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.

References

1 Hankinson JL, Odencrantz JR & Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.

2 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.

3 Juniper EF, Svensson K, Mörk AC, et al. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;99:553-8.

4 Juniper EF, O'Byrne PM, Ferrie PJ, et al. Measuring asthma control. Clinic questionnaire or daily diary? *Am J Respir Crit Care Med* 2000;162:1330-4.

5 ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912-30.

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

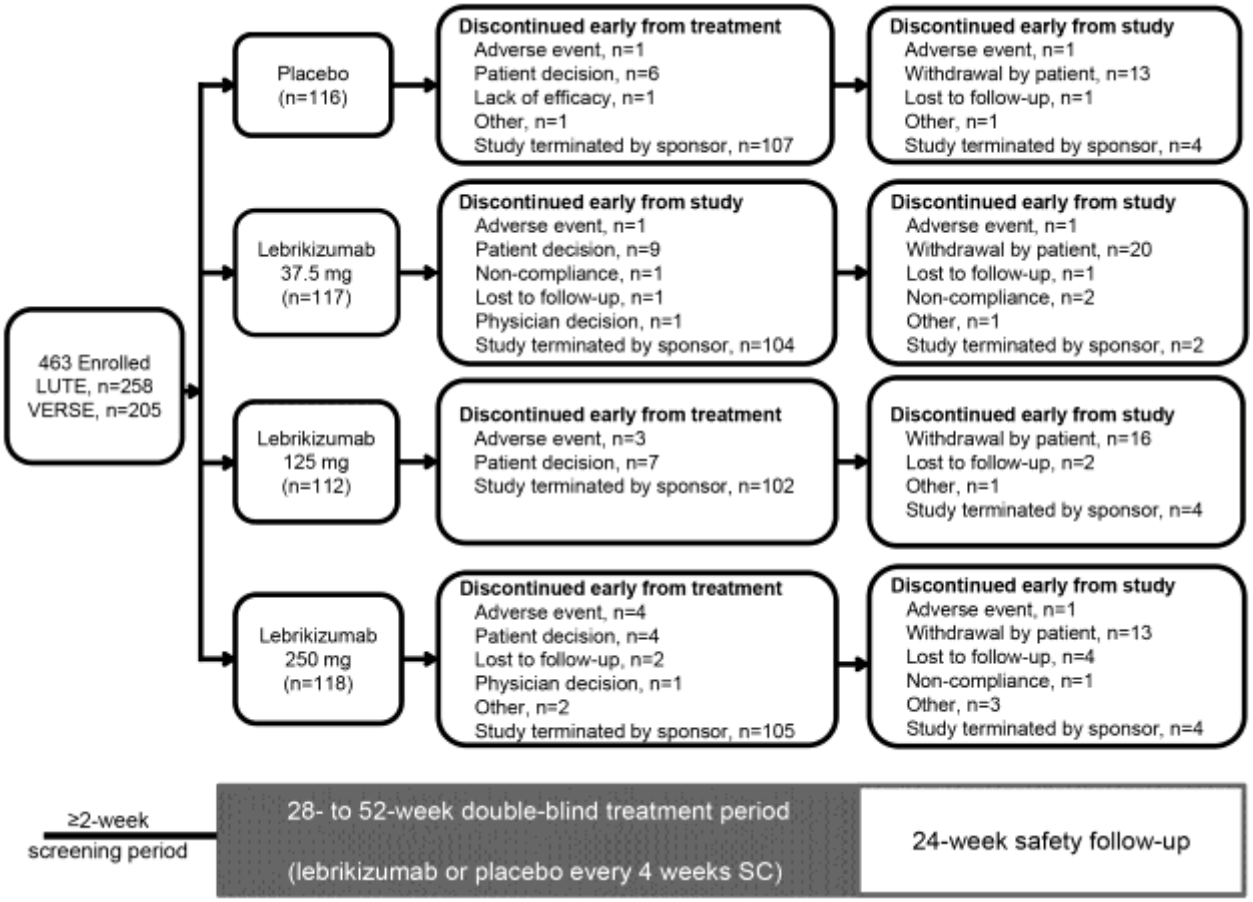

Figure S2. Kaplan-Meier plots of time to first exacerbation in a) periostin-high patients and b) periostin-low patients

