Original Article

# Lebrikizumab in Uncontrolled Asthma: Reanalysis in a Well-Defined Type 2 Population

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***What is already known about this topic?*** Clinical trials of lebrikizumab have not demonstrated consistent reductions in asthma exacerbations, possibly owing to suboptimal patient selection. Appropriate subanalyses in patients with type 2 high phenotype are required to determine whether specific inhibition of IL-13 is effective in asthma.

***What does this article add to our knowledge?*** In a subset of asthma patients with baseline blood eosinophils of 300 cells/μL or greater and a history of exacerbations, lebrikizumab resulted in a significant reduction in asthma exacerbations, indicating that IL-13 inhibition is effective in asthma patients with a high type 2 phenotype.

***How does this study impact current management guidelines?*** Lebrikizumab is currently under consideration by the US Food and Drug Administration for approval in atopic dermatitis and has been approved in the European Union for the treatment of moderate to severe atopic dermatitis in adults and adolescents (aged 12 to less than 18 years, body weight of at least 40 kg) who are candidates for systemic therapy. This *post hoc* analysis demonstrated that asthma patients with a type 2 phenotype who were treated with lebrikizumab had a reduction in asthma exacerbations.

**BACKGROUND: LAVOLTA (L)I, LII, and ACOUSTICS were randomized, placebo-controlled, Phase 3 trials of lebrikizumab, a monoclonal antibody targeting IL-13 in patients with uncontrolled asthma. Failure to demonstrate efficacy may have been related to patient selection in those trials.**

**OBJECTIVE: To assess the efficacy in a well-defined subpopulation of patients with elevated blood eosinophil counts and a minimum number of prior asthma exacerbations. We performed an additional analysis in a subpopulation of patients with elevated FeNO and prior exacerbations.**

**METHODS: Adult (LI and LII) and adolescent patients (aged 12-17 years weighing ≥40 kg, ACOUSTICS) with uncontrolled asthma received lebrikizumab (125 mg, n = 832; or 37.5 mg, n = 829) or placebo (n = 833) subcutaneously every 4 weeks. *Post hoc* analysis of the annualized adjusted exacerbation rate (AER) was performed in a subpopulation of patients with baseline blood eosinophils of 300 cells/μL or greater and history of one or more exacerbations. In this subpopulation, there were 227 patients in the placebo group, 222 in the lebrikizumab 37.5-mg group, and 217 in the lebrikizumab 125-mg group. We**

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Conflicts of interest: J. Corren has served as a speaker and/or consultant for and/or received research grants and/or clinical trial funds from: Amgen, AstraZeneca, Eli Lilly and Company, Genentech, Novartis, Optinose, Regeneron, and Sanofi. S.J. Szefler has consulted for AstraZeneca, Boehringer-Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Moderna, OM Pharma, Propeller Health, Regeneron, and Sanofi, and has received research support from the National Institutes of

*Abbreviations used*
*AE- Adverse event*
*AER- Adjusted exacerbation rate*
*ITT- Intent-to-treat*
*LI- LAVOLTA I*
*LII- LAVOLTA II*
*RR- Rate ratio*
*T2- Type 2*
*TEAE- Treatment-emergent AE*

**summarized safety in patients who received at least one dose of lebrikizumab using adverse events.**
**RESULTS: Lebrikizumab significantly reduced AER compared with placebo in adults (AER reduction: 125 mg [38%]; and 37.5 mg [41%]) and adolescents (AER reduction:125 mg [59%]; 37.5 mg [64%]) with baseline blood eosinophils of 300 cells/μL or greater and one or more exacerbations. Most adverse events were mild or moderate in severity and did not lead to treatment discontinuation.**
**CONCLUSION: Lebrikizumab significantly reduced asthma exacerbations in a subpopulation of patients with elevated blood eosinophils, elevated FeNO, and a history of asthma exacerbation.**  **(J Allergy Clin Immunol Pract 2024;■:■-■)**

***Key words:*** *Allergic asthma; Lebrikizumab; IL-13; Efficacy; Post hoc analysis; Safety*

## INTRODUCTION

In the past decade, an improved understanding of the complex pathophysiology of asthma has resulted in the development of new treatment options and a move toward a personalized treatment strategy based on patient-specific characteristics and underlying endotype.[1] The emergence of biologic therapies for the treatment of asthma provides a promising therapeutic strategy for patients by targeting specific inflammatory modulators and pathways implicated in the pathogenesis of asthma, particularly in patients with an endotype driven by type 2 (T2) inflammation.[2]

IL-13 is a pleiotropic effector cytokine that has a dominant role in T2 inflammation. IL-13 is important in several characteristic pathophysiologic processes of asthma including goblet hyperplasia, mucus production, airway remodeling, central regulation of IgE synthesis, smooth muscle hyperplasia, airway hyperresponsiveness, and inflammatory cell recruitment and activation.[3] Increased IL-13 expression has been detected during acute exacerbations in patients with asthma.[4,5]

Given the important central role that IL-13 likely has in asthma, the past decade has witnessed the development of agents that specifically block the effects of this cytokine. Lebrikizumab is a novel IgG4 mAb that binds with high affinity and slow off-rate to IL-13 and selectively inhibits IL-13 signaling through the IL-13Rα1/IL-4Rα pathway, blocking the downstream effects of IL-13 with high potency.[6-8] Because the effects of lebrikizumab are limited to inhibiting IL-13, it might be expected that it would be efficacious in patients with a T2 biologic signature.

With these characteristics in mind, we investigated lebrikizumab for the treatment of patients with moderate to severe, poorly controlled asthma. Phase 3 clinical trials of lebrikizumab in this population of patients did not demonstrate consistent reductions in asthma exacerbations,[9,10] which raised the question whether specific inhibition of IL-13, in the absence of IL-4 antagonism, was an effective treatment approach in patients with difficult to control asthma. In retrospect, however, certain aspects of trial design did not optimize the sponsor's ability to detect a significant effect of the medication. First, patients were not required to have a history of recent prior asthma exacerbations; thus, a group of patients was selected who might not have

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been at risk of having exacerbations during the trial. Second, the trials did not rely exclusively on the blood eosinophil count for assessing inclusion in the trial, but rather used both blood eosinophils and serum periostin to define a T2 phenotype. Periostin was later shown to be poorly predictive of severe exacerbations and correlated only weakly with FeNO and blood eosinophil counts.[6,11] These potential shortcomings in patient selection raise the question of whether lebrikizumab would have demonstrated more consistent efficacy in a population of patients with poorly controlled T2-high asthma.

The purpose of the current *post hoc* analysis was to determine the efficacy of lebrikizumab in a subpopulation of patients from the Phase 3 trials in asthma who had a documented recent (past year) history of severe asthma exacerbations and well-defined T2 phenotype based on an elevation of the blood eosinophil count alone.

