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ORIGINAL ARTICLE

Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies

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ABSTRACT

Introduction In a subset of patients with asthma, standard-of-care treatment does not achieve disease control, highlighting the need for novel therapeutic approaches. Lebrikizumab is a humanised, monoclonal antibody that binds to and blocks interleukin-13 activity.

Methods LUTE and VERSE were replicate, randomised, double-blind, placebo-controlled studies, evaluating multiple doses of lebrikizumab in patients with uncontrolled asthma despite the use of medium-to-high-dose inhaled corticosteroid and a second controller. Patients received lebrikizumab 37.5, 125, 250 mg or placebo subcutaneously every four weeks. The primary endpoint was the rate of asthma exacerbations during the placebo-controlled period. Analyses were performed on prespecified subgroups based on baseline serum periostin levels. Following the discovery of a host-cell impurity in the study drug material, protocols were amended to convert from phase III to phase IIb. Subsequently, dosing of study medication was discontinued early as a precautionary measure. The data collected for analysis were from a placebo-controlled period of variable duration and pooled across both studies.

Results The median duration of treatment was approximately 24 weeks. Treatment with lebrikizumab reduced the rate of asthma exacerbations, which was more pronounced in the periostin-high patients (all doses: 60% reduction) than in the periostin-low patients (all doses: 5% reduction); no dose–response was evident. Lung function also improved following lebrikizumab treatment, with greatest increase in FEV_1 in periostin-high patients (all doses: 9.1% placebo-adjusted improvement) compared with periostin-low patients (all doses: 2.6% placebo-adjusted improvement). Lebrikizumab was well tolerated and no clinically important safety signals were observed.

Conclusions These data are consistent with, and extend, previously published results demonstrating the efficacy of lebrikizumab in improving rate of asthma exacerbations and lung function in patients with moderate-to-severe asthma who remain uncontrolled despite current standard-of-care treatment.

Trial registration numbers The LUTE study was registered under NCT01545440 and the VERSE study under NCT01545453 at http://www.clinicaltrials.gov

Key messages

What is the key question?

- Does anti-interleukin-13 (IL-13) treatment improve outcomes in patients with moderate-to-severe asthma?

What is the bottom line?

- Lebrikizumab, a potent anti-IL-13 monoclonal antibody, reduces exacerbations and improves lung function in moderate-to-severe asthma patients in a pooled analysis of two phase IIb studies.

Why read on?

- To gain understanding of how targeted anti-IL-13 therapy can help asthma patients who remain uncontrolled despite current standard-of-care treatment and how biomarkers can help ensure that patients receive the most appropriate therapy.

INTRODUCTION

Asthma is a complex, heterogeneous disease characterised by a variable clinical course, severity and response to treatment.[1 2] In a subset of patients with asthma, standard-of-care treatment does not adequately control symptoms,[1–4] and this is associated with increased healthcare use and high burden of disease.[5]

Several phenotypes of asthma have been defined[2 6 7] that can be grouped into at least two distinct molecular phenotypes based on the level of expression and activity of type 2 cytokines.[8 9] Type 2 cytokines, which include interleukin (IL)-13, IL-4 and IL-5, contribute to many aspects of asthma pathology including airway inflammation and hyperresponsiveness.[9–11] Of these cytokines, IL-13 has been identified as a central effector cytokine in asthma and recognised as a potential therapeutic target.

Identifying patients whose asthma is type 2-driven is important. Periostin is a matricellular protein that is associated with type 2 inflammation and subepithelial fibrosis in the lung. Bronchial epithelial cells stimulated with IL-13 secrete periostin basolaterally into the extracellular compartment

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and subsequently periostin accumulates in peripheral blood. Periostin in the circulation therefore serves as a surrogate marker for IL-13 activity in the lung.[9 11–13]

Lebrikizumab is a humanised monoclonal antibody that binds to soluble IL-13 with high affinity and blocks signalling through the active IL-4Rα/IL-13Rα1 heterodimer.[8 14 15] In a previous phase II study (MILLY) in patients whose asthma was inadequately controlled despite treatment with inhaled corticosteroids (ICS), lebrikizumab treatment significantly improved the primary endpoint, FEV_1, particularly in patients with higher serum periostin levels.[8] The current studies, LUTE and VERSE, were designed to evaluate the efficacy and safety of different doses of lebrikizumab in a larger number of patients with moderate-to-severe asthma, treated for a longer duration and evaluating the rate of exacerbations as the primary endpoint.

METHODS

Study design

LUTE and VERSE were replicate, randomised, multicentre, double-blind, placebo-controlled studies (NCT01545440 and NCT01545453). The studies were initially designed to enrol approximately 1400 patients each and to include a 52-week double-blind treatment period (see below for study modification). Patients were randomised in a 1:1:1:1 ratio to receive lebrikizumab 37.5, 125, 250 mg, or placebo subcutaneously every four weeks. Randomisation was stratified by baseline serum periostin level, history of asthma exacerbations within the last 12 months and baseline asthma medications. All patients remained on their standard-of-care therapy that consisted of 500–2000 μg/day ICS therapy (fluticasone propionate dry powder inhaler (DPI) or equivalent) and a second eligible asthma controller medication.

Study population

Patients aged 18–75 years with uncontrolled asthma despite daily use of 500–2000 μg/day of fluticasone propionate DPI or equivalent and a second asthma controller medication were included in the studies.[1 16] Second controller medications included long-acting β_2-agonists, leukotriene receptor antagonists, long-acting muscarinic antagonists or theophylline.

Detailed inclusion and exclusion criteria are included in the online supplementary material. Briefly, inclusion criteria included diagnosis of asthma ≥12 months, acute bronchodilator response (≥12% relative improvement) and pre-bronchodilator FEV_1 40–80% of predicted. Uncontrolled asthma was defined as an Asthma Control Questionnaire-5 score ≥1.5 and at least one of the following: symptoms >2 days/week, night-time awakenings ≥1 time/week, use of a short-acting β_2-agonist as rescue medication >2 days/week or interference with normal daily activities. During the screening period, patients were asked to report adherence with background controller medications, and only patients who reported adherence with controller medications could be considered for randomisation. Patients continued their stable background asthma controller medications for the duration of the studies. There was no run-in period as patients remained on their own stable medications and randomised treatment with lebrikizumab or placebo started on day 1. Patients were excluded if they had received maintenance oral corticosteroid treatment within the previous three months or treatment with systemic corticosteroids within the previous four weeks for any reason.

Efficacy and safety assessments

The primary endpoint was the rate of asthma exacerbations during the placebo-controlled period. Due to early termination of dosing, the observation period was variable for each individual patient; see study modification below. An asthma exacerbation was defined as new or increased asthma symptoms that led to treatment with systemic corticosteroids or to hospitalisation. Treatment with systemic corticosteroids was defined as oral, intravenous or intramuscular corticosteroid treatment for ≥3 days or an emergency room visit with ≥1 dose of intravenous or intramuscular corticosteroids. Asthma exacerbations were assessed at each study visit by the investigator using directed questions to assess whether the patient had experienced any asthma exacerbations since the last visit. It was prespecified that the primary and all secondary endpoints would be evaluated separately in the periostin-high and periostin-low groups (based on a cut-point of 50 ng/mL). Spirometry (pre-bronchodilator and post-bronchodilator) was assessed throughout the study, and methods are described in the online supplementary material. A peak flow/eDiary device was used for once-daily measurement of peak expiratory flow (between 5:00 and 11:00) and recording of asthma rescue medication and controller use.

Prespecified secondary endpoints were relative change in pre-bronchodilator FEV_1 from baseline, time to first asthma exacerbation during the placebo-controlled period, change from baseline in the asthma-specific health-related quality-of-life measure, Asthma Quality-of-Life Questionnaire (standardised; (AQLQ (S))), change in asthma rescue medication use from baseline, rate of urgent asthma-related healthcare use (ie, hospitalisations, emergency department visits and acute care visits) during the placebo-controlled period.

Safety endpoints were the rate and severity of adverse events (AEs) during the placebo-controlled and follow-up periods and the incidence of antitherapeutic antibodies (ATAs) during the study relative to baseline.

Study modification

A host cell protein impurity (PLBL2)[17] was identified after the initiation of the studies. This required manufacturing process changes to the drug product. As a consequence, the studies were no longer considered pivotal studies and the protocols were amended from phase III to phase IIb. Upon conversion to phase IIb, it was decided that each study would enrol 225 patients from approximately 70 sites located in the USA (for a total of 450 patients). The planned placebo-controlled period was of 28–52 weeks' duration, with a variable number of doses administered depending on when the patients enrolled in the studies. After the treatment period, patients were followed for safety for 24 weeks (>5 half-lives of the drug) following the last dose of study drug, including those who discontinued treatment early (see online supplementary figure S1). The protocols further specified that data from the two studies would be pooled for analysis and an internal administrative review of the unblinded data would inform the design of subsequent phase III clinical studies.

Coincident with the administrative data readout, results from an immunoassay designed to measure immune response to the host cell protein impurity demonstrated that nearly all lebrikizumab-treated patients showed an immune response. At that point, a decision was made to discontinue dosing early as a precautionary measure to avoid patients' further exposure to the impurity-containing study drug material. All patients were asked to complete the safety follow-up period.

Statistical analyses

Data obtained from LUTE and VERSE were pooled for analysis. Based on the sample size and treatment duration as originally

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planned in the phase IIb protocols, the combined sample size of approximately 450 patients (56 patients per treatment arm per periostin subgroup) was estimated to provide 70% power to detect a 50% reduction in the rate of exacerbations within each periostin subgroup for a given lebrikizumab dose group compared with placebo. Calculations were based on a Poisson regression model and two-sided test at the $\alpha=0.20$ level with the assumption of an average rate of 0.6 exacerbations per patient-year in the placebo arm, a 20% dropout rate and 20% Poisson over-dispersion.

