

Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials

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Summary

Background In phase 2 trials, lebrikizumab, an anti-interleukin-13 monoclonal antibody, reduced exacerbation rates and improved FEV₁ in patients with uncontrolled asthma, particularly in those with high concentrations of type 2 biomarkers (eg, periostin or blood eosinophils). We undertook replicate phase 3 studies to assess the efficacy and safety of lebrikizumab in patients with uncontrolled asthma despite inhaled corticosteroids and at least one second controller medication.

Methods Adult patients with uncontrolled asthma, pre-bronchodilator FEV₁ 40–80% predicted, and stable background therapy were randomly assigned (1:1:1) with an interactive voice–web-based response system to receive lebrikizumab 37·5 mg or 125 mg, or placebo subcutaneously, once every 4 weeks. Randomisation was stratified by screening serum periostin concentration, history of asthma exacerbations within the last 12 months, baseline asthma medications, and country. The primary efficacy endpoint was the rate of asthma exacerbations over 52 weeks in biomarker-high patients (periostin ≥50 ng/mL or blood eosinophils ≥300 cells per μ L), analysed with a Poisson regression model corrected for overdispersion with Pearson χ^2 that included terms for treatment group, number of asthma exacerbations within the 12 months before study entry, baseline asthma medications, geographic region, screening periostin concentration, and blood eosinophil counts as covariates. Both trials are registered at ClinicalTrials.gov, LAVOLTA I, number NCT01867125, and LAVOLTA II, number NCT01868061.

Findings 1081 patients were treated in LAVOLTA I and 1067 patients in LAVOLTA II. Over 52 weeks, lebrikizumab reduced exacerbation rates in biomarker-high patients in the 37·5 mg dose group (rate ratio [RR] 0·49 [95% CI 0·34–0·69], $p < 0·0001$) and in the 125 mg dose group (RR 0·70 [0·51–0·95], $p = 0·0232$) versus placebo in LAVOLTA I. Exacerbation rates were also reduced in biomarker-high patients in both dose groups versus placebo in LAVOLTA II (37·5 mg: RR 0·74 [95% CI 0·54–1·01], $p = 0·0609$; 125 mg: RR 0·74 [0·54–1·02], $p = 0·0626$). Pooling both studies, the proportion of patients who experienced treatment-emergent adverse events (79% [1125 of 1432 patients] for both lebrikizumab doses vs 80% [576 of 716 patients] for placebo), serious adverse events (8% [115 patients] for both lebrikizumab doses vs 9% [65 patients] for placebo), and adverse events leading to study drug discontinuation (3% [49 patients] for both lebrikizumab doses vs 4% [31 patients] for placebo) were similar between lebrikizumab and placebo. The following serious adverse events were reported in the placebo-controlled period: one event of aplastic anaemia and five serious adverse events related to raised concentrations of eosinophils in patients treated with lebrikizumab and one event of eosinophilic pneumonia in the placebo group.

Interpretation Lebrikizumab did not consistently show significant reduction in asthma exacerbations in biomarker-high patients. However, it blocked interleukin-13 as evidenced by the effect on interleukin-13-related pharmacodynamic biomarkers, and clinically relevant changes could not be ruled out.

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Introduction

Asthma is a heterogeneous disease with notable variation in its clinical course and response to treatment.^{1–3} Despite management with standard-of-care therapies,⁴ a proportion of patients remain uncontrolled and at risk of life-threatening exacerbations and disease worsening.^{5,6} Advances in understanding of the heterogeneity of asthma have helped identify patients who will benefit from a personalised management approach.^{7,8}

Interleukin-13 is a pleiotropic effector cytokine central to type 2 inflammation in severe asthma. It contributes

to many of the characteristic features of asthma, including mucus production, eosinophilic airway inflammation, IgE synthesis, bronchial fibrosis, and airway hyper-responsiveness.^{9–12} Interleukin-13 is, therefore, recognised as a potential therapeutic target in patients with uncontrolled asthma and higher concentrations of type 2 biomarkers.^{13,14}

Type 2 biomarkers that can be measured in the circulation include blood eosinophils and serum periostin. Blood eosinophil counts tend to be higher in a proportion of patients with asthma (although the size of the population