## METHODS

### Study design and patients

LAVOLTA I (LI) (NCT01867125), LAVOLTA II (LII) (NCT01868061), and ACOUSTICS (NCT01875003) were Phase 3, randomized, multicenter, multinational, double-blind, placebo-controlled, parallel-group clinical trials designed to assess the efficacy and safety of lebrikizumab in adult (LAVOLTA) and adolescent (ACOUSTICS) patients with moderate to severe uncontrolled asthma. LI and LII failed to provide consistent significant efficacy results; consequently, ACOUSTICS was terminated prematurely. These studies consisted of a screening period, a 52-week placebo-controlled period, and a 20-week safety follow-up. Detailed descriptions of the LAVOLTA and ACOUSTICS study designs and inclusion and exclusion criteria were published elsewhere.[9,10]

After completion of the screening period and patient eligibility requirements were confirmed, patients were randomly assigned to one of three treatment arms in a 1:1:1 ratio. LAVOLTA patients received lebrikizumab 125 mg (LI, n = 359; and LII, n = 357) or 37.5 mg (LI, n = 360; and LII, n = 356) or placebo (LI, n = 362; and LII, n = 354). In ACOUSTICS, patients were randomly assigned to receive lebrikizumab 125 mg (n = 116), lebrikizumab 37.5 mg (n = 113), or placebo (n = 117).

### Efficacy and safety assessments

This *post hoc* analysis pooled efficacy data from the LI and LII trials, whereas ACOUSTICS efficacy data were analyzed separately owing to early termination of the study. All randomized patients were included in this *post hoc* analysis. Efficacy analysis was carried out on the intent-to-treat (ITT) population; in the subpopulations with eosinophils less than 150 cells/μL, 150 cells/μL or greater to less than 300 cells/μL, and 300 cells/μL or greater at baseline and at least one asthma exacerbation in the preceding 12 months; and in the subpopulations with FeNO less than 25 mean parts per billion (ppb), 25 or greater mean ppb to less than 50 mean ppb, and 50 or greater mean ppb and at least one asthma exacerbation in the preceding 12 months. Furthermore, an integrated safety analysis was carried out with data from the LI, LII, and ACOUSTICS studies.

The primary objective of this analysis was to evaluate the efficacy of lebrikizumab compared with placebo as measured by the rate of protocol-defined asthma exacerbations over the 52-week placebo-controlled period. Briefly, exacerbation events were defined as any new or increased asthma symptoms that led to treatment with systemic corticosteroids or to hospitalization. Treatment with corticosteroids was defined as treatment with oral, intravenous, or intramuscular corticosteroids for at least 3 days or an emergency department visit with at least one dose of intravenous or intramuscular corticosteroids.[9] We performed comparisons between each lebrikizumab dose and the placebo group.

The secondary outcome of this analysis was to evaluate the change in $FEV_1$ from baseline at week 52. We collected $FEV_1$ measurements at each visit in accordance with the American Thoracic Society/European Respiratory Society Consensus Statement "Standardization of Spirometry."[12] Asthma therapies with the potential to affect $FEV_1$ were withheld until prebronchodilator $FEV_1$ measurements were completed. Measurement of FeNO was performed using a handheld portable NIOXMINO analyzer device (Aerocrine, Solna, Sweden) in accordance with guidelines published by the American Thoracic Society. We performed FeNO measurement before spirometry testing.

Safety was assessed during the placebo-control period by monitoring adverse events (AEs), AEs leading to treatment discontinuation, and serum laboratory evaluations. Safety outcomes reported here include treatment-emergent AEs (TEAEs), AEs leading to treatment discontinuation, serious AEs, and death.

### Statistical analysis

We developed a prespecified statistical analysis plan before we conducted the *post hoc* analyses. The analysis plan specified that from the originally randomized populations within each lebrikizumab asthma study, the *post hoc* analysis would be based on the subset of patients who met the same entry criteria that were used in the IL-5 and IL-13/4R antagonist asthma studies, largely defined as patients with moderateto severe T2-high asthma who had elevated blood eosinophils and those who were exacerbation-prone.[13-16] All analyses are considered *post hoc*, with no multiplicity control and nominal *P* values reported. Efficacy analyses were assessed in the ITT population, with patients grouped according to treatment assigned at randomization. This *post hoc* analysis also reported select subpopulations that had baseline blood eosinophils of 300 cells/μL or greater and at least one asthma exacerbation in the preceding 12 months. Asthma exacerbation rate was analyzed by Poisson regression model with overdispersion adjustment for lebrikizumab versus placebo during the 52-week placebo-controlled period. By recording the number of asthma exacerbations, we calculated the adjusted exacerbation rate (AER) and the adjusted rate ratio (RR). Absolute change in prebronchodilator $FEV_1$ from baseline for lebrikizumab versus placebo was analyzed using mixed-model for repeated measures. The number of asthma exacerbations within the past 12 months, baseline asthma medication, and geographic region were adjusted for in the LAVOLTA analyses; the number of asthma exacerbations within the past 12 months, baseline asthma medication, and age group were adjusted for in the ACOUSTIC analyses. Safety *post hoc* analyses were based on all patients who received at least one dose of study drug, with patients grouped by assigned treatment. We summarized safety using an integrated descriptive analysis.

### Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization Guideline for Good Clinical Practice. Independent ethics committee approval was obtained at all participating centers, and all patients provided written informed assent, when appropriate, with consent from legal guardians. An independent data monitoring committee reviewed safety data at regular intervals throughout the trial.

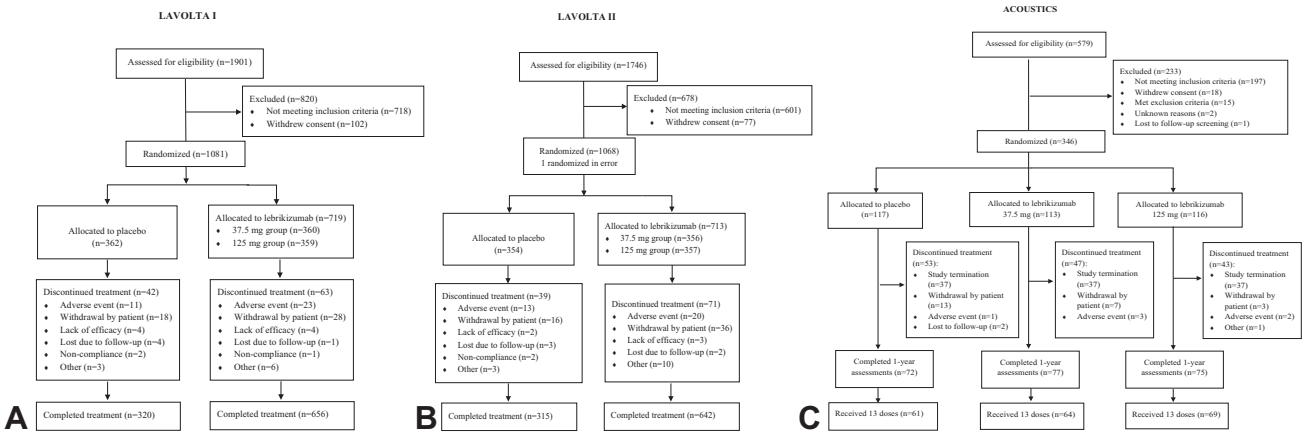


**FIGURE 1.** Consolidated Standards of Reporting Trials diagrams for (A) LAVOLTA I (LI), (B) LAVOLTA II (LII), and (C) ACOUSTICS studies.