As prespecified in the protocols, analysis of the primary efficacy and all secondary efficacy endpoints were performed separately in periostin-high (≥50 ng/mL) and periostin-low (<50 ng/mL) subgroups.

Because dosing was stopped early, all efficacy analyses were considered at that point to be exploratory, and results for efficacy outcomes were primarily summarised in a descriptive fashion. Point estimates of treatment effect were provided along with 95% CIs. P values for specific comparisons of interest were included, as supportive information, without adjustments for multiplicity comparisons. Owing to incomplete data at later time points, the primary time point used for comparison of the lebrikizumab arms versus the placebo arm for secondary or exploratory outcomes was week 12.

RESULTS

Patients

The pooled population included a total of 463 patients. The LUTE study randomised 258 (56%) patients and the VERSE study 205 (44%) patients. At the time of dosing termination, patients discontinued the placebo-controlled treatment period and entered into the 24-week safety follow-up period.

The baseline demographic and disease characteristics were similar across treatment groups (table 1).

Because dosing was terminated early, not all patients had the opportunity to participate in the placebo-controlled treatment period for the minimum duration (ie, seven doses of study drug over 28 weeks) as specified in the amended protocols.

The median duration of treatment was 24.1 weeks, and the median time spent in the study, including the safety follow-up period, was 44.1 weeks (table 2). Patients received a median of six (range 1–12) doses of study drug during the placebo-controlled period (table 2).

Efficacy

Asthma exacerbations

For the primary outcome, lower exacerbation rates were observed in the lebrikizumab treatment groups compared with placebo (table 3). The exacerbation rate reduction compared with placebo was more pronounced in periostin-high patients than in periostin-low patients (table 3). In periostin-high patients, there was a 60% (95% CI 18% to 80%) reduction in the rate of exacerbations for the lebrikizumab dose groups combined compared with placebo in periostin-high patients. In the periostin-low patients, only a 5% (95% CI −81% to 47%) reduction was observed (table 3).

Table 1 Patient baseline characteristics

	Placebo (n=116)	Lebrikizumab 37.5 mg (n=117)	Lebrikizumab 125 mg (n=112)	Lebrikizumab 250 mg (n=118)
Age, mean (SD), years	50.0 (13.3)	48.7 (13.1)	46.8 (13.4)	47.9 (11.9)
Female, n (%)	74 (63.8)	72 (61.5)	60 (53.6)	69 (58.5)
Weight, mean (SD), kg	86.1 (17.3)	85.2 (17.4)	86.7 (18.1)	87.1 (17.0)
Race				
White	84 (72.4)	91 (77.8)	87 (77.7)	86 (72.9)
Black	25 (21.6)	21 (17.9)	17 (15.2)	17 (14.4)
Asian	1 (0.9)	4 (3.4)	2 (1.8)	6 (5.1)
Other	6 (5.2)	1 (0.9)	6 (5.4)	9 (7.6)
Ethnicity				
Hispanic or Latino	14 (12.1)	13 (11.1)	6 (5.4)	18 (15.3)
Not Hispano or Latino	102 (87.9)	104 (88.9)	105 (93.8)	100 (84.7)
Not reported	0	0	1 (0.9)	0
Number of asthma exacerbations in the last 12 months, n (%)				
0	59 (50.9)	60 (51.3)	61 (54.5)	62 (52.5)
1–2	47 (40.5)	47 (40.2)	43 (38.4)	44 (37.3)
≥3	10 (8.6)	10 (8.5)	8 (7.1)	12 (10.2)
Baseline ICS* dose ≥1000 μg/day+LABA use, n (%)	46 (39.7)	49 (41.9)	53 (47.3)	54 (45.8)
Pre-bronchodilator FEV_1 (% of predicted), mean (SD)	62.7 (10.2)	62.5 (10.2)	62.8 (10.9)	60.9 (10.2)
Best bronchodilator response (% relative improvement), mean (SD)	21.9 (11.4)	23.4 (16.7)	23.2 (17.5)	23.8 (14.6)
AQLQ(S), mean (SD)	4.4 (0.8)	4.5 (0.8)	4.5 (0.7)	4.4 (0.8)
ACQ-5, mean (SD)	3.3 (0.8)	3.2 (0.8)	3.2 (0.7)	3.3 (1.0)
IgE, median, IU/mL	149.0	153.0	146.5	124.0
Periostin, median (day −7) (ng/mL)	46.4	49.5	47.3	48.7
<50, n (%)	74 (63.8)	60 (51.3)	69 (61.6)	65 (55.1)
≥50 , n (%)	42 (36.2)	57 (48.7)	43 (38.4)	53 (44.9)
Eosinophils, mean (SD),10^3/μL	0.36 (0.69)	0.30 (0.18)	0.28 (0.22)	0.31 (0.30)
FeNO, mean (SD), ppb	26.8 (24.9)	27.8 (30.0)	31.3 (24.6)	29.3 (27.6)

*Fluticasone dry powder inhaler or equivalent.
ACQ-5, Asthma Control Questionnaire-5; AQLQ(S), Asthma Quality-of-Life Questionnaire (standardised); ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting β_2-agonist.

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Table 2 Time in study and drug exposure

	Placebo (n=116)	Lebrikizumab 37.5 mg (n=117)	Lebrikizumab 125 mg (n=112)	Lebrikizumab 250 mg (n=118)
LUTE, n (%)	66 (56.9)	64 (54.7)	62 (55.4)	66 (55.9)
VERSE, n (%)	50 (43.1)	53 (45.3)	50 (44.6)	52 (44.1)
Time in placebo-controlled period (weeks)				
Median	24.1	24.1	28.1	24.1
<12, n (%)	17 (14.7)	21 (17.9)	13 (11.6)	22 (18.6)
12 to <24, n (%)	34 (29.3)	33 (28.2)	31 (27.7)	35 (29.7)
24 to <36, n (%)	37 (31.9)	37 (31.6)	33 (29.5)	31 (26.3)
≥36, n (%)	28 (24.1)	26 (22.2)	35 (31.3)	30 (25.4)
Time in study (weeks)				
Median	44.0	41.0	44.5	41.1
<24, n (%)	6 (5.2)	10 (8.5)	9 (8.0)	10 (8.5)
24 to <36, n (%)	28 (24.1)	27 (23.1)	23 (20.5)	31 (26.3)
≥36, n (%)	82 (70.7)	80 (68.4)	80 (71.4)	77 (65.3)
Number of doses received				
Median (range)	6.0 (2–12)	6.0 (1–12)	7.0 (1–12)	6.0 (1–12)

There was no clear dose–response for lebrikizumab on exacerbations. Compared with placebo, the exacerbation rate was reduced by 81% (95% CI 35% to 97%), 77% (95% CI 26% to 95%) and 22% (95% CI −62% to 63%) in periostin-high patients and by 33% (95% CI −53% to 73%), −17% (95% CI −141% to 42%) and 5% (95% CI −114% to 59%) in periostin-low patients in the lebrikizumab 37.5, 125 and 250 mg groups, respectively (figure 1). Kaplan–Meier plots of time to first exacerbation are shown in the online supplementary material (see online supplementary figure S2) as are exacerbation data for each trial (see online supplementary table S1).

Lung function

The mean relative change in FEV_1 for the pooled lebrikizumab group versus placebo from baseline to week 12 in periostin-high patients was 9.1% and 2.6% in periostin-low patients. By dose, in periostin-high patients, this was 6.8% (95% CI −0.7% to 14.4%) in the lebrikizumab 37.5 mg group, 10.7% (95% CI 0.6% to 20.7%) in the lebrikizumab 125 mg group and 10.1% (95% CI 1.3% to 18.9%) in the lebrikizumab 250 mg group (figure 2). In comparison, in periostin-low patients, the mean relative change from baseline in FEV_1 versus placebo was −1.9% (95% CI −8.3% to 4.6%) in the lebrikizumab 37.5 mg group, 2.2% (95% CI −3.4% to 7.9%) in the lebrikizumab 125 mg group and 7.2% (95% CI −0.7% to 15.2%) in the lebrikizumab 250 mg group.

Secondary outcomes

Other secondary outcomes at week 12 are summarised in table 4 and described in more detail in the online supplementary material. Briefly, there was evidence of increased time to first exacerbation with lebrikizumab treatment in periostin-high patients, especially in the 37.5 and 125 mg groups, and a similar effect reducing the rate of urgent asthma-related healthcare use in periostin-high patients. For other outcomes including the patient-reported AQLQ, there was little indication of treatment differences but CI were wide, thus limiting interpretation.

