table S4 in the Supplementary Appendix).

SECONDARY EFFICACY OUTCOMES

Treatment with lebrikizumab had no significant effects on the ACQ5 score or on the daily diary measures (asthma symptom score, change in the use of rescue medication, or change in the frequency of nocturnal awakening) (Table 2). There were no significant changes in the rates of protocol-defined exacerbations. At week 24, there was a trend for the rate of protocol-defined exacerbations in the total cohort to be lower in the lebrikizumab group than in the placebo group (P=0.16) (Table 2). In the high-Th2 subgroup, the rate of protocol-defined exacerbations was 60% lower in the lebrikizumab group than in the placebo group (P=0.03). There was a trend toward similar effects in the high-periostin group, with the exacerbation rate being 26% lower (P=0.40) (Table 2, and Table S5 in the Supplementary Appendix).

Overall, there was a nonsignificant trend toward lower rates of severe exacerbations among patients in the lebrikizumab group than among patients in the placebo group (P=0.10) (Table 2). The observed rates of severe exacerbations were nonsignificantly reduced in subgroups according to periostin level and study treatment (Table S6). High Th2 and high FE_{NO} (median FE_{NO} level or higher; a post hoc analysis) were also associated with greater reductions in the rates of severe exacerbations in the lebrikizumab group than in the placebo group (Table S6).

SAFETY

Four patients in the lebrikizumab group had a serious adverse event; two had asthma exacerbations requiring hospitalization, one had community-acquired pneumonia, and one had traumatic pneumothorax related to an automobile accident. Six patients in the placebo group had a serious adverse event: two had asthma exacerbations requiring hospitalization, and one each had headache (cerebrospinal fluid leakage after a glucocorticoid epidural injection for right-leg pain), shingles, acute purulent meningitis, and addiction to pain medication.

The overall frequency of adverse events was similar in the two groups (74.5% in the lebrikizumab group and 78.6% in the placebo group), as was the frequency of severe adverse events (3.8% and 5.4% in the two groups, respectively) (Table 3). Musculoskeletal events occurred more frequently in the lebrikizumab group than in the placebo group (13.2% vs. 5.4%, P=0.045) (Table 3, and Table S7 in the Supplementary Appendix). A total of 25 patients — 13 in the lebrikizumab group and 12 in the placebo group — discontinued the study early (11.5%); the reasons for discontinuation are shown in Table S8 in the Supplementary Appendix.

EXPLORATORY EFFICACY OUTCOMES

Lebrikizumab was associated with a 19% mean decline in FE_{NO} at week 12, as compared with a 10% increase with placebo (P<0.001). Among patients in the lebrikizumab group, there was a greater reduction in FE_{NO} in the high-periostin subgroup than in the low-periostin subgroup (34.4% vs. 4.3%, P<0.001 for the comparison of lebrikizumab with placebo in the high-periostin subgroup and P=0.28 for the comparison in the low-periostin subgroup). The average FE_{NO} value at baseline in the lebrikizumab group was 37±3.8 ppb in the high-periostin subgroup and 25.3±3 ppb in the low-periostin subgroup (Table S9 and Fig. S6 in the Supplementary Appendix). Serum CCL13, CCL17, and total IgE levels decreased and peripheral-blood eosinophil counts slightly increased in the lebrikizumab group during the 24-week treatment period (Table S9 and Fig. S7 in the Supplementary Appendix). At week 20, the post-bronchodilator FEV_1 had increased by 3.4% in the lebrikizumab group, whereas it had decreased by 1.5% in the placebo group, representing a between-group difference in the change from baseline of 4.9 percentage points (95% CI, 0.2 to 9.6; P=0.04) (Table S10 in the Supplementary Appendix).

DISCUSSION

In this study involving patients with poorly controlled asthma, treatment with lebrikizumab was associated with a significant improvement in pre-bronchodilator FEV_1, the primary outcome. The

Table 3. Adverse Events.*

Variable	Placebo (N=112)	Lebrikizumab (N=106)	All (N=218)
		no. of patients (%)	
Any adverse event	88 (78.6)	79 (74.5)	167 (76.6)
Any serious adverse event	6 (5.4)	4 (3.8)	10 (4.6)
Study discontinuation owing to adverse event	3 (2.7)	3 (2.8)	6 (2.8)
Treatment discontinuation owing to adverse event	3 (2.7)	4 (3.8)	7 (3.2)
Severity of adverse event			
Mild	67 (59.8)	59 (55.7)	126 (57.8)
Moderate	58 (51.8)	51 (48.1)	109 (50.0)
Severe	20 (17.9)	15 (14.2)	35 (16.1)
Death	0	0	0
Pregnancy	0	0	0
Cancer†	1 (0.9)	0	1 (0.5)
Infection or infestation	55 (49.1)	51 (48.1)	106 (48.6)
Respiratory, thoracic, or mediastinal disorder	52 (46.4)	38 (35.8)	90 (41.3)
General disorder or event due to administration-site conditions‡	15 (13.4)	16 (15.1)	31 (14.2)
Musculoskeletal or connective-tissue disorder§	6 (5.4)	14 (13.2)	20 (9.2)
Gastrointestinal disorder	14 (12.5)	5 (4.7)	19 (8.7)
Skin or subcutaneous-tissue disorder	11 (9.8)	7 (6.6)	18 (8.3)
Nervous system disorder	8 (7.1)	6 (5.7)	14 (6.4)
Abnormal laboratory test result¶	6 (5.4)	8 (7.5)	14 (6.4)
Metabolic or nutritional disorder	3 (2.7)	3 (2.8)	6 (2.8)
Renal or urinary tract disorder	5 (4.5)	1 (0.9)	6 (2.8)
Vascular disorder	4 (3.6)	2 (1.9)	6 (2.8)
Blood or lymphatic system disorder	3 (2.7)	1 (0.9)	4 (1.8)
Psychiatric disorder	1 (0.9)	3 (2.8)	4 (1.8)
Immune system disorder	1 (0.9)	2 (1.9)	3 (1.4)
Reproductive system or breast disorder	2 (1.8)	1 (0.9)	3 (1.4)
Cardiac disorder	1 (0.9)	1 (0.9)	2 (0.9)
Eye disorder	1 (0.9)	0	1 (0.5)
Event due to surgical or medical procedure	1 (0.9)	0	1 (0.5)