## RESULTS

Across both LAVOLTA studies, 2,149 patients were enrolled at 367 sites in 28 countries. A total of 1,081 and 1,067 patients with moderate to severe uncontrolled asthma were randomly assigned to the ITT population in LI and LII, respectively. Of these patients, 976 (90%) completed treatment in LI and 957 (90%) completed treatment in LII (Figure 1, *A* and 1, *B*). Patients were screened for the ACOUSTICS study at 78 sites in 20 countries. A total of 346 (of 375 planned) adolescent patients were enrolled in ACOUSTICS; 224 of 346 patients (65%) completed the 52-week placebo-controlled period, and 133 of 229 patients (58%) treated with lebrikizumab received the full 13 doses of study drug (Figure 1, *C*).

Demographics and baseline disease activity for these patients were reported elsewhere.[9,10] Baseline disease characteristics were generally well-balanced across the treatment groups in the LAVOLTA studies. In ACOUSTICS, baseline characteristics were similar across treatment groups, with the exception of eosinophil counts, which were slightly higher in the placebo group (median, 330 cells/μL) compared with the lebrikizumab 125 mg group (median, 295 cells/μL) and lebrikizumab 37.5 mg group (median, 280 cells/μL) (Table I).

### Efficacy

Combining LI and LII studies, 495 asthma exacerbations were reported in the placebo group: 365 with lebrikizumab 125 mg and 334 with 37.5 mg. In ACOUSTICS, 113 exacerbations were reported during the 52-week placebo-controlled period, including 51 in placebo (98.4 patient-years of follow-up) and 31 each with lebrikizumab 125 mg and 37.5 mg (105.1 and 100.8 patient-years, respectively).[9,10]

For LI and LII pooled analysis, patients receiving lebrikizumab 125 mg or 37.5 mg had significant reductions in the AER compared with placebo (Figure 2). The adjusted RR was 0.71 (95% CI, 0.62-0.81) for the 125-mg group and 0.65 (95% CI, 0.57-0.75) for the 37.5-mg group, corresponding to a 29% and 35% reduction, respectively, in asthma exacerbation rate compared with placebo. *Post hoc* analyses showed that asthma exacerbation rate reduction was more pronounced in patients with baseline peripheral blood eosinophils of 300 cells/μL or greater and one or more asthma exacerbations in the preceding year (Figure 2). The adjusted RR improved to 0.62 (95% CI, 0.50-0.76) for the 125-mg dose and 0.59 (95% CI, 0.48-0.73) for the 37.5-mg dose, corresponding to a 38% and 41% reduction, respectively, in asthma exacerbation rate compared with placebo. Comparative data for baseline blood eosinophils of less than 150 cells/μL, 150 or greater cells/μL to less than 300 cells/μL, and 300 cells/μL or greater and one or more asthma exacerbations in the previous year are provided in Figure E1 (in this article's Online Repository at www.jaci-inpractice.org). For LI and LII pooled analysis, the subgroup with baseline peripheral blood eosinophils of 300 cells/μL or greater and two or more exacerbations in the preceding year demonstrated further risk reduction in the adjusted RR (44% for the 125-mg dose and 48% for the 37.5-mg dose) (data not shown). For the pooled analysis of LI and LII studies, patients with prior exacerbations and an FeNO value of 50 or greater mean ppb had lower AER with lebrikizumab compared with placebo (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

In ACOUSTICS, treatment with lebrikizumab reduced the AER in adolescent patients during the 52-week placebo-controlled period (Figure 3). Patients in the 125-mg lebrikizumab group (n = 116) demonstrated greater improvement over placebo compared with the 37.5-mg group (n = 113). The adjusted RR was 0.49 (95% CI, 0.28-0.83) for the 125-mg group and 0.60 (95% CI, 0.35-1.03) for the 37.5-mg group, corresponding to 51% and 40% reduction in AER, respectively, compared with placebo. Exacerbation rates were further reduced in patients with elevated baseline blood eosinophils. In patients with baseline peripheral blood eosinophils of 300 cells/μL or greater and one or more asthma exacerbations in the preceding year, the adjusted RR was 0.41 in the lebrikizumab 125-mg group (95% CI, 0.19-0.88) and 0.36 for the lebrikizumab 37.5-mg group (95% CI, 0.15-0.87), corresponding to a 59% and 64% respective reduction in asthma exacerbation rates compared with placebo.

A secondary efficacy end point from the LAVOLTA studies, indicative of lung function, was the absolute change from baseline in prebronchodilator $FEV_1$. In *post hoc* analyses of the pooled LAVOLTA studies, patients receiving either lebrikizumab 125 mg or 37.5 mg had improvements in $FEV_1$ compared with placebo (Figure 4, *A*). Placebo-corrected mean change from

**TABLE I.** Baseline demographics and disease characteristics for LAVOLTA and ACOUSTICS studies

| | LAVOLTA I | | | LAVOLTA II | | | ACOUSTICS | | |
|---|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **PBO every 4 wk (n = 362)** | **LEB 37.5 mg every 4 wk (n = 360)** | **LEB 125 mg every 4 wk (n = 359)** | **PBO every 4 wk (n = 354)** | **LEB 37.5 mg every 4 wk (n = 356)** | **LEB 125 mg every 4 wk (n = 357)** | **PBO every 4 wk (n = 117)** | **LEB 37.5 mg every 4 wk (n = 113)** | **LEB 125 mg every 4 wk (n = 116)** |
| Age, y | 51.3 (12.3) | 51.4 (12.9) | 51.0 (12.6) | 49.5 (13.3) | 50.9 (12.9) | 50.2 (12.6) | 14.1 (1.7) | 14.2 (1.5) | 14.2 (1.6) |
| Female, n (%) | 231 (63.8) | 234 (65.0) | 248 (69.1) | 219 (61.9) | 202 (56.7) | 237 (66.4) | 49.0 (41.9) | 43 (38.1) | 59 (50.9) |
| Race, n (%)* | | | | | | | | | |
| Asian | 41 (11.3) | 39 (10.8) | 40 (11.1) | 41 (11.6) | 43 (12.1) | 36 (10.1) | 3 (2.6) | 3 (2.7) | 3 (2.6) |
| Black | 29 (8.0) | 19 (5.3) | 15 (4.2) | 22 (6.2) | 25 (7.0) | 25 (7.0) | 9 (7.7) | 13 (11.5) | 13 (11.2) |
| Other | 6 (1.7) | 11 (3.1) | 9 (2.5) | 21 (5.9) | 22 (6.2) | 24 (6.7) | 21 (17.9) | 22 (19.5) | 26 (22.4) |
| White | 286 (79.0) | 291 (80.8) | 295 (82.2) | 270 (76.3) | 266 (74.7) | 272 (76.2) | 84 (71.8) | 75 (66.4) | 74 (63.8) |
| Asthma duration, y (median [range]) | 17.0 (1-68) | 17.0 (1-65) | 17.0 (1-70) | 18.0 (1-72) | 19.0 (1-69) | 16.0 (1-71) | 9.0 (1-17) | 11.0 (1-17) | 11.0 (1-17) |
| Prebronchodilator $FEV_1$, % predicted | 61.0 (10.6) | 60.6 (10.3) | 61.3 (10.5) | 61.1 (10.6) | 60.5 (10.5) | 60.7 (10.6) | 69.8 (12.5) | 73.3 (9.9) | 70.9 (10.7) |
| FeNO, median parts per billion | 27 | 27 | 28 | 23 | 24 | 24 | 30 | 37 | 33 |
| Asthma Control Questionnaire-5 | 2.69 (0.76) | 2.61 (0.73) | 2.60 (0.74) | 2.77 (0.73) | 2.72 (0.75) | 2.76 (0.70) | 2.76 (0.83) | 2.57 (0.84) | 2.69 (0.90) |
| Eosinophil count, cells/μL (median [range]) | 230 (170-400) | 245 (145-430) | 240 (150-380) | 240 (150-400) | 230 (150-410) | 240 (140-390) | 330 (190-530) | 280 (140-420) | 295 (180-515) |
| ≥1 asthma exacerbation in preceding year, n (%) | 228 (63.0) | 228 (63.7) | 226 (63.0) | 225 (63.6) | 226 (63.7) | 237 (66.4) | 76 (65.0) | 70 (62.5) | 83 (71.6) |
| Baseline asthma controller—ICS, n (%)† | 362 (100%) | 360 (100%) | 359 (100%) | 354 (100%) | 356 (100%) | 357 (100%) | 116 (99.1%) | 113 (100%) | 116 (100%) |
| Baseline ICS, μg/d (mean [SD]) | 779.6 (353.8) | 773.3 (331.2) | 773.3 (322.1) | 816.9 (348.7) | 807.8 (354.5) | 821.8 (364.6) | 699.8 (397.8) | 751.8 (621.3) | 672.0 (416.9) |
| Baseline ICS ≥1,000 μg/d, n (%) | 161 (44.5%) | 162 (45.0%) | 163 (45.4%) | 182 (51.4%) | 170 (47.8%) | 181 (50.7%) | 32 (27.4%) | 27 (23.9%) | 28 (24.1%) |