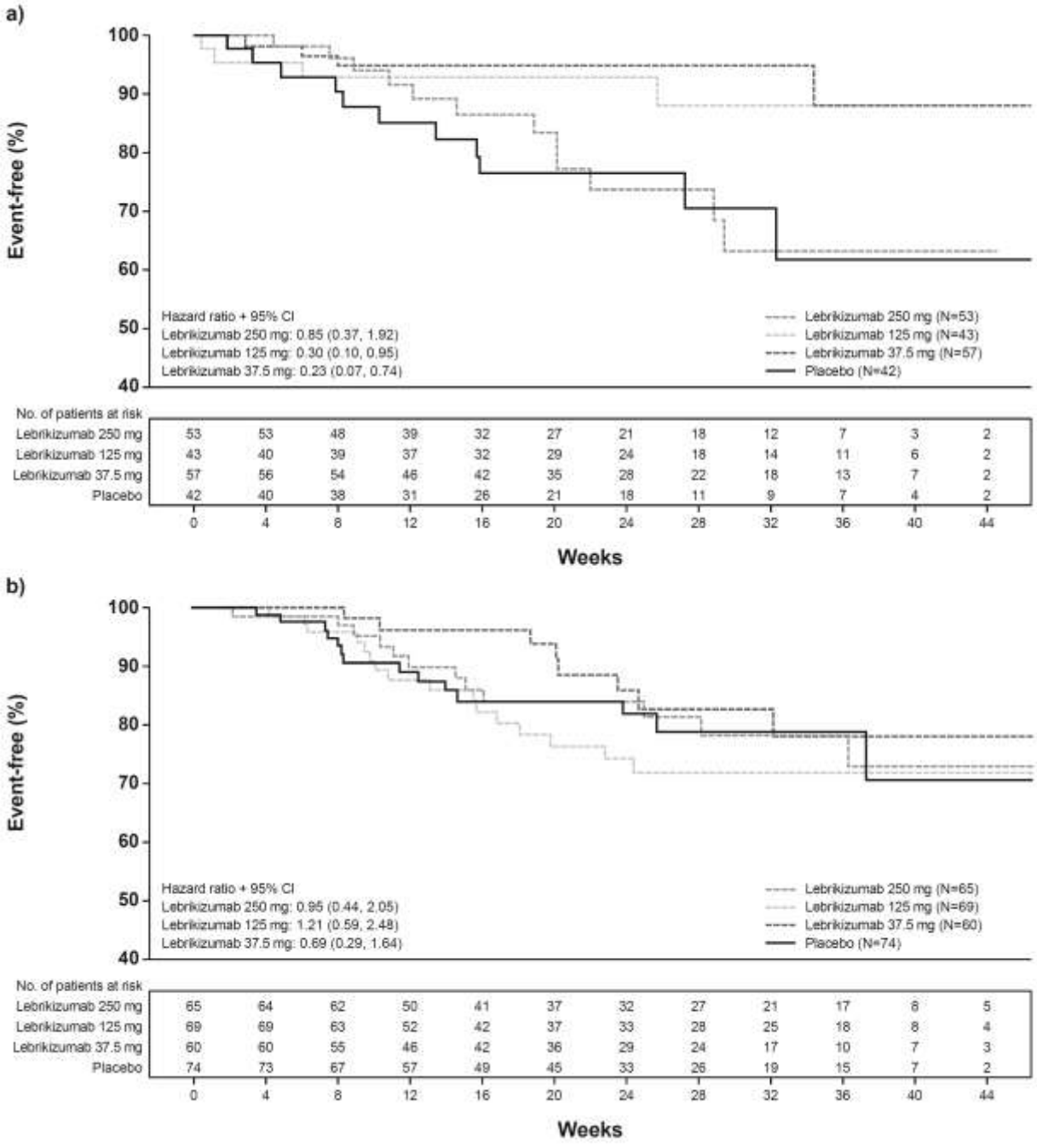

Figure S3. Mean change from baseline in A) FeNO B) periostin and C) blood eosinophils over 12 weeks