Biomarkers

Figure 3 shows the average change in biomarker values (FeNO, blood eosinophils and serum periostin) at each study visit through to week 12 by treatment group in periostin-high and

Table 3 Protocol-defined asthma exacerbations during the placebo-controlled period

	Placebo (n=116)	Lebrikizumab 37.5 mg (n=117)	Lebrikizumab 125 mg (n=112)	Lebrikizumab 250 mg (n=118)	Lebrikizumab dose groups combined (n=347)
Periostin-high patients (≥50 ng/mL), n	42	57	43	53	153
Total number of exacerbations	21	5	5	19	29
Total patient-years	20.7	26.6	21.2	24.1	72.0
Exacerbation rate per year	1.01	0.19	0.24	0.79	0.40
Rate reduction vs placebo					
Absolute rate reduction	–	0.82	0.77	0.22	0.61
Percentage rate reduction (95% CI)	–	81% (35 to 97)	77% (26 to 95)	22% (−62 to 63)	60% (18 to 80)
Periostin-low patients (<50 ng/mL), n	74	60	69	65	194
Total number of exacerbations	17	9	20	14	43
Total patient-years	35.4	28.1	35.5	30.7	94.3
Exacerbation rate per year	0.48	0.32	0.56	0.46	0.46
Rate reduction vs placebo					
Absolute rate reduction	–	0.16	−0.08	0.02	0.02
Percentage rate reduction (95% CI)	–	33% (−53 to 73)	−17% (−141 to 42)	5% (−114 to 59)	5% (−81 to 47)

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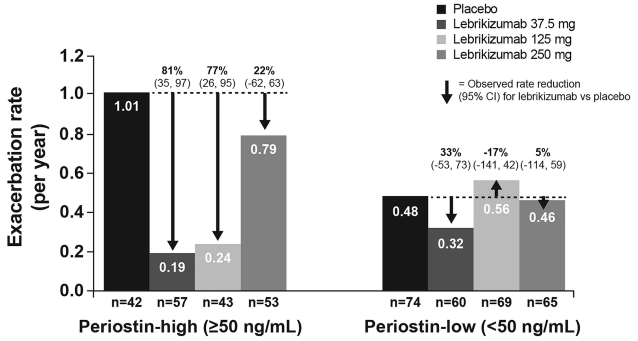

Figure 1 Rate of asthma exacerbations during the placebo-controlled period.

periostin-low patients. More detailed description of methods and results is presented in the online supplementary material.

Preliminary analyses of exacerbation and lung function data stratified by baseline FeNO and blood eosinophil count are provided in the online summary (see online supplementary table S3). Raised FeNO (≥21 ppb) and blood eosinophils (≥240 cells/μL) were both predictive of treatment response to lebrikizumab.

Pharmacokinetics

Pharmacokinetic analyses showed that lebrikizumab concentrations in serum increased roughly proportionally with the dose levels. Overall, the pharmacokinetics of lebrikizumab were as expected based on data from previous trials. The observed mean (SD) of trough concentrations at week 12 were 4.0 (±1.9), 14.2 (±6.4) and 26.5 (±11.1) μg/mL for the 37.5, 125 and 250 mg dose groups, respectively. As expected, this shows overlap in the ranges of exposure for the 125 and 250 mg dose.

Safety

Among all patients, 9.7% of patients discontinued treatment prior to the discontinuation of dosing, with similar rates across treatment groups (see online supplementary figure S1). The incidence of AEs was generally similar across the treatment groups (table 5). In total, 30 serious adverse events (SAEs) were reported in 21 patients during the entire study (including the safety follow-up period) and 12 SAEs were reported in nine patients during the placebo-controlled part of the study (see online supplementary material for details). Injection site reactions were numerically higher in the lebrikizumab 125 and 250 mg dose groups compared with the lebrikizumab 37.5 mg group or placebo (20.5%, 20.3%, 11.1% and 6.0%, respectively). There were 11 AEs leading to withdrawal of study drug, 8 in lebrikizumab-treated patients and 3 in placebo (see online supplementary material for details). AEs leading to discontinuation were varied and did not suggest a safety concern.

Five neoplasms (capturing benign, malignant and unspecified neoplasms including cysts and polyps) were reported during the study, none of which were considered related to study drug (see online supplementary material for details). Two non-serious hypersensitivity reactions were reported in the placebo group and one each in the lebrikizumab 125 and 250 mg groups. There were no cases of anaphylaxis, anaphylactoid or serious hypersensitivity reactions reported during the study. ATAs and antibody response to the impurity identified (PLBL2) were detected but not associated with any AE (more details are available in the online supplementary material).

DISCUSSION

In two replicate studies in patients with moderate-to-severe asthma uncontrolled despite ICS therapy and an additional controller, lebrikizumab administered subcutaneously every four weeks reduced asthma exacerbation rate by 60% (95% CI 18% to 80%) compared with placebo in periostin-high patients and by 5% (95% CI −81% to 47%) in periostin-low patients. In addition, lebrikizumab improved lung function, as measured by change in FEV_1, in periostin-high patients. However, the wide CIs in both exacerbations and lung function measures must be acknowledged. Despite these improvements in lung function, lebrikizumab treatment did not lead to clinically meaningful placebo-corrected improvements in asthma symptoms or quality of life, potentially due to the limited power of the studies for these endpoints. Furthermore, lung function does not always correlate with subjective measures in clinical trials and previous trials of biological therapy that have shown improvements in symptoms or quality of life have reduced background therapy or have involved larger patient populations.[18 19] Lebrikizumab was generally well tolerated and no clinically important safety signals were observed. It is also notable that, besides periostin, both blood eosinophil count and FeNO were predictive of clinically meaningful treatment benefit using biomarker high and low groups defined by the median values for these biomarkers.

In the previous phase II (MILLY) study in moderate-to-severe asthma, lebrikizumab significantly improved lung function, with the greatest changes in periostin-high patients. There was a non-significant trend for a lower exacerbation rate through 24 weeks with lebrikizumab treatment compared with placebo.[8] The placebo-corrected rate of exacerbations was reduced by 67% in periostin-high patients and by 29% in periostin-low patients.[8] The results from the combined phase IIb studies, LUTE and VERSE, extend the findings described previously, in a larger population with more severe asthma. The results from

Figure 2 Mean (SE) percentage change in FEV_1 from baseline up to week 12.

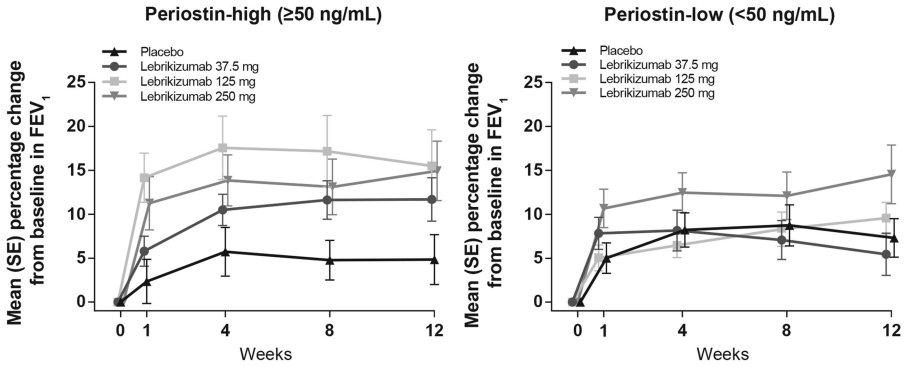

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Table 4 Secondary and exploratory efficacy and pharmacodynamic endpoints

		Lebrikizumab		
	Placebo	37.5 mg	125 mg	250 mg
Change in FEV_1 from baseline to week 12 (%)				
Periostin-high patients (≥50 ng/mL), n	32	42	34	37
Mean (SD)	4.8 (16.1)	11.7 (16.0)	15.5 (24.1)	14.9 (20.6)
Difference in means vs placebo (95% CI)	–	6.8 (−0.7 to 14.4)	10.7 (0.6 to 20.7)	10.1 (1.3 to 18.9)
Periostin-low patients (<50 ng/mL), n	54	41	50	44
Mean (SD)	7.3 (16.2)	5.4 (15.4)	9.6 (12.8)	14.5 (22.1)
Difference in means vs placebo (95% CI)	–	−1.9 (−8.3 to 4.6)	2.2 (−3.4 to 7.9)	7.2 (−0.7 to 15.2)
Change in morning peak expiratory flow from baseline to week 12 (L/min)				
Periostin-high patients (≥50 ng/mL), n	41	49	40	48
Mean (SD)	−2.54 (55.30)	0.40 (52.04)	14.44 (62.72)	8.64 (86.84)
Difference in means vs placebo (95% CI)	–	2.95 (−19.72 to 25.61)	16.98 (−9.20 to 43.16)	11.18 (−19.10 to 41.47)
Periostin-low patients (<50 ng/mL), n	67	52	61	60
Mean (SD)	−3.84 (62.11)	−0.67 (42.42)	4.29 (42.67)	17.08 (44.97)
Difference in means vs placebo (95% CI)	–	3.17 (−15.84 to 22.19)	8.13 (−10.38 to 26.65)	20.92 (2.00 to 39.84)
Time to first asthma exacerbation during the placebo-controlled period				
Periostin-high patients (≥50 ng/mL), n	42	57	43	53
HR (95% CI)	–	0.23 (0.07 to 0.74)	0.30 (0.10 to 0.95)	0.85 (0.37 to 1.92)
Periostin-low patients (<50 ng/mL), n	74	60	69	65
HR (95% CI)	–	0.69 (0.29 to 1.64)	1.21 (0.59 to 2.48)	0.95 (0.44 to 2.05)
Change in AQLQ(S) from baseline to week 12				
Periostin-high patients (≥50 ng/mL), n	34	44	34	39
Mean (SD)	0.7 (0.7)	0.6 (0.7)	1.0 (1.1)	0.8 (0.8)
Difference in means vs placebo (95% CI)	–	−0.1 (−0.4 to 0.3)	0.3 (−0.1 to 0.8)	0.1 (−0.3 to 0.5)
Periostin-low patients (<50 ng/mL), n	55	43	53	46
Mean (SD)	0.6 (0.9)	0.7 (0.8)	0.5 (0.7)	0.8 (0.8)
Difference in means vs placebo (95% CI)	–	0.2 (−0.2 to 0.5)	0.0 (−0.3 to 0.3)	0.3 (−0.1 to 0.6)
Change in asthma rescue medication use from baseline to week 12 (inhalations per day)				
Periostin-high patients (≥50 ng/mL), n	41	49	40	49
Mean (SD)	−1.0 (1.3)	−0.4 (4.1)	−1.3 (2.4)	−0.9 (1.6)
Difference in means vs placebo	–	0.6 (−0.6 to 1.8)	−0.3 (−1.2 to 0.6)	0.0 (−0.6 to 0.6)
Periostin-low patients (<50 ng/mL), n	67	52	61	60
Mean (SD)	−0.5 (1.4)	−0.7 (1.5)	−0.7 (1.4)	−1.1 (1.7)
Difference in means vs placebo	–	−0.2 (−0.7 to 0.3)	−0.2 (−0.7 to 0.3)	−0.6 (−1.1 to 0.0)
Rate of urgent asthma-related healthcare use during placebo-controlled period				
Periostin-high patients (≥50 ng/mL), n	42	57	43	53
Event rate/year	0.58	0.08	0.19	0.41
Rate reduction vs placebo (95% CI), %	–	87 (31 to 99)	67 (−25 to 94)	28 (−88 to 74)
Periostin-low patients (<50 ng/mL), n	74	60	69	65
Event rate/year	0.31	0.18	0.42	0.23
Rate reduction vs placebo (95% CI), %	–	43 (−73 to 84)	−36 (−265 to 47)	27 (−130 to 79)