*FeNO*, fractional exhaled nitric oxide; $FEV_1$, forced expiratory volume in 1 second; *ICS*, inhaled corticosteroids; *LEB*, lebrikizumab; *PBO*, placebo.
Data are presented as mean (SD) unless otherwise specified. Other = not White, Black or African American, or Asian.
*Race was self-reported.
†Patients receiving maintenance dose of oral corticosteroids were excluded from the study.

| Group | N | AER per py | Rate reduction | Rate ratio (95% CI) LEB vs PBO | P-value | Rate ratio (95% CI) |
|---|---|---|---|---|---|---|
| **All patients** | | | | | | |
| **Placebo** | 716 | 0.73 | | | | |
| **LEB 37.5 mg** | 716 | 0.48 | 35% | 0.65 (0.57-0.75) | <.0001 | |
| **LEB 125 mg** | 716 | 0.52 | 29% | 0.71 (0.62-0.81) | <.0001 | |
| **E ≥300 cells/μL and Ex ≥1** | | | | | | |
| **Placebo** | 183 | 1.43 | | | | |
| **LEB 37.5 mg** | 187 | 0.84 | 41% | 0.59 (0.48-0.73) | <.001 | |
| **LEB 125 mg** | 174 | 0.88 | 38% | 0.62 (0.50-0.76) | <.001 | |

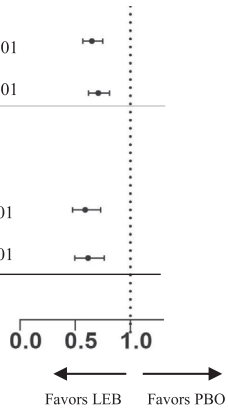


**FIGURE 2.** Annualized asthma exacerbation (Ex) rates at week 52 for patients in the pooled LAVOLTA I and LAVOLTA II analysis with eosinophil (E) count of 300 cells/μL or greater and one or more prior Ex. Patients receiving lebrikizumab (LEB) 125 mg or 37.5 mg had reductions in the adjusted Ex rate (AER) compared with placebo (PBO). *py,* patient-year.

| Group | N | AER per py | Rate reduction | Rate ratio (95% CI) LEB vs PBO | P-value | Rate ratio (95% CI) |
|---|---|---|---|---|---|---|
| **All patients** | | | | | | |
| **Placebo** | 117 | 0.43 | - | - | - | |
| **LEB 37.5 mg** | 113 | 0.26 | 40% | 0.60 (0.35-1.03) | 0.07 | |
| **LEB 125 mg** | 116 | 0.21 | 51% | 0.49 (0.28-0.83) | 0.01 | |
| **E ≥300 cells/μL and Ex ≥1** | | | | | | |
| **Placebo** | 44 | 1.12 | - | - | - | |
| **LEB 37.5 mg** | 35 | 0.41 | 64% | 0.36 (0.15-0.87) | 0.02 | |
| **LEB 125 mg** | 43 | 0.46 | 59% | 0.41 (0.19-0.88) | 0.02 | |

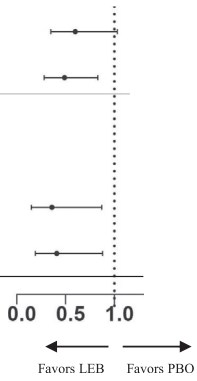


**FIGURE 3.** Rate of asthma exacerbations (Ex) over 52 weeks in ACOUSTICS patients with eosinophil (E) count of 300 cells/μL or greater and one or more prior Ex. Reduction in asthma Ex rate with lebrikizumab (LEB) vs placebo (PBO) was greatest in patients with E of greater than 300 cells/μL and prior Ex.

baseline to week 52 was 0.09 L (95% CI, 0.05-0.13 L) in the 125-mg group and 0.07 L (95% CI, 0.03-0.11 L) in the 37.5-mg group. There was a further improvement in $FEV_1$ in patients with baseline peripheral blood eosinophils of 300 cells/μL or greater and one or more exacerbations in the preceding year compared with placebo (0.15 L; 95% CI, 0.07-0.24 L in the 125-mg group, and 0.13 L; 95% CI, 0.04-0.21 L in the 37.5-mg group) (Figure 4, *B*). No significant differences were seen between lebrikizumab and placebo groups in patients with baseline peripheral blood eosinophils of less than 150 cells/μL or 150 or greater to less than 300 cells/μL and one or more exacerbations in the preceding year (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org). There was a significant improvement in $FEV_1$ in patients with an FeNO value of 50 or less mean ppb and one or more exacerbations in the preceding year but not in patients with FeNO values of less than 25 mean ppb or 25 or greater mean ppb to less than 50 mean ppb (see Figure E4 in this article's Online Repository at www.jaci-inpractice.org).