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Research in context

Evidence before this study

Interleukin-13 is thought to play an important role in the effector phase of the inflammatory response and induces the main manifestations of allergic disease including airway hyper-responsiveness, mucus production, airway smooth muscle alterations, and subepithelial fibrosis. In completed phase 2 trials with lebrikizumab, an anti-interleukin-13 antibody in patients with uncontrolled asthma, it reduced the rate of asthma exacerbations and improved lung function (FEV₁) to a greater extent in patients with biomarker evidence of type 2 asthma (eg, higher concentrations of periostin). Additionally, results of phase 2 clinical trials with another anti-interleukin-13 monoclonal antibody, tralokinumab, and the anti-interleukin-4Rα monoclonal antibody, dupilumab (which inhibits both interleukin-4 and interleukin-13 signalling), have also been reported. Phase 2a and phase 2b trials of tralokinumab have shown improvement in FEV₁ but no significant effect on exacerbations in patients with severe uncontrolled asthma. A phase 2b trial of dupilumab demonstrated a reduction in severe exacerbations and improved lung function in patients with uncontrolled persistent asthma. Other molecules targeting interleukin-13 in asthma have not advanced beyond early-stage

trials. The trials described here are the first reported phase 3 trials of a therapy targeting interleukin-13 in patients with uncontrolled asthma.

Added value of this study

Here we report findings from replicate phase 3 randomised controlled trials designed to further assess the efficacy and safety of lebrikizumab in patients with uncontrolled asthma despite treatment with standard-of-care medications. The studies failed to provide consistently significant results for the primary endpoint or a clear dose response. The overall efficacy of lebrikizumab in these trials did not meet the clinically meaningful exacerbation rate reduction or FEV₁ improvement expected from phase 2 results in this patient population. Furthermore, the biomarker strategy, which focused on patients who were in the high groups for either eosinophils or periostin, did not consistently identify those who achieved benefit from lebrikizumab treatment.

Implications of all the available evidence

These studies suggest that blocking interleukin-13 in this patient population using lebrikizumab might not be sufficient to provide clinically meaningful improvements in asthma endpoints.

with high eosinophil counts depends on the cutoff used to define those counts)^{15,16} and have been used to identify patients suitable for treatment with recently approved biological asthma therapies targeting interleukin-5.^{17,18} Interleukin-5 plays a crucial role in maturation of eosinophils in the bone marrow, whereas both interleukin-5 and interleukin-13 have been reported to be implicated in promoting eosinophil survival, activation, and recruitment,^{19–22} and therefore blood eosinophils might also be predictive for benefit from anti-interleukin-13 treatment. Periostin is an interleukin-13-induced matricellular protein basally secreted from the bronchial epithelial cells and can be detected in serum. Some patients with asthma have higher concentrations of serum periostin^{23–25} and it has been shown that these patients benefit most from anti-interleukin-13 treatment in previous studies with lebrikizumab.^{13,14}

Lebrikizumab is a humanised monoclonal antibody that binds to soluble interleukin-13 with high affinity and blocks signalling through the active interleukin-4 receptor (R)α/interleukin-13Rα1 heterodimer.^{13,26,27} Results from phase 2 studies suggest that in patients with uncontrolled asthma, lebrikizumab can reduce the rate of exacerbations¹⁴ and improve lung function to a greater extent in patients with higher concentrations of periostin.^{13,14} Here we report findings from replicate phase 3 randomised controlled trials designed to further assess the efficacy and safety of lebrikizumab in patients with uncontrolled asthma despite treatment with standard-of-care medications, and also to assess serum periostin concentration and blood eosinophil count as

biomarkers for identifying patients who are most likely to benefit from lebrikizumab treatment.

Methods

Study design and participants

LAVOLTA I and LAVOLTA II are replicate phase 3, randomised, multicentre, multinational, double-blind, placebo-controlled trials. The protocol was amended to update the prespecified biomarker subgroup for the primary analysis to include blood eosinophil count, in addition to serum periostin. Biomarker-high patients were defined as patients with screening periostin of at least 50 ng/mL or screening blood eosinophils of at least 300 cells per μ L. This amendment did not alter the conduct of the study at the clinical trial sites.

Both studies consisted of at least a 2-week screening period, a 52-week placebo-controlled period, a 52-week active-treatment extension, and a 20-week safety follow-up period. Here we report the findings from the 52-week placebo-controlled period.