AQLQ(S), Asthma Quality-of-Life Questionnaire (standardised).

these studies also support the finding that baseline periostin level can be predictive of lebrikizumab treatment benefit. Of note was that periostin-low patients in the placebo group experienced fewer exacerbations than periostin-high patients in the placebo group in the combined phase IIb studies, LUTE and VERSE. Larger phase III trials, currently underway, are required to confirm over longer duration of treatment the effects observed in this study on the rate of asthma exacerbations and lung function, as well as to further investigate whether these improvements can translate into symptom benefits for patients.

The IL-13 contribution to the pathophysiology is not limited to patients with a history of exacerbations. Accordingly, in neither the current studies nor the previous phase II study (MILLY) was a history of exacerbation required. In the combined phase IIb studies, LUTE and VERSE, approximately 52% of patients had not experienced an exacerbation in the previous year. We observed no dose–response for lebrikizumab on exacerbation rates; paradoxically, the lowest rate reduction was observed in the highest dose group. The higher rate of exacerbations in the pooled 250 mg lebrikizumab group is largely driven by a higher number of exacerbations in the periostin-high arm of the VERSE trial (see online supplementary table S1). The reason for this higher rate is unclear. The small sample sizes and short median observation period also contributed to the decrease in precision in the analyses.

The apparently smaller rate reduction in the 250 mg group is unexpected given that a previous study in a similar patient population[8] showed efficacy at 250 mg comparable to that of 125 mg in this study. Furthermore, data from secondary efficacy endpoints and biomarkers reported here do not show a lower

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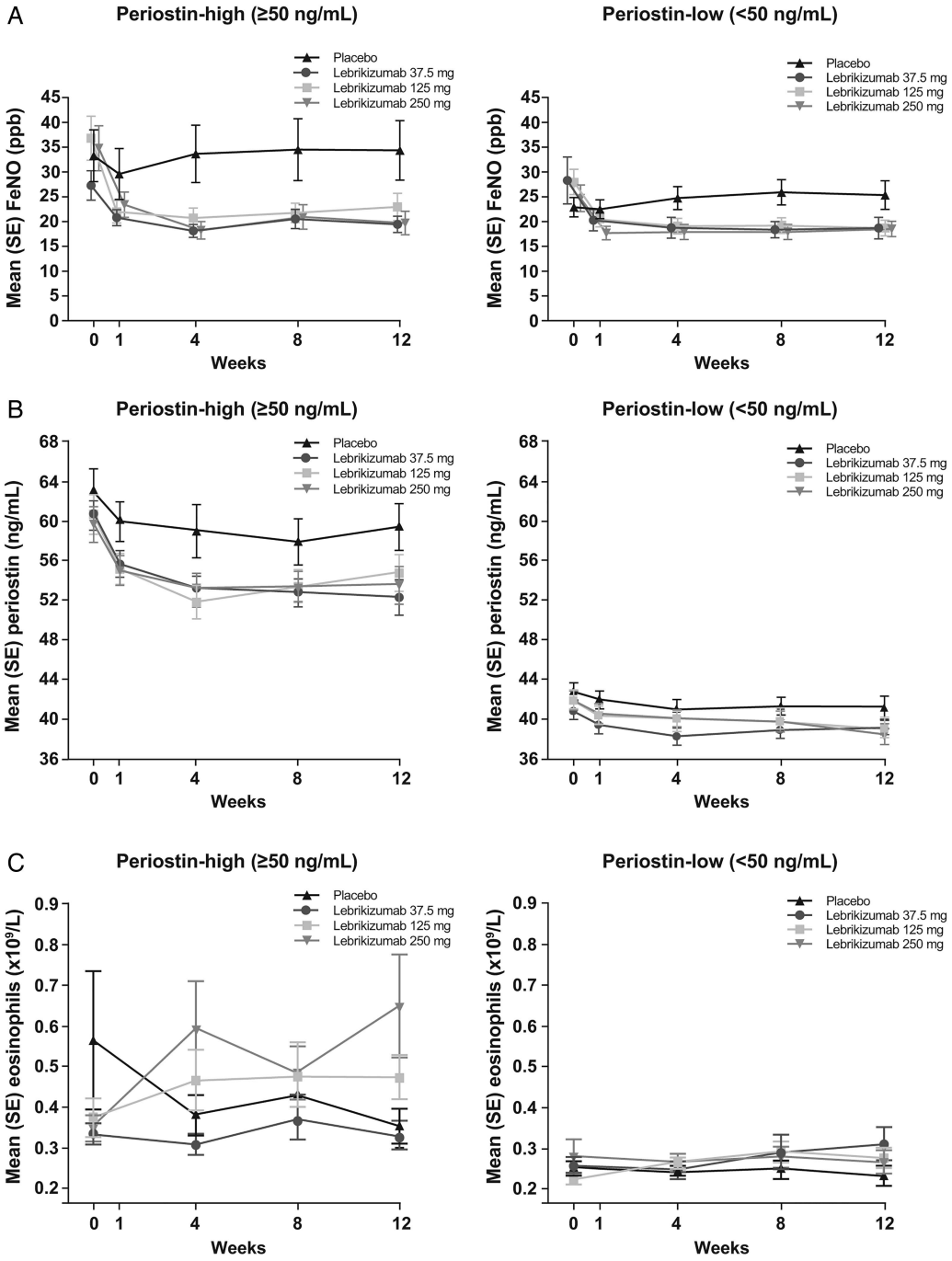

Figure 3 Mean values for (A) FeNO, (B) periostin and (C) blood eosinophils over 12 weeks.

response at 250 mg compared with 125 mg. While there was approximately a twofold difference in the average exposure of the 125 and 250 mg dose groups, there is a partial overlap in the concentration ranges. As there was no apparent relationship between lebrikizumab concentration and exacerbation rate, it suggests a potential plateau in the dose–response. Improvement in FEV_1 was less pronounced in the lebrikizumab 37.5 mg dose cohort compared with the 125 and 250 mg dose cohorts in the periostin-high group, suggesting the 37.5 mg dose was a partially effective dose. The FEV_1 response to lebrikizumab was rapid with improvement within 1 week and near maximal improvements reached by week 4—a pattern also seen in the previous phase II study (MILLY).[8] The mechanism for this rapid response is unclear, although it has been suggested previously that enrolment in a clinical trial may be associated with rapid improvements simply due to improved adherence to background therapy. However, in this study, the patients completed a screening period lasting at least 14 days, during which patients were assessed for adherence with their background asthma therapy and the degree of asthma control provided by their standard-of-care asthma medications. Patients whose symptoms remained uncontrolled during this screening period despite adherence with controller medicines were eligible to participate. Therefore, placebo-corrected improvements in lung function seen during week 1 are unlikely to be due to improved adherence to therapy.

Changes in peripheral blood eosinophil counts have been reported previously[8 20] and may reflect blocking of IL-13

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Table 5 Adverse events (AEs) reported during the entire study

Patients experiencing ≥1 event	Placebo (n=116)	Lebrikizumab 37.5 mg (n=117)	Lebrikizumab 125 mg (n=112)	Lebrikizumab 250 mg (n=118)
Any AE	81 (69.8)	87 (74.4)	90 (80.4)	87 (73.7)
Any serious AE	7 (6.0)	1 (0.9)	6 (5.4)	7 (5.9)
Severe AE	14 (12.1)	14 (12.0)	9 (8.0)	11 (9.3)
Most common AEs (>5% in any treatment group)				
Asthma	33 (28.4)	26 (22.2)	29 (25.9)	33 (28.0)
Upper respiratory tract infection	13 (11.2)	17 (14.5)	26 (23.2)	18 (15.3)
Nasopharyngitis	15 (12.9)	7 (6.0)	13 (11.6)	13 (11.0)
Sinusitis	12 (10.3)	10 (8.5)	12 (10.7)	7 (5.9)
Bronchitis	8 (6.9)	6 (5.1)	9 (8.0)	9 (7.6)
Injection site erythema	2 (1.7)	3 (2.6)	9 (8.0)	12 (10.2)
Acute sinusitis	7 (6.0)	1 (0.9)	7 (6.3)	9 (7.6)
Influenza	5 (4.3)	3 (2.6)	7 (6.3)	6 (5.1)
Injection site pain	4 (3.4)	4 (3.4)	8 (7.1)	4 (3.4)
Back pain	8 (6.9)	4 (3.4)	3 (2.7)	4 (3.4)
Cough	6 (5.2)	4 (3.4)	2 (1.8)	4 (3.4)
Arthralgia	3 (2.6)	2 (1.7)	6 (5.4)	3 (2.5)
Vomiting	2 (1.7)	2 (1.7)	1 (0.9)	6 (5.1)
Erythema	1 (0.9)	2 (1.7)	7 (6.3)	0
AEs of interest				
Any ISR	7 (6.0)	13 (11.1)	23 (20.5)	24 (20.3)
Hypersensitivity reactions (broad*)	2 (1.7)	0	1 (0.9)	1 (0.8)
All infections	62 (53.4)	54 (46.2)	68 (60.7)	60 (50.8)
Neoplasms	1 (0.9)	2 (1.7)	1 (0.9)	2 (1.7)