We also observed improvements compared with placebo in absolute change from baseline in prebronchodilator $FEV_1$ at week 52 in ACOUSTICS (Figure 4, *C*). Prebronchodilator $FEV_1$ had noticeably increased in patients treated with lebrikizumab 37.5 mg. The placebo-corrected mean change from baseline to

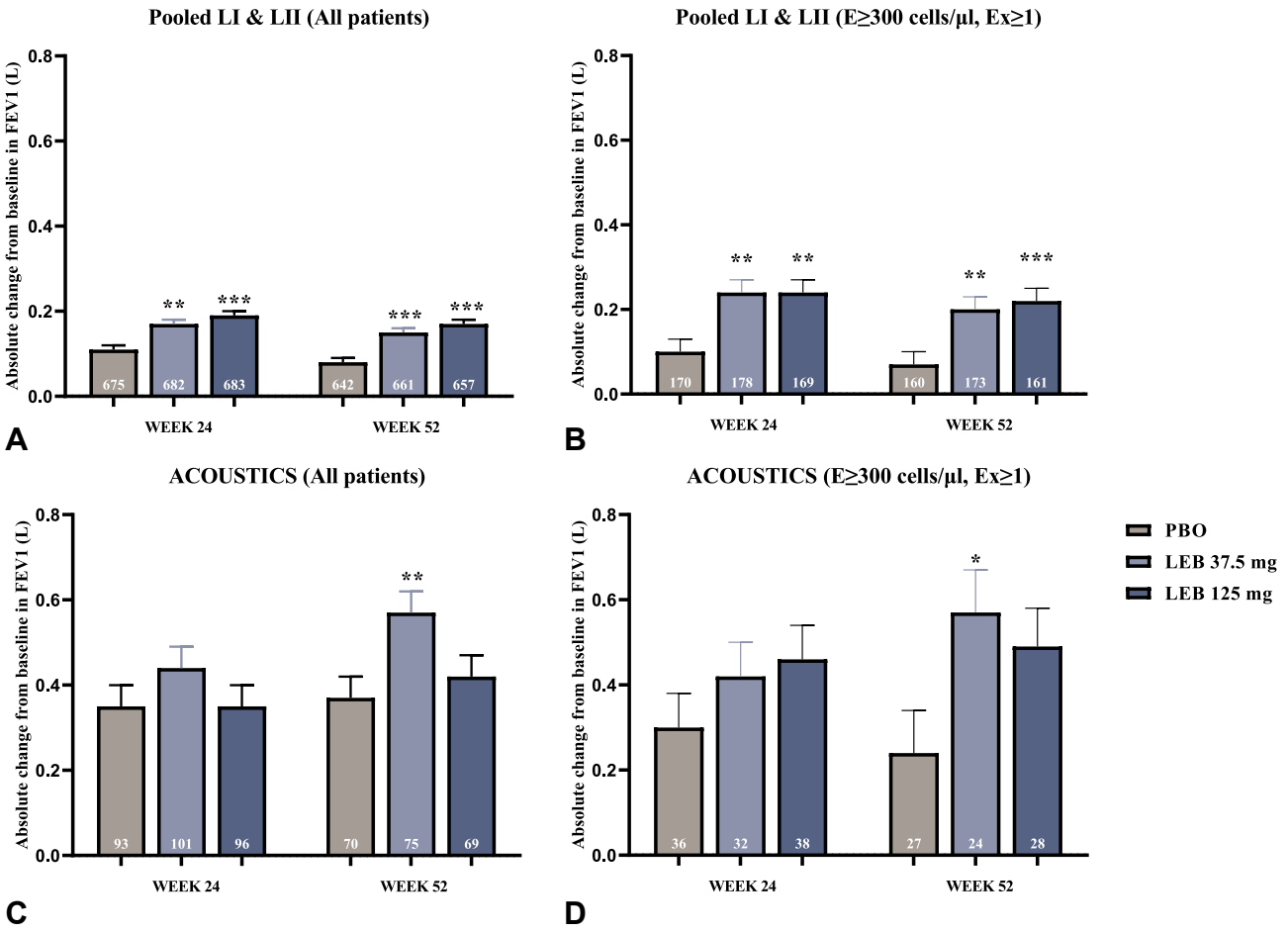


**FIGURE 4.** Absolute change from baseline in (**A**) prebronchodilator $FEV_1$ (L) at weeks 24 and 52 in the pooled LAVOLTA I (LI) and LAVOLTA II (LII) population, (**B**) in LAVOLTA patients with eosinophils (E) of 300 cells/µL or greater and prior exacerbations (Ex), (**C**) in the total ACOUSTICS population, and (**D**) in ACOUSTICS patients with E of 300 cells/µL or greater and prior Ex. ***$P < .001$, **$P < .01$, *$P < .05$ vs placebo. *LEB*, lebrikizumab; *PBO*, placebo.

week 52 was 0.20 L (95% CI, 0.05-0.34 L) in the lebrikizumab 37.5-mg group and 0.05 L (95% CI, −0.09 to 0.2 L) in the lebrikizumab 125-mg group. Furthermore, in patients with baseline peripheral blood eosinophils of 300 cells/µL or greater and one or more asthma exacerbations in the preceding year, placebo-corrected mean change from baseline to week 52 was 0.25 L (95% CI, −0.01 to 0.51 L) in the 125-mg group and 0.33 L (95% CI, 0.06-0.60 L) in the 37.5-mg group (Figure 4, *D*).

## Safety

In a pooled analysis of LI, LII, and ACOUSTICS, a similar proportion of patients reported TEAEs (pooled lebrikizumab doses, 1,281 of 1,661 patients [77%] vs placebo, 650 of 883 patients [78%]) (Table II). Most AEs were nonserious, mild (pooled lebrikizumab doses, 20.5% vs placebo, 18.8%), or moderate (pooled lebrikizumab doses, 48.8% vs placebo, 50.4%) in severity and did not lead to treatment discontinuation. The most frequently reported TEAEs (≥5%) included asthma (30.6% for lebrikizumab; 37.6% for placebo), nasopharyngitis (13.2% for lebrikizumab; 14.2% for placebo), upper respiratory tract infection (11.5% for lebrikizumab; 9.1% for placebo), bronchitis (7.7% for lebrikizumab; 7.6% for placebo), headache (6.4% for lebrikizumab; 6.4% for placebo), pharyngitis (4.2% for lebrikizumab; 4.8% for placebo), and sinusitis (4.1% for lebrikizumab; 5.9% for placebo) (Table III).

Study discontinuation owing to AEs was similar between lebrikizumab (n = 56; 3.4%) and placebo (n = 30; 3.6%; Table II). Similar frequencies of serious AEs were reported in the lebrikizumab (7.6%) and placebo groups (8.5%). One death occurred in the placebo group. Treatment groups reported similar frequencies of conjunctivitis (lebrikizumab, 1.6%; placebo, 1.7%) and infections and infestations defined by system organ class (lebrikizumab, 51.6%; placebo, 50.7%). Overall, herpes infections were reported at a higher frequency in the lebrikizumab group (1.8%) compared with the placebo group (0.6%).