* Included are data from all patients in the intention-to-treat population (patients who received at least one dose of study drug) who had at least one reported event.

† Breast cancer was diagnosed by means of screening mammography in one patient in the placebo group after one dose of study drug had been administered. After the second dose of study drug had been administered, a biopsy confirmed breast cancer (maximum tumor size, 1.7 cm, with questionable margins and requiring a second surgical excision), with infiltrating ductal cancer (Nottingham grade 5, node-negative, estrogen-receptor–positive, progesterone-receptor–positive, HER2-negative). The patient was withdrawn from the study at that time.

‡ Administration-site conditions included injection-site erythema, pruritus, rash, swelling, paresthesia, and other reactions.

§ The incidences of subcategories of musculoskeletal and connective-tissue disorders are provided in Table S8 in the Supplementary Appendix.

¶ Included were tests measuring blood glucose, hematocrit, and liver enzyme levels; proteinuria; red-cell count; hemoglobin level; and blood pressure.

improvement in FEV_1 occurred soon after the initiation of treatment, indicating that inhibition of interleukin-13 had a relatively quick effect on measures of airflow. Treatment with lebrikizumab did not lead to significant reductions in the rates of protocol-defined exacerbations or severe exacerbations and did not reduce asthma symptoms, as measured by the symptom-only version of the ACQ5 (which excluded measures of FEV_1 and of the use of rescue short-acting $beta_2$-agonists), nor did it have an effect on the measures assessed in daily diary entries.

The reductions in serum Th2 chemokines (CCL13 and CCL17) and IgE support a lebrikizumab-mediated biologic effect that underlies the clinical effect measured in the airway. The slight increase in the peripheral-blood eosinophil count is consistent with an overall reduction in the migration of eosinophils from the blood to the lung compartment after inhibition of eosinophil-attracting chemokines. The finding that lebrikizumab decreased FE_{NO} is consistent with this hypothesis. However, lebrikizumab may have decreased FE_{NO} by indirectly inhibiting the expression of nitric oxide synthase through interleukin-13 blockade,[27] rather than by modifying eosinophilic inflammation (which is also thought to affect FE_{NO}).

In this study, we first hypothesized that the combination of a high serum IgE level and a high peripheral-blood eosinophil count would serve as a surrogate for identifying patients with increased expression of interleukin-13–related genes in the lung (interleukin-13 signature surrogate, or high Th2). Before the treatment codes were broken, we wrote a statistical analysis plan in which the groups were differentiated on the basis of serum periostin levels. This subgroup analysis showed that the effectiveness of lebrikizumab treatment was greater in patients with high periostin levels than in patients with low periostin levels, as evidenced by both a more robust increase in FEV_1 and a greater decline in FE_{NO}, as well as by a significant test for interaction. These findings suggest that the prespecified marker, serum periostin, could potentially be used to identify patients with asthma who may have an increased response to lebrikizumab treatment. This finding requires replication. In a post hoc analysis, high baseline FE_{NO}, as compared with low baseline FE_{NO}, was also associated with greater efficacy of lebrikizumab in improving FEV_1; high baseline FE_{NO} was also associated with a lower rate of severe exacerbations among patients receiving lebrikizumab than among those receiving placebo. However, there was greater intrapatient variability in baseline FE_{NO} than in periostin levels during the run-in period (mean coefficient of variation, 19.8% vs. 5.0%) (Table S3 in the Supplementary Appendix).

In this study, the enhanced effects of lebrikizumab on lung function in patients with high periostin levels or high FE_{NO} are consistent with the hypothesis that phenomena driven by interleukin-13 are clinically important in such patients. These results provide additional evidence of heterogeneity in the pathogenesis of asthma in patients with moderate-to-severe disease. Furthermore, our findings suggest the potential importance of biomarkers in identifying patients who will have a response to specific therapies for asthma.[28] Additional studies involving larger groups of patients are now needed to confirm our findings.

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port and stock or stock options from Genentech, and being named as an inventor on a patent application regarding asthma diagnosis and treatment with Genentech. Dr. Matthews also reports that Roche/Genentech is developing a periostin assay as a potential companion diagnostic for lebrikizumab. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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