*Broad search using Anaphylaxis Standardised MedDRA Query (SMQ) as algorithm (based on applying Sampson's criteria as a bucket of search terms) plus the term hypersensitivity. These cases were all cases of hypersensitivity that did not meet criteria for anaphylaxis and none were serious hypersensitivity.
ISR, injection site reaction.

activity. The increased eosinophil counts in blood may be due to decreased migration from blood to the airways due to reduced chemotaxis.[21 22]

Our study has several limitations. The change in study design after initiation of the studies resulted in variation of study drug exposure among patients; however, on average, the exposure was balanced between the treatment arms. Some patients were treated for a relatively short period of time (eg, 1–2 doses) and drug exposures did not reach steady state in all patients. The sample size of 463 patients may not be sufficient to completely understand the dose–response—especially considering exacerbations are relatively infrequent events. In spite of these limitations, these studies confirm the role of periostin as a predictor of response to IL-13-targeted therapy in moderate-to-severe, uncontrolled asthmatics. Neutralising IL-13 activity in periostin-high patients reduced the rate of acute exacerbations and improved FEV_1.

In addition, these studies further confirm the safety profile of lebrikizumab. Injection site reactions were more common in patients with the higher doses of lebrikizumab than with the lower dose or placebo. The assay for antibodies against the host cell impurity PLBL2 detected a response in the majority of lebrikizumab-treated patients; however, the clinical significance of anti-PLBL2 antibodies is not known. No clinically important safety signals were identified in this study.

The results of these studies, while providing further evidence of the safety and efficacy of lebrikizumab in patients with moderate-to-severe uncontrolled asthma, need to be confirmed in larger randomised, double-blind, placebo-controlled phase III clinical studies, which are currently underway.

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Patient consent Obtained.

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Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies

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Supplementary methods

Inclusion criteria

Patients had to meet the following criteria for study entry:

1. Ability and willingness to provide written informed consent and to comply with the study protocol
2. Age 18–75 years old at Visit 1
3. Asthma diagnosis for ≥ 12 months prior to the start of screening (Visit 1)
4. Bronchodilator response at Visits 1, 2, or 3

   A bronchodilator response requires a minimum of 12% relative improvement in the volume of FEV_1 after bronchodilator administration.
5. Pre-bronchodilator FEV_1 40%–80% of predicted at both Visits 2 and 3
6. On ICS therapy corresponding to 500–2000 μg/day of fluticasone propionate DPI or equivalent (total daily dose) for ≥ 6 months prior to the start of screening (Visit 1) with no anticipated changes throughout the study
7. On an eligible second controller medication (LABA, LAMA, LTRA, or theophylline within the prescribed dosing range) for 6 months prior to the start of screening (Visit 1) with no anticipated changes throughout the study
8. Uncontrolled asthma demonstrated both during the screening period (i.e., Visit 1 [Day –14] or Visit 2 [Day –7]) and at the time of randomization (Visit 3 [Day 1]), defined as follows:

   ACQ-5 score ≥ 1.5 **and**

   At least one of the following symptoms of asthma that is not controlled based upon the EPR-3 (2007) and GINA (2010) guidelines:

   - Symptoms > 2 days/week
   - Night-time awakenings ≥ 1 time/week
   - Use of a SABA as rescue medication > 2 days/week
   - Interference with normal daily activities
9. Chest X-ray or computed tomography (CT) scan obtained within the 12 months prior to Visit 1 or chest X-ray during the screening period confirming the absence of other lung disease

   If a chest X-ray (or CT scan) within the 12 months preceding screening (Visit 1) is not available and a chest X-ray cannot be performed and reviewed prior to randomization (Visit 3), the patient will not be eligible for the study.
10. Demonstrated adherence with controller medication of ≥ 70% during the screening period

Adherence is defined as patients responding affirmatively that they have taken their asthma controller therapy ≥ 70% of days during the screening period (Visit 1 to Visit 3) as recorded in their peak flow / diary device.

Exclusion criteria

Patients who met any of the following criteria prior to randomization were excluded from study entry:

1. History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the lebrikizumab injection
2. Maintenance oral corticosteroid therapy, defined as daily or alternate day oral corticosteroid maintenance therapy within the 3 months prior to Visit 1
3. Treatment with systemic (e.g. oral, IV, or IM) corticosteroids within the 4 weeks prior to Visit 1 or at any time during the screening period for any reason, including an acute exacerbation event, or treatment with intraarticular corticosteroids within the 4 weeks prior to Visit 1 or at any time during the screening period
4. A major episode of infection requiring any of the following:
   Admission to the hospital for ≥ 24 hours within the 4 weeks prior to Visit 1 or during screening
   Treatment with IV antibiotics within the 4 weeks prior to Visit 1 or during screening
   Treatment with oral antibiotics within the 2 weeks prior to Visit 1 or during screening
5. Active parasitic infection or *Listeria monocytogenes* infection within the 6 months prior to Visit 1 or during screening
6. Active tuberculosis requiring treatment within the 12 months prior to Visit 1 (patients treated for tuberculosis with no recurrence within the 12 months after completing treatment are permitted)
7. Known immunodeficiency, including, but not limited to, HIV infection
8. Evidence of acute or chronic hepatitis or known liver cirrhosis
9. AST *or* ALT elevation ≥ 2.0 × the upper limit of normal (ULN)
10. History of cystic fibrosis, COPD, and/or other clinically significant lung disease other than asthma
11. Known current malignancy or current evaluation for a potential malignancy
12. Other clinically significant medical disease that is uncontrolled despite treatment or that is likely, in the opinion of the investigator, to require a change in therapy or impact the ability to participate in the study

13. History of alcohol, drug, or chemical abuse that would impair or risk the patient's full participation in the study, in the opinion of the investigator
14. Current smoker, or former smoker with a smoking history of > 10 pack-years

    A current smoker is defined as someone who has smoked one or more cigarettes per day (or marijuana or pipe or cigar) for ≥ 30 days within the 24 months prior to Visit 1 (Day –14).

    Any individual who smokes (cigarettes, marijuana, pipe, or cigar) occasionally, even if for < 30 days within the 24 months prior to Visit 1 (Day –14), must agree to abstain from all smoking from the time of consent through completion of the study.

    A former smoker is defined as someone who has smoked one or more cigarettes per day (or marijuana or pipe or cigar) for ≥ 30 days in his or her lifetime (as long as the 30-day total did not include the 24 months prior to Visit 1 [Day –14]).

    A pack-year is defined as the average number of packs per day times the number of years of smoking.
15. Current use of an immunomodulatory/immunosuppressive therapy or past use within 3 months or 5 drug half-lives prior to Visit 1
16. Use of a biologic therapy including omalizumab at any time during the 6 months prior to Visit 1
17. Use of zileuton or roflumilast at any time during the 4 weeks prior to Visit 1
18. Traditional herbal medicine for treatment of allergic disease or asthma within the 3 months prior to Visit 1
19. Initiation of or change in allergen immunotherapy within the 3 months prior to Visit 1
20. Treatment with an investigational agent within the 30 days prior to Visit 1 (or 5 half-lives of the investigational agent, whichever is longer)
21. Receipt of a live attenuated vaccine within the 4 weeks prior to Visit 1
22. Female patients of reproductive potential who are not willing to use a highly effective method of contraception (e.g., contraceptive pill or transdermal patch, spermicide and barrier [condom], intrauterine device, implants for contraception, injections for contraception [with prolonged release], hormonal vaginal device, sterilization, surgical tubal ligation, or hysterectomy) for the duration of the study (i.e., during the 28- to 52-week placebo-controlled period and for at least 24 weeks after the last dose of study treatment)
23. Female patients who are pregnant or lactating
24. Body mass index > 38 kg/m^2
25. Body weight < 40 kg

Randomisation

Patients were randomised to the treatment arms through the interactive voice/web-based response system (IxRS) provided by Perceptive Informatics, Inc. The IxRS also assigned study treatment kits to patients at each visit during the placebo-controlled period. The placebo and active kits were filled and packaged to look identical.

Efficacy and safety assessments

Asthma exacerbations

At each study visit, the investigator asked directed questions to assess whether the patient had experienced any asthma exacerbations per protocol since the preceding visit. Given that exacerbations were the primary endpoint in this study, a dedicated eCRF was used to record information regarding protocol-defined exacerbation events.

Spirometry

Spirometric measures collected included FEV_1, FVC (volume in litres) and PEF (litres per minute). The percentage of predicted FEV_1 and FVC was derived from these volume measurements using the equations derived from the National Health and Nutrition Examination Survey dataset as described by Hankinson and colleagues.[1] The acceptability of the data, including the graphic representations of the manoeuvres, was determined by blinded over-readers. Calculations for the reproducibility of the acceptable manoeuvres were programmed. The last dose of a short-acting bronchodilator had to be at least 4 hours before testing, the last dose of a LABA at least 12 hours before testing, and the last dose of a LAMA at least 24 hours before testing. For patients who were not properly prepared for testing (e.g. had taken a bronchodilator before arrival), the visit was rescheduled.