Treatment-emergent AEs of eosinophilia were reported by 1.1% of patients in the lebrikizumab groups compared with zero patients in the placebo group. Eosinophil-related disorders

**TABLE II.** Overview of AEs through wk 52 in integrated safety analysis

| Safety event | Placebo (n = 833) | LEB 37.5 mg (n = 829) | LEB 125 mg (n = 832) | Total LEB (n = 1,661) |
|---|---|---|---|---|
| Patients with ≥1 treatment-emergent AE, n (%) | 650 (78.0) | 643 (77.6) | 638 (76.7) | 1281 (77.1) |
| Mild | 157 (18.8) | 181 (21.8) | 159 (19.1) | 340 (20.5) |
| Moderate | 420 (50.4) | 403 (48.6) | 408 (49.0) | 811 (48.8) |
| Severe | 73 (8.8) | 59 (7.1) | 71 (8.5) | 130 (7.8) |
| Serious AEs | 71 (8.5) | 61 (7.4) | 65 (7.8) | 126 (7.6) |
| Death | 1 (0.1) | 0 | 0 | 0 |
| AEs leading to study drug discontinuation | 30 (3.6) | 19 (2.3) | 37 (4.4) | 56 (3.4) |
| Special safety topics of interest | | | | |
| Conjunctivitis cluster* | 14 (1.7) | 12 (1.4) | 15 (1.8) | 27 (1.6) |
| Keratitis cluster† | 0 | 0 | 0 | 0 |
| Infections‡,§ | 422 (50.7) | 426 (51.4) | 431 (51.8) | 857 (51.6) |
| Skin infections | 11 (1.3) | 14 (1.7) | 6 (0.7) | 20 (1.2) |
| Herpes infection‖ | 5 (0.6) | 16 (1.9) | 14 (1.7) | 30 (1.8) |
| Herpes zoster | 2 (0.2) | 10 (1.2) | 6 (0.7) | 16 (1.0) |
| Parasitic infections | 0 (0) | 0 (0) | 1 (0.1) | 1 (0.1) |
| Potential opportunistic infections | 18 (2.2) | 19 (2.3) | 16 (1.9) | 35 (2.1) |
| Injection site reactions¶ | 64 (7.7) | 49 (5.9) | 87 (10.5) | 136 (8.2) |
| Eosinophilia# | 0 | 6 (0.7) | 13 (1.6) | 19 (1.1) |
| Eosinophil-related disorders** | 2 (0.2) | 1 (0.1) | 2 (0.2) | 3 (0.2) |
| Malignancies | 3 (0.4) | 5 (0.6) | 2 (0.2) | 7 (0.4) |
| Non-melanoma skin cancer | 0 (0) | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Non−non melanoma skin cancer | 3 (0.4) | 4 (0.5) | 1 (0.1) | 5 (0.3) |
| Anaphylactic reaction†† | 0 | 0 | 0 | 0 |

*AE*, adverse event; *LEB*, lebrikizumab; *MedDRA*, Medical Dictionary for Regulatory Activities.
Data are shown as n (%). Patients with multiple occurrences are counted once for each category, and patients may be counted in more than one category.
*Defined as these preferred terms: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and giant papillary conjunctivitis.
†Defined as these preferred terms: keratitis, atopic keratoconjunctivitis, allergic keratitis, ulcerative keratitis, and vernal keratoconjunctivitis.
‡One event of parasitic infection reported in the LEB 125 mg every 4 weeks.
§Defined using MedDRA system organ class Infections and Infestations.
‖Defined using MedDRA high-level term herpes-viral infection.
¶Defined using MedDRA high-level term injection site reactions.
#Defined as eosinophilia, allergic eosinophilia, eosinophil count abnormal, eosinophil count increased, and eosinophil percentage increased.
**Events reported were eosinophilic pneumonia, eosinophilia granulomatosis with polyangiitis, and pulmonary eosinophilia.
††Defined as anaphylactic reaction standardized MedDRA Queries including narrow and algorithm cases per standardized MedDRA Queries guide reported on the same day of study drug administration.

TEAEs were similar between groups (lebrikizumab, 0.2%; placebo, 0.2%). Preferred terms included eosinophilic pneumonia (lebrikizumab, 0.1%; placebo, 0.1%) and eosinophilic granulomatosis with polyangiitis (lebrikizumab, 0.1%; placebo 0%; Table II). The frequency of patients with increased blood eosinophils at any point after baseline was higher in the lebrikizumab group (37.6%) compared with placebo (22.0%). Eosinophil shifts were also evaluated according to the categories of normal (<500/μL), mild (500 to <1,500/μL), moderate (1,500 to <5,000/μL), and severe (≥5,000/μL). Most shifts were from the normal to mild category. However, 15 lebrikizumab-treated patients (0.9%) and two placebo-treated patients (0.2%) had an increase in blood eosinophils to the severe category.

## DISCUSSION

This *post hoc* analysis of three Phase 3 clinical trials of lebrikizumab in adults and adolescents with uncontrolled asthma demonstrated that lebrikizumab 125 mg and 37.5 mg resulted in greater reductions in the AER compared with placebo in patients with blood eosinophils of 300 cells/μL or greater and one or more asthma exacerbations in the preceding year and in patients with FeNO levels of 50 or greater mean ppb. These results indicate that lebrikizumab may be efficacious in asthma when the appropriate population of patients with previous exacerbations and T2 inflammation is targeted. This *post hoc* analysis highlights the importance of using appropriate predictive biomarkers and targeting the appropriate study population when selecting a specific biologic medication for asthma.

Multiple possible explanations may account for the inconsistent overall efficacy results in the LAVOLTA and ACOUSTICS studies in the ITT populations. First, periostin was used as the primary predictive biomarker in efficacy analyses in the LAVOLTA studies. Although serum periostin was predictive of improvements in $FEV_1$ in early studies of lebrikizumab, it was later shown to be poorly predictive of severe exacerbations and correlated only weakly with FeNO and blood eosinophil counts.[17] In contrast to FeNO, an airway biomarker of T2 inflammation, serum periostin is derived from many other tissues including bone, skin, and the gastrointestinal tract. Blood eosinophil count and FeNO are complementary noninvasive biomarkers of T2 inflammation, which have demonstrated consistent value in identifying patients with severe asthma who

**TABLE III.** Most common treatment-emergent adverse events (≥5%) through wk 52

| Treatment-emergent adverse event | Placebo (n = 833) | LEB 37.5 mg (n = 829) | LEB 125 mg (n = 832) | Total LEB (n = 1,661) |
|---|---|---|---|---|
| Asthma | 313 (37.6) | 251 (30.3) | 258 (31.0) | 509 (30.6) |
| Nasopharyngitis | 118 (14.2) | 113 (13.6) | 107 (12.9) | 220 (13.2) |
| Upper respiratory tract infection | 76 (9.1) | 81 (9.8) | 110 (13.2) | 191 (11.5) |
| Bronchitis | 63 (7.6) | 68 (8.2) | 60 (7.2) | 128 (7.7) |
| Headache | 53 (6.4) | 50 (6.0) | 56 (6.7) | 106 (6.4) |
| Pharyngitis | 40 (4.8) | 31 (3.7) | 38 (4.6) | 69 (4.2) |
| Sinusitis | 49 (5.9) | 32 (3.9) | 36 (4.3) | 68 (4.1) |

*LEB*, lebrikizumab.
Data are shown as n (%). Patients with multiple occurrences are counted once for each category, and patients may be counted in more than one category.

are likely to respond to biologic agents targeting T2 cytokines including IL-5, IL-4, and IL-13.[13,18] This is not the first time an asthma biologic failed in clinical trials owing to researchers not selecting the optimal phenotype biomarkers and not fully understanding the role of eosinophils and other biomarkers in asthma.[19,20] Mepolizumab initially failed in patients with moderate persistent asthma. This study was performed before it was fully understood that eosinophils were a major biomarker in phenotyping asthma.

Second, in the LAVOLTA and ACOUSTICS studies, inclusion criteria did not stipulate the requirement for prior exacerbations, allowing patients with milder disease to enter the trials and potentially reducing the probability of detecting a significant effect of the drug on exacerbations. These baseline characteristics differ considerably from asthma studies of other biologics, including mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab.[21,22] In the LAVOLTA studies, the definition of uncontrolled asthma was based on the Asthma Control Questionnaire-5 score and not the exacerbation history. The adjusted annual exacerbation rate in the ITT population treated with placebo, 0.84 in LI and 0.61 in LII, reflected the low risk among the study cohort, indicating a possible explanation for the inconsistent results between the studies, particularly the negative result in LII.

This *post hoc* analysis provides evidence that inhibition of IL-13 significantly reduces asthma exacerbations in patients with moderate to severe, poorly controlled eosinophilic asthma. However, these data cannot be extrapolated to all inhibitors of IL-13, such as tralokinumab, because there are significant pharmacologic differences between these medications. *In vitro* studies demonstrated that lebrikizumab binds to IL-13 with about 140-fold stronger affinity than tralokinumab, and the rate of dissociation of IL-13 from tralokinumab occurs more rapidly than that of IL-13 bound to lebrikizumab.[23]

Limitations of the current analyses were that these were *post hoc* analyses, and no adjustments were made for multiple comparisons. Important limitations of the ACOUSTICS study was its premature termination and that no inferential statistical analyses were performed. Furthermore, point estimates and 95% CIs were presented only for descriptive purposes, limiting the ability to make meaningful comparisons between treatment groups.

## CONCLUSION

This *post hoc* analysis demonstrated that lebrikizumab may be efficacious in patients with uncontrolled asthma who have elevated blood eosinophil counts and FeNO levels and a history of recent exacerbations. The safety profile was similar across treatment groups in adults and adolescents with uncontrolled asthma.

## Acknowledgments

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## ONLINE REPOSITORY

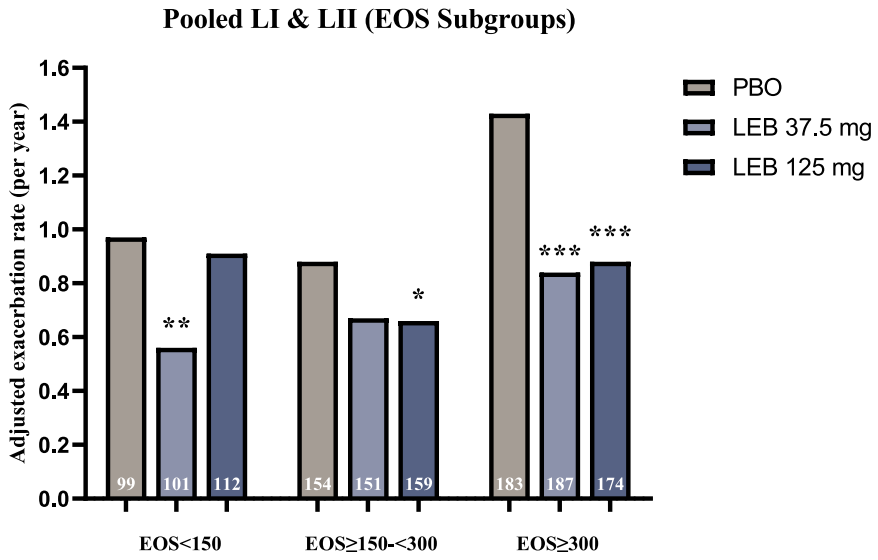


**FIGURE E1.** Annualized asthma exacerbation rates at week 52 for patients in pooled LAVOLTA I (LI) and LAVOLTA II (LII) analysis with eosinophils (EOS) less than 150 cells/μL, EOS 150 or greater cells/μL to less than 300 cells/μL, and EOS 300 cells/μL or greater and one or more prior exacerbations. $***P < .001$, $**P < .01$, $*P < .05$ vs placebo (PBO). *LEB*, lebrikizumab.

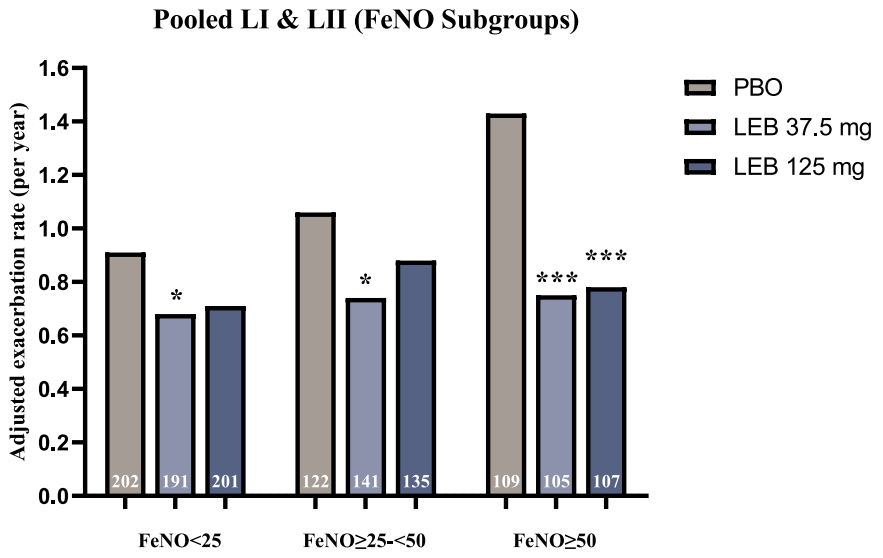


**FIGURE E2.** Annualized asthma exacerbation rates at week 52 for patients in pooled LAVOLTA I (LI) and LAVOLTA II (LII) analysis with FeNO less than 25 mean parts per billion, FeNO 25 or greater mean parts per billion to less than 50 mean parts per billion, and FeNO 50 or greater mean parts per billion and one or more prior exacerbations. $***P < .001$, $*P < .05$ vs placebo (PBO). *LEB*, lebrikizumab.