Measurement of spirometry was performed on a computerised spirometry system, Vitalograph® Spirotrac® with 6800 Spirometer (Vitalograph; Ennis, Ireland) configured to the requirements of the study and in accordance with guidelines published by the ATS/ERS Standardisation of Spirometry.[2]

Peak flow

Patients were provided with a hand-held peak flow/diary device, Vitalograph® 2120 In2itive e-Diary (Vitalograph), for once daily PEF measurements and e-Diary recording of asthma rescue and controller medication use during the study.

During the screening period, patients established their best baseline value for PEF using the In2itive device. PEF was recorded between 5 am and 11 am daily. Patients were asked to record their PEF prior to taking their morning inhaled medications.

Patients monitored their daily PEF during the placebo-controlled period and during the safety follow-up period using the In2itive device provided.

Inhaled corticosteroid and second controller adherence

Patients were instructed to record the use of ICS plus eligible second controller standard therapy daily in the In2itive device. Patients not adherent with their ICS and second controller standard therapy use from Visits 1–3 (Days –14, –7, and 1), as evidenced by < 70% adherence during the screening period, were not eligible for the study.

Rescue medication

Rescue asthma therapy in this study was defined as SABA therapy use. SABA use was recorded daily in the In2itive device. Each daily recording captured SABA use for the period since the last recording.

Asthma Quality-of-Life Questionnaire (Standardised)

The AQLQ(S) was used to assess the patients' asthma-specific health-related quality of life.[3] The questionnaire contains four domains: activity limitations, symptoms, emotional function, and environmental stimuli. The AQLQ(S) has been validated for use in this study population. The AQLQ(S) has a recall specification of 2 weeks. The AQLQ(S) was administered to the patient prior to all other non-PRO assessments and before the patient received any disease-status information or study treatment during that assessment.

Asthma Control Questionnaire-5

Asthma control as measured by the ACQ-5 [4] was assessed by asking patients to recall their experiences during the previous week and to respond to five questions (i.e. night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheeze). The ACQ-5 had a recall period of 1 week. The items were scored on a scale between 0 (totally controlled) and 6 (extremely poorly controlled). The items were equally weighted, and the score was the mean of five items. During the placebo-controlled period, ACQ-5 was to be measured at baseline, Week 24, and treatment completion. However, given the median treatment duration of 24.1 weeks less than 50% of subjects contributed data for this endpoint.

Biomarker assessments

FeNO was assessed at baseline and at each subsequent study visit, using a hand-held portable device (NIOX MINO®, Aerocrine; Solna, Sweden) in accordance with the American Thoracic Society guidelines.[5] Serum to evaluate periostin levels was collected at screening, baseline, and each subsequent study visit. Periostin was measured using the clinical trial version of the Roche Elecsys® Periostin assay (Roche Diagnostics, Penzberg Germany) on the Cobas e601 platform, which is an electrochemiluminescence immunoassay, using the sandwich principle. Patients, physicians and site staff were blinded to FeNO and periostin values during the study. Haematological assessments, including peripheral blood eosinophil counts, were performed at screening, baseline, and at each subsequent study visit beginning at Week 4 using a central laboratory.

Efficacy analysis by baseline FeNO and blood eosinophil count

Efficacy data were also analysed by FeNO and blood eosinophil levels based on the median FeNO value at baseline (21 ppb) and the median blood eosinophil count at baseline (240 cells/µl).

Antibodies

A bridging immunoassay was used to first screen for and then confirm the presence of ATAs in patient samples. The level of response was measured by titering the confirmed positive samples. The same strategy was used in testing for antibodies to the host cell impurity PLBL2

PK assessments

Free lebrikizumab levels (PK) in serum were measured in quantitative immunoassays

Amended protocol

The placebo-controlled period was changed from 52 weeks to a range of 28–52 weeks. In the original protocol, all patients were to receive 13 doses of lebrikizumab or placebo during a 52 week period. With the amendment, all patients were to receive at least 7 doses of lebrikizumab or placebo during the 24 weeks of minimum-dosing visits. Patients were to continue to receive study drug treatment during the extended-dosing visits (for a maximum of 13 doses during a 48-week period) until the last patient in the study has received 7 doses. All patients were to have a treatment completion visit 4 weeks after completing their last dosing visit, thereby completing a 28- to 52-week placebo-controlled period.

Supplementary results

Exacerbations by trial

The distributions of the number of exacerbations by trial are shown in Table S1. Lebrikizumab appeared to reduce exacerbations in both trials, although not in a dose-dependent manner. There were a higher number of exacerbations in a few patients in the 250 mg lebrikizumab arm of the VERSE trial (8.3% with 2 exacerbations and 8.3% with 3 exacerbations in the periostin-high subgroup and 7.1% with 2 exacerbations in the periostin-low subgroup) that were not apparent in the LUTE trial (3.4% with 2 exacerbations in the periostin-high subgroup). Kaplan-Meier plots for the secondary endpoint 'time to first asthma exacerbation during the placebo-controlled period', are provided (see **Figure S2**). These plots show consistent findings to those from the primary analysis.

Secondary outcomes at Week 12

As shown in Table 4 there was evidence of increased time to first exacerbation with lebrikizumab treatment in periostin-high patients, especially in the 37.5 mg and 125 mg groups. However, there was no indication of change in AQLQ(S) and no change in asthma rescue medication use. There was a trend towards a reduction in the rate of urgent asthma-related healthcare utilisation in periostin-high patients, particularly with 37.5 mg and 125 mg lebrikizumab.

Biomarkers

Figure 3 (main paper) shows the average FeNO value at each study visit through to Week 12 by treatment group in periostin-high and periostin-low patients. Baseline FeNO levels were lower in the placebo and lebrikizumab 37.5 mg groups, as well as in periostin-low patients (**fig. 3**). The changes relative to placebo at Week 12 in periostin-high patients were –3.9 to –12.5 parts per billion (ppb) across the different lebrikizumab dose groups. At Week 12 in periostin-low patients the differences between the means in FeNO were –8.9 to –11.0 ppb across the lebrikizumab dose groups relative to placebo.

Baseline levels of peripheral blood eosinophils were well balanced across different treatment arms (**table 1**). At Week 12 there was a small increase in absolute blood eosinophil levels with lebrikizumab, particularly in periostin-high subjects. The placebo-corrected change ranged from 0.29 to 0.56 $x10^3$/μL in periostin-high patients and from –0.01 to 0.07 $x10^3$/μL in the periostin-low group (**table S2**). In the periostin-high group, the increase in peripheral blood eosinophils appeared to be dose dependent, with the 37.5 mg demonstrating the smallest changes (**fig. 3**).

Baseline levels of serum periostin were also well balanced across different treatment arms (**table 1**) with a median (Day –7) value across all groups of 47.9 ng/mL. At Week 12, following lebrikizumab treatment, there was a placebo-corrected decrease of 3.7–8.3% in periostin in periostin-high subjects (**table S2**) and little change in periostin-low subjects. There was no clear evidence of dose-dependent changes in periostin levels (**fig. 3**). Supplement **figure S3** shows the biomarker data as mean change from baseline.

Efficacy data by baseline FeNO and blood eosinophil measurement

Asthma exacerbations

As for periostin, the exacerbation rate reduction compared with placebo was more pronounced in FeNO-high (≥ 21 ppb) and eosinophil-high patients (≥ 240 cells/µl) than in respective FeNO-low (< 21 ppb) and eosinophil-low patients (< 240 cells/µl) (**table S3**). In FeNO-high patients there was a 48% reduction in the rate of exacerbations for the lebrikizumab dose groups combined compared with placebo. In the FeNO-low patients, a 27% reduction was observed (**table S3**). In eosinophil-high patients there was a 39% reduction in the rate of exacerbations for the lebrikizumab dose groups combined compared with placebo. In the eosinophil-low patients, a 19% reduction was observed.

Lung function

Similarly, for relative change in FEV_1 from baseline to Week 12 there was 7.2% improvement with lebrikizumab compared with placebo in FeNO-high patients and 2.0% in FeNO-low patients, and an 8.7% improvement with lebrikizumab compared with placebo in eosinophil-high patients and 2.6% in eosinophil-low patients (**table S3**).

Anti-therapeutic antibodies and anti-PLBL2

Of the 347 lebrikizumab-treated patients, 329 had adequate samples for ATA evaluation (i.e. pre-treatment as well as an appropriately timed post-treatment sample). A total of 26 patients tested positive for ATA after receiving study drug (plus one patient in the placebo group). This included 12 (10%) patients in the lebrikizumab 37.5 mg, 7 (6%) patients in the lebrikizumab 125 mg, and 7 (6%) in the lebrikizumab 250 mg groups. A total of 6 patients, all in the lebrikizumab arms (2% of total) were positive at baseline (three patients in the 37.5 mg group, two patients in the 125 mg group and one patient in the 250 mg group). Fifteen of the positive patients were considered to be transiently positive (duration of response lasting less than 16 weeks), while the

remaining 11 patients were considered to be persistently positive. Onset of the positive response was by Week 12 in nearly all cases.

Two of these patients (one patient in the 125 mg group and one patient in the 250 mg group) showed potential impact of ATA on their pharmacokinetic profiles. However, no clear evidence of the effect of ATA development on efficacy and PD biomarkers was observed. No apparent differences in safety were evident when comparing data from these patients with data from other similarly treated patients. There was no correlation between ATA status and injection site reactions or any hypersensitivity or immunological events. There was dose-dependent correlation with ATA detection.

A process-related Chinese hamster ovary CHO-derived protein impurity was identified in the lebrikizumab clinical trial material used in this study. This material has been identified as CHO PLBL2.

Samples were tested for the presence of anti-PLBL2 antibodies at the same time points as ATA (**Table S4**). The clinical significance of anti-PLBL2 antibodies is not known. No clinically important safety signals were identified in this study and no correlation between safety events could be made.

Safety

Twelve serious AEs were reported in nine patients during the placebo-controlled part of the study: two patients in the placebo group (umbilical hernia, muscle strain), three patients in the lebrikizumab 125 mg group (intervertebral disc protrusion, gonococcal arthritis, organ donation, anaemia, rectal haemorrhage) and four patients in the lebrikizumab 250 mg group (back pain, chest pain, syncope, fractured coccyx, pleural effusion [presentation of non-Hodgkin's lymphoma noted below]).

The events leading to study drug withdrawal included two cases of asthma and one case of hypersensitivity in the placebo group, one injection site rash in the lebrikizumab 37.5 mg group, one case each of cough, rash and injection site pruritus in the lebrikizumab 125 mg group and one case each of injection site reaction, hypersensitivity, pleural effusion and fibromyalgia in the lebrikizumab 250 mg group.

Five neoplasms (capturing benign, malignant and unspecified neoplasms including cysts and polyps) were reported during the study, none of which were considered related to study drug;

placebo group: skin papilloma, lebrikizumab 37.5 mg group: stage I breast cancer, lebrikizumab 125 mg group: a uterine leiomyoma, and lebrikizumab 250 mg group: non-Hodgkin's lymphoma and an intraductal proliferative breast lesion. In addition, a benign pituitary tumour was reported in the lebrikizumab 37.5 mg group.

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Supplementary data

Table S1. Number of exacerbations per patient during the placebo-controlled period, pooled data and by trial

		Placebo (n=116)		Lebrikizumab 37.5 mg (n=117)		Lebrikizumab 125 mg (n=112)		Lebrikizumab 250 mg (n=118)	
		Periostin -high	Periostin -low	Periostin -high	Periostin -low	Periostin -high	Periostin -low	Periostin -high	Periostin -low
Pooled									
Number of	0	73.8	81.1	93.0	86.7	90.7	76.8	77.4	81.5
exacerbations	1	9.5	14.9	5.3	11.7	7.0	17.4	13.2	15.4
per patient	2	9.5	4.1	1.8	1.7	2.3	5.8	5.7	3.1
	3	7.1	0.0	0.0	0.0	0.0	0.0	3.8	0.0
LUTE									
Number of	0	70.8	81.0	96.9	84.4	96.0	75.7	89.7	81.1
exacerbations	1	12.5	16.7	3.1	12.5	4.0	18.9	6.9	18.9
per patient	2	12.5	2.4	0.0	3.1	0.0	5.4	3.4	0.0
	3	4.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
VERSE									
Number of	0	77.8	81.3	88.0	89.3	83.3	78.1	62.5	82.1
exacerbations	1	5.6	12.5	8.0	10.7	11.1	15.6	20.8	10.7
per patient	2	5.6	6.3	4.0	0.0	5.6	6.3	8.3	7.1
	3	11.1	0.0	0.0	0.0	0.0	0.0	8.3	0.0

All values are percentage of patients

Table S2. Secondary and exploratory efficacy and pharmacodynamic endpoints

	Placebo	Lebrikizumab		
		37.5 mg	125 mg	250 mg
Change in FeNO from baseline to Week 12 (ppb)				
Periostin-high patients (≥50 ng/mL), n	34	42	34	39
Mean (SD)	–1.94 (11.92)	–5.80 (14.88)	–14.40 (24.54)	–11.32 (22.37)
Difference in means vs placebo (95% CI)	—	–3.86 (–9.98, 2.27)	–12.46 (–21.86, –3.05)	–9.38 (–17.63, –1.13)
Periostin-low patients (<50 ng/mL), n	54	43	52	46
Mean (SD)	2.54 (12.43)	–6.35 (16.25)	–6.45 (14.71)	–8.43 (20.52)
Difference in means vs placebo (95% CI)	—	–8.89 (–14.86, –2.91)	–8.99 (–14.25, –3.73)	–10.97 (–17.88, –4.06)
Change in blood eosinophils from baseline to Week 12 ($x10^3$/μL)				
Periostin-high patients (≥50 ng/mL), n	31	39	31	37
Mean (SD)	–0.28 (1.18)	0.01 (0.19)	0.12 (0.22)	0.28 (0.60)
Difference in means vs placebo (95% CI)	—	0.29 (–0.15, 0.72)	0.39 (–0.04, 0.83)	0.56 (0.09, 1.03)
Periostin-low patients (<50 ng/mL), n	54	43	50	45
Mean (SD)	–0.01 (0.13)	0.07 (0.23)	0.06 (0.13)	–0.02 (0.38)
Difference in means vs placebo (95% CI)	—	0.07 (0.00, 0.15)	0.07 (0.02, 0.12)	–0.01 (–0.13, 0.11)
Change in serum periostin from baseline to Week 12 (%)				
Periostin-high patients (≥50 ng/mL), n	28	34	29	35
Mean (SD)	–5.4 (13.6)	–13.7 (14.1)	–9.1 (14.5)	–9.1 (12.5)
Difference in means vs placebo (95% CI)	—	–8.3 (–15.4, –1.2)	–3.7 (–11.2, 3.8)	–3.7 (–10.3, 3.0)
Periostin-low patients (<50 ng/mL), n	53	41	47	44
Mean (SD)	–4.0 (12.5)	–1.7 (18.5)	–4.3 (15.7)	–7.7 (13.4)
Difference in means vs placebo (95% CI)	—	2.2 (–4.5, 8.9)	–0.3 (–6.0, 5.4)	–3.7 (–9.0, 1.6)

FEV_1: forced expiratory volume in 1 sec; AQLQ(S): Asthma Quality of Life Questionnaire (Standardised); FeNO: fractional exhaled nitric oxide.

Table S3. Efficacy data by FeNO and blood eosinophil stratification

		Placebo	Lebrikizumab (dose groups pooled)
Asthma exacerbations during placebo-controlled period			
FeNO ≥ 21 ppb	n	49	178
	Rate (per year)	0.98	0.51
	Rate reduction* (95% CI)	--	48% (2%, 72%)
FeNO < 21 ppb	n	63	163
	Rate (per year)	0.48	0.35
	Rate reduction* (95% CI)	--	27% (-48%, 62%)
Eosinophil count ≥ 240 cells/µl	n	66	176
	Rate (per year)	0.88	0.53
	Rate reduction* (95% CI)	--	39% (-7%, 65%)
Eosinophil count < 240 cells/µl	n	50	171
	Rate (per year)	0.41	0.33
	Rate reduction* (95% CI)	--	19% (-101%, 63%)
Relative change in FEV_1 from baseline to Week 12 (%)			
FeNO ≥ 21 ppb	n	36	128
	Mean (SD)	9.0 (19.6)	16.2 (22.0)
	Difference in means (95% CI)	--	7.2 (-0.4, 14.7)
FeNO < 21 ppb	n	48	116
	Mean (SD)	4.6 (13.1)	6.6 (12.6)
	Difference in means (95% CI)	--	2.0 (-2.4, 6.5)
Eosinophil count ≥ 240 cells/µl	n	50	127
	Mean (SD)	8.4 (16.7)	17.0 (19.9)
	Difference in means (95% CI)	--	8.7 (2.8, 14.5)
Eosinophil count < 240 cells/µl	n	36	121
	Mean (SD)	3.6 (15.1)	6.2 (15.7)
	Difference in means (95% CI)	--	2.6 (-3.2, 8.3)

* lebrikizumab vs. placebo

Table S4. Immunogenicity results

Treatment (mg)	Pre-dose positives (%)	Negative, all time points (%)	Post-dose positives, any time (%)
Anti-therapeutic antibodies			
Placebo	0	99	1
Lebrikizumab 37.5	3	90	10
Lebrikizumab 125	2	94	6
Lebrikizumab 250	1	94	6
Anti-CHO PLBL2			
Placebo	10	89	11
Lebrikizumab 37.5	11	24	76
Lebrikizumab 125	10	10	90
Lebrikizumab 250	8	10	90