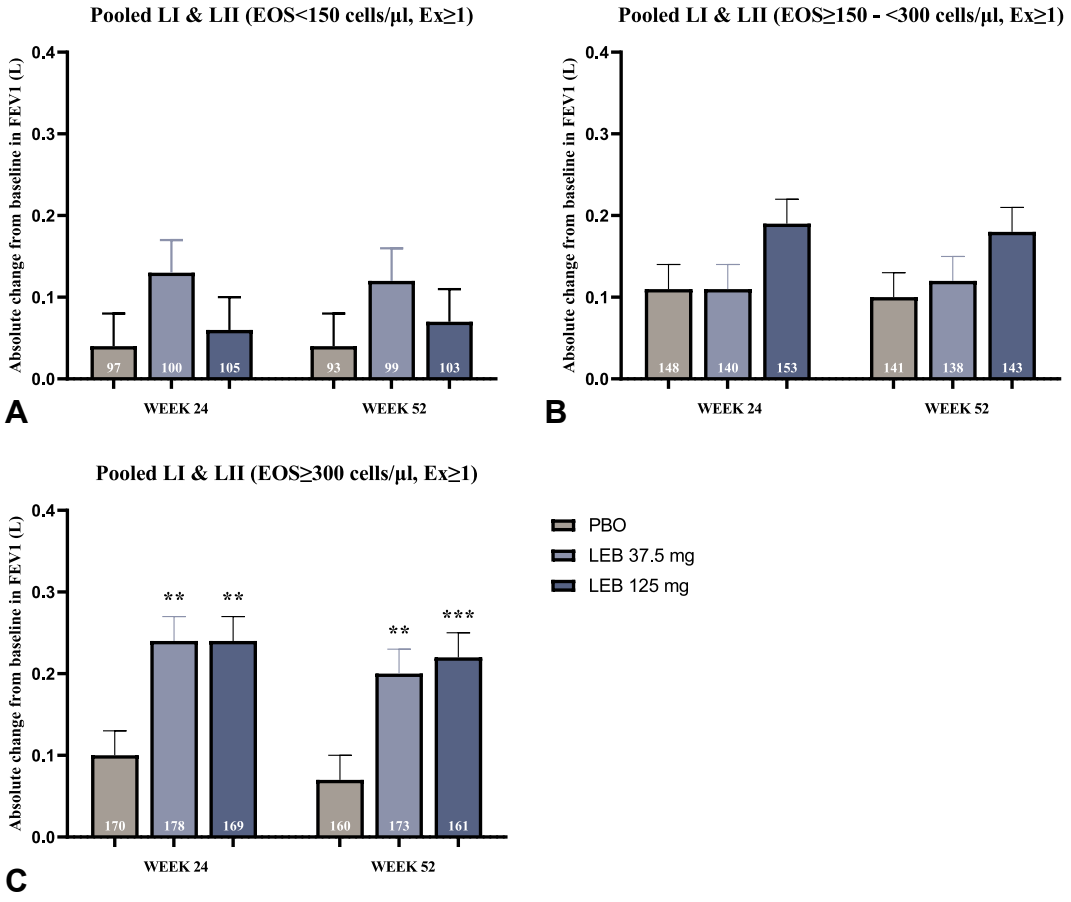


**FIGURE E3.** Absolute change from baseline (**A**) in prebronchodilator $FEV_1$ (L) at weeks 24 and 52 in LAVOLTA patients with eosinophils (EOS) less than 150 cells/µL and one or more prior exacerbations (Ex), (**B**) in LAVOLTA patients with EOS 150 or greater cells/µL to less than 300 cells/µL and one or more prior exacerbations, and (**C**) in LAVOLTA patients with EOS 300 or greater cells/µL and or more prior exacerbations. $***P < .001$, $**P < .01$ vs placebo (PBO). *LEB*, lebrikizumab.

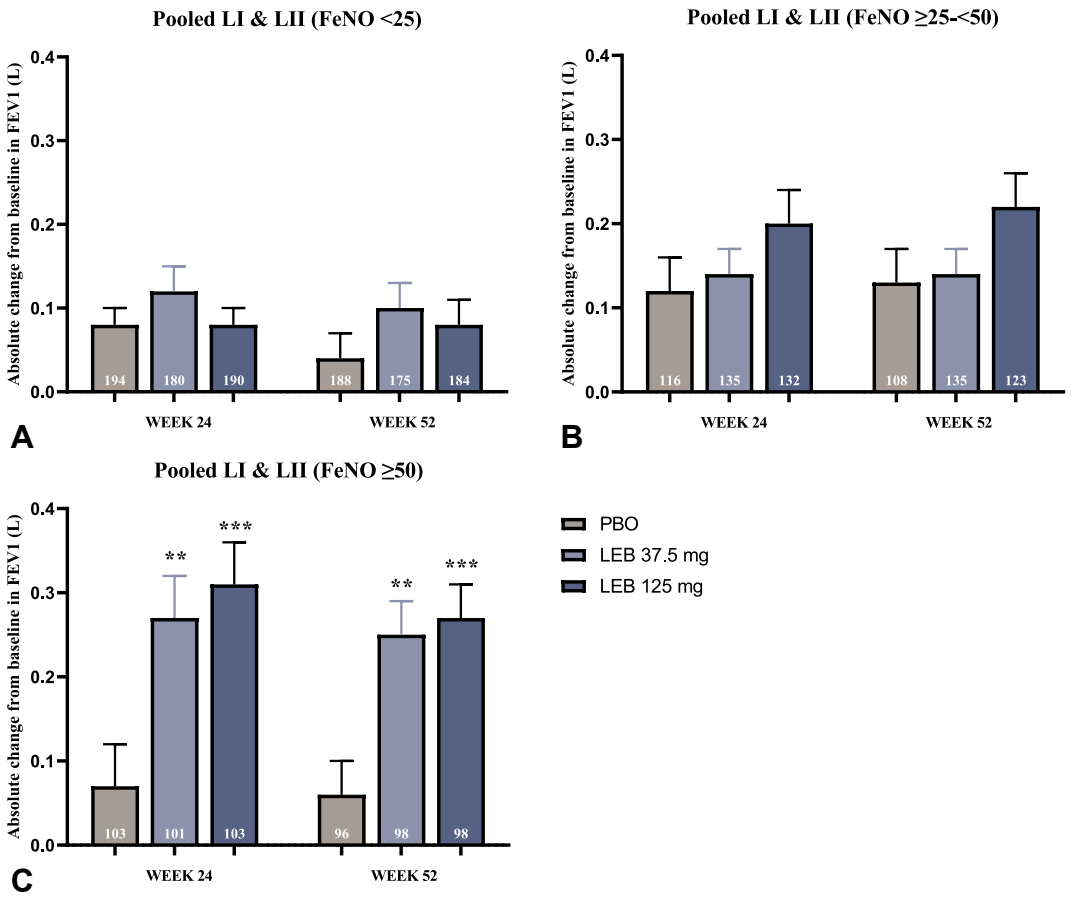


**FIGURE E4.** Absolute change from baseline in (**A**) prebronchodilator $FEV_1$ (L) at weeks 24 and 52 in LAVOLTA patients with FeNO less than 25 mean parts per billion (ppb) and one or more prior exacerbations, (**B**) in LAVOLTA patients with FeNO 25 or greater mean ppb to less than 50 mean ppb and one or more prior exacerbations, and (**C**) in LAVOLTA patients with FeNO 50 or greater mean ppb and one or more prior exacerbations. ***$P < .001$, **$P < .01$ vs placebo (PBO). *PBO*, placebo.