Figures

Figure S1. Study design and patient disposition

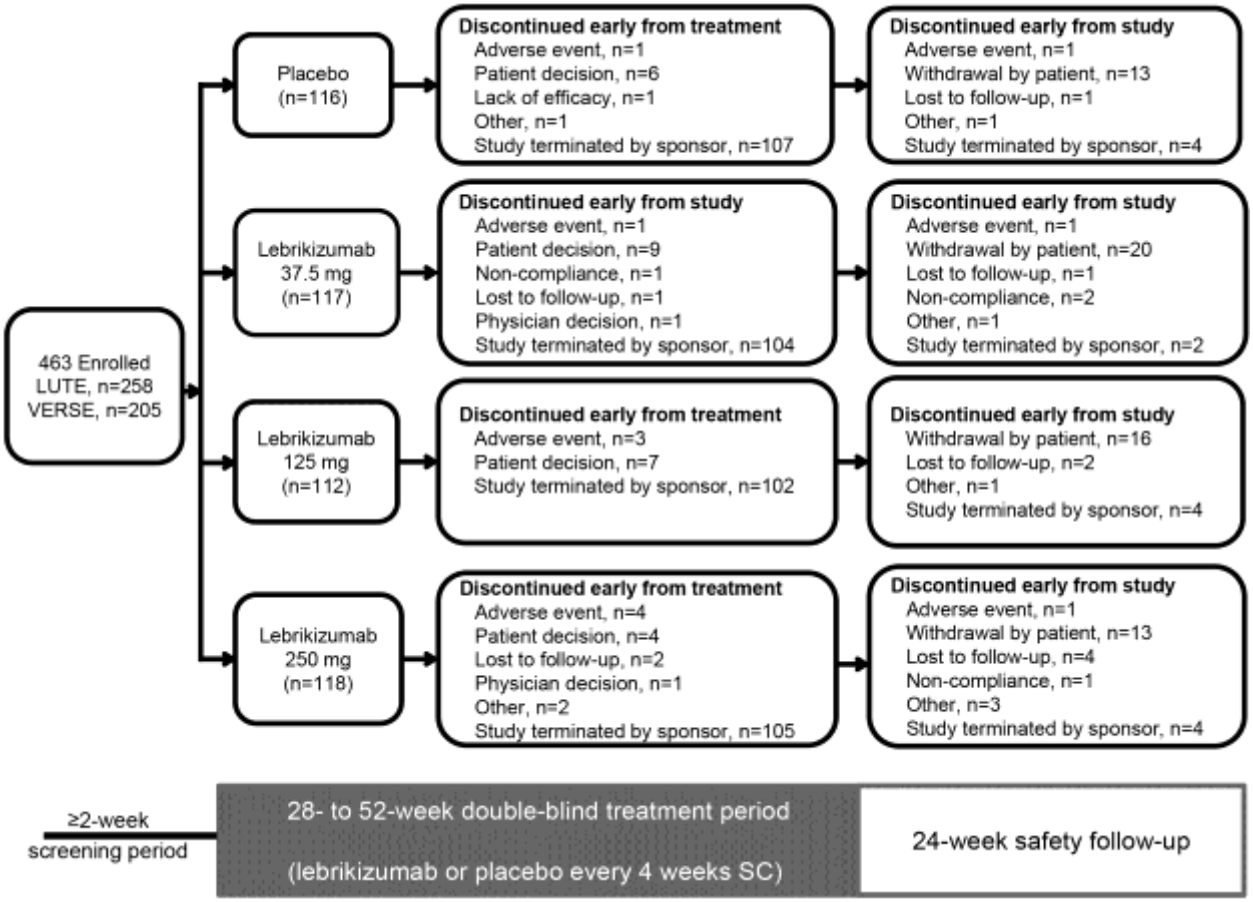

Figure S2. Kaplan-Meier plots of time to first exacerbation in a) periostin-high patients and b) periostin-low patients

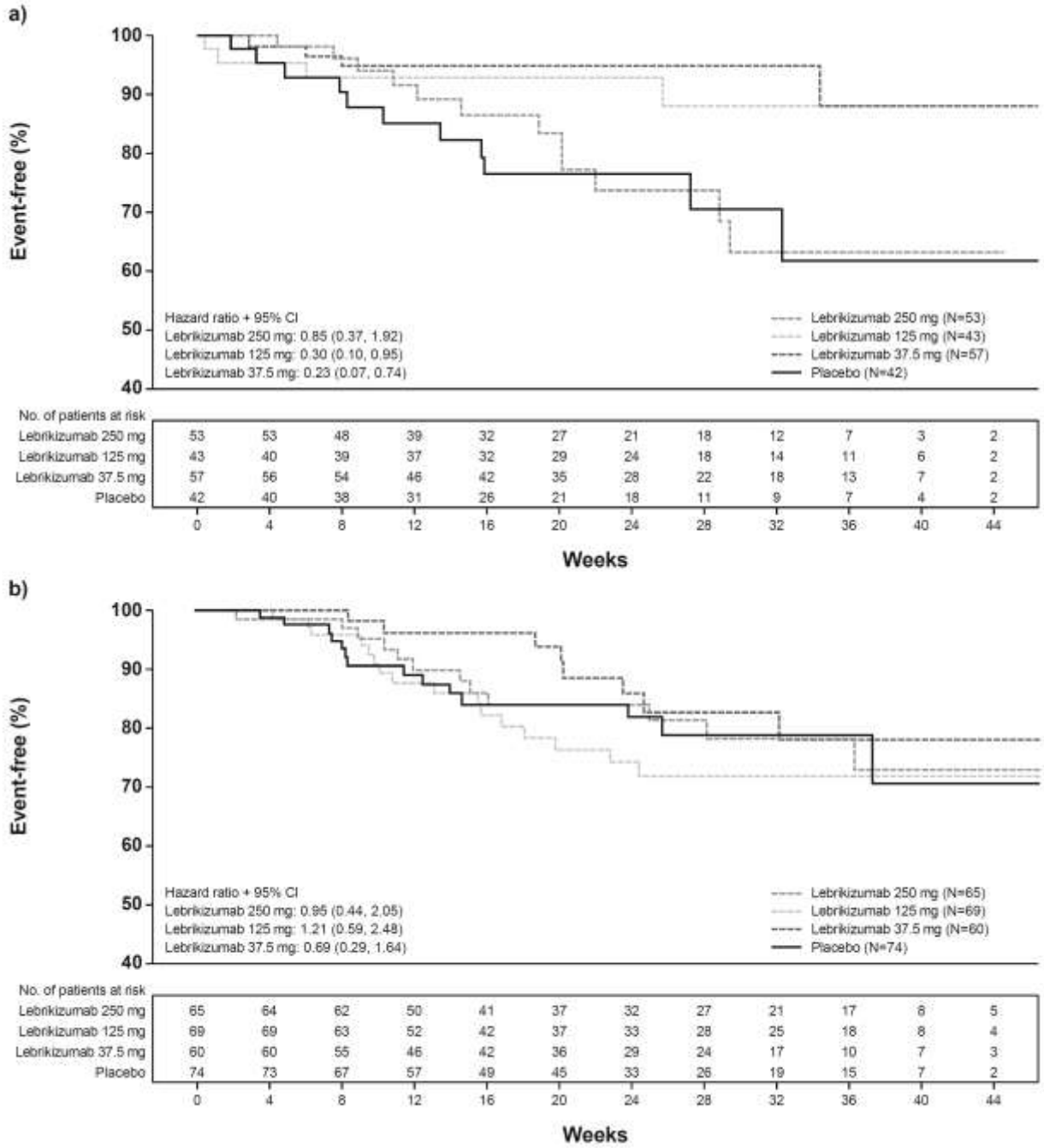
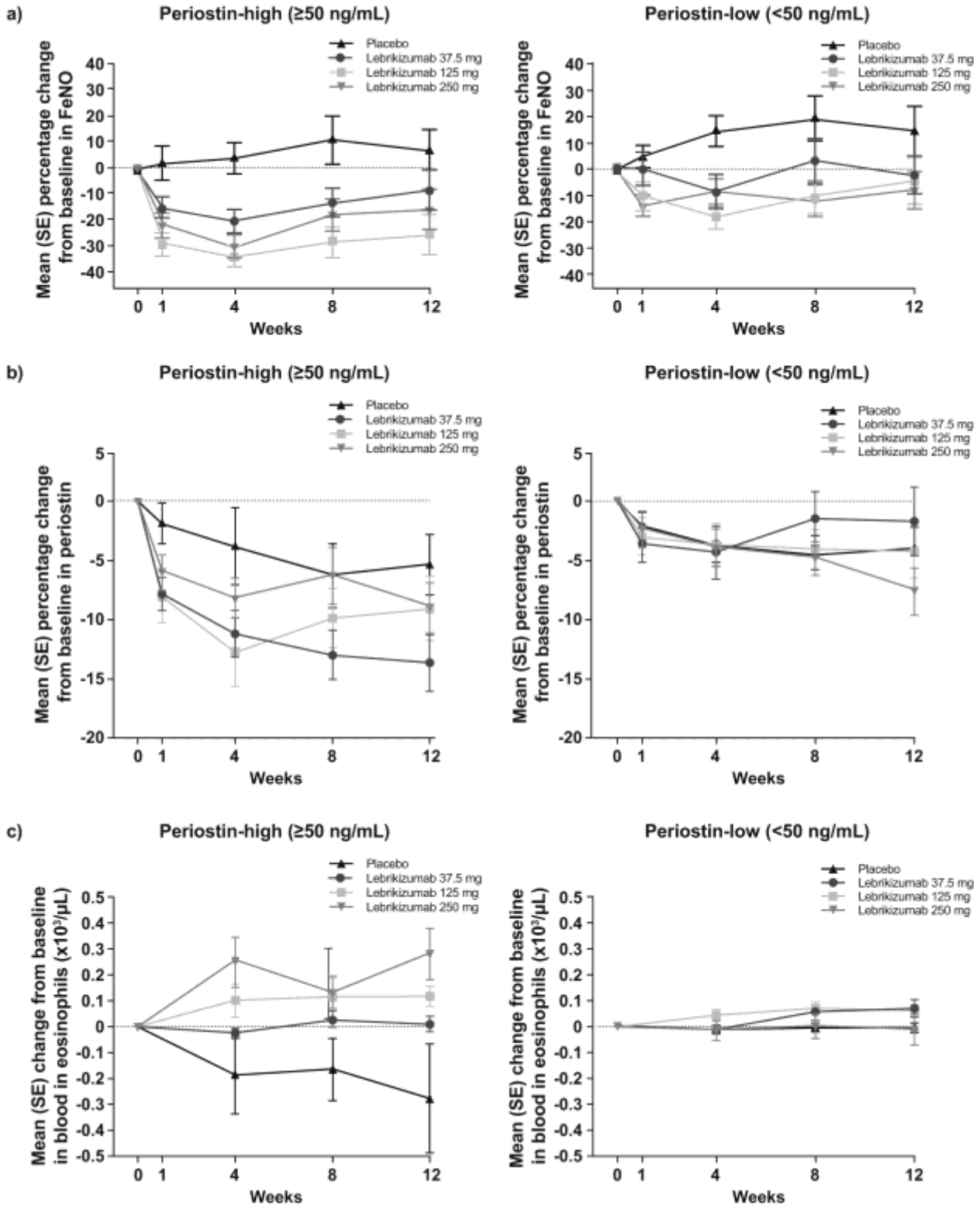
Figure S3. Mean change from baseline in A) FeNO B) periostin and C) blood eosinophils over 12 weeks