Eligible patients were aged 18–75 years with uncontrolled asthma, pre-bronchodilator FEV₁ 40–80% predicted, bronchodilator response of at least 12%, and on stable background therapy with inhaled corticosteroids (500–2000 μ g per day fluticasone propionate or equivalent) for at least 6 months and at least one additional controller medication. The screening period was included in the study design to prospectively determine that patients had uncontrolled asthma and also to obtain the results of the periostin concentrations for stratified randomisation. Blood eosinophil counts

were also measured during screening. The screening period included an asthma control questionnaire and FEV₁ measurements at three visits before randomisation occurred at the third visit. Patients had to confirm adherence with asthma controller medication during screening with daily entries in the In2itive e-Diary (Vitalograph 2120), and continued on stable doses of their standard-of-care asthma control medications for the trial duration. Uncontrolled asthma was defined as a Five-Item Asthma Control Questionnaire-5 (ACQ-5) score of at least 1.5 and at least one of the following during the screening period: symptoms for more than 2 days per week; night-time awakenings at least once per week; use of short-acting β -agonist as rescue medication for more than 2 days per week; or interference with normal daily activities. Exclusion criteria included current smoker or former smoker with more than 10 pack-years, pregnancy, parasitic infection within the preceding 6 months, clinically significant lung disease other than asthma, and maintenance oral corticosteroid treatment within the previous 3 months.

We did this study in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidance for Good Clinical Practice. Independent ethics committee approval was obtained at all participating centres and all patients provided written informed consent. An independent data monitoring committee reviewed safety data at regular intervals throughout the trials.

Randomisation and masking

Patients were randomly assigned to the treatment groups through an interactive voice–web-based response system (IxRS). Following completion of the screening period and after all patient eligibility requirements were confirmed, patients were randomly assigned (1:1:1) to one of three treatment groups (lebrizumab 37.5 mg, lebrizumab 125 mg, or placebo every 4 weeks) for the placebo-controlled period. Patients were randomly assigned on the same day that treatment was to be initiated.

Randomisation was stratified by screening serum periostin concentration (<42 ng/mL, $\geq$ 42 to <50 ng/mL, $\geq$ 50 to <58 ng/mL, $\geq$ 58 ng/mL), history of asthma exacerbations within the last 12 months (0, 1–2, $\geq$ 3 events), baseline asthma medications (inhaled corticosteroids, total daily dose $\geq$ 1000 μ g of fluticasone propionate dry-powder inhaler or equivalent plus long-acting β -agonist [LABA] [yes, no]), and country. A dynamic randomisation method was used to obtain an approximate 1:1:1 ratio between the three treatment groups and within each stratum. The method is a generalisation of the hierarchical method proposed by Signorini and colleagues.²⁸ A biased coin assignment was used when the imbalance within a stratum had exceeded a specified threshold.

The IxRS service provider made the study-drug kit assignments. Patient randomisation and the study-drug

kit assignments were verified on an ongoing basis by an external and independent data coordinating centre (DCC) provider. Since the start of study, the randomisation and kit number assignment logs were transferred from the IxRS service provider to the DCC monthly until 100 patients were enrolled and then quarterly until completion of all randomisation. The DCC independently reviewed the logs to ensure that randomisation and kit assignments were done correctly by the IxRS.

Lebrizumab and placebo were identical in appearance and were supplied by Roche in two configurations: a pre-filled syringe and a vial. The 125 mg dose of lebrizumab was supplied as a pre-filled syringe and the 37.5 mg dose supplied in a vial. All patients received an injection from the pre-filled syringe and from the vial to ensure masking of study treatment.

Patients, investigators, study site personnel, and the funder were masked to treatment assignment during the study.

Procedures

Lebrizumab (at a dose of 37.5 mg or 125 mg) or placebo was given subcutaneously every 4 weeks during the 52-week placebo-controlled period. The dosing frequency is supported by the half-life of lebrizumab of about 25 days. Based on phase 2 data, a dose of 125 mg was expected to show clinical efficacy in phase 3, whereas a lower dose of 37.5 mg (corresponding to a 0.3 mL injection) was proposed for the purpose of dose ranging. This dose was selected because it has a reasonable (3.3 fold or log fold) separation from the 125 mg dose, with minimum overlap in the simulated range of serum exposures between the two doses.

Assessments during the study included recording of exacerbation events, health-care use, spirometry, patient-reported outcome questionnaires and adverse events every 4 weeks. Pharmacokinetics, biomarkers, and antitherapeutic antibodies were measured at weeks 4, 12, 24, 36, and 52 (see [appendix](#) for further details).

The order of assessments conformed to the following requirements: asthma therapies that might affect spirometry were withheld until pre-bronchodilator spirometry measurements were completed. Patients were made aware that twice-daily LABA and twice-daily long-acting muscarinic antagonist (LAMA) use was prohibited within 12 h before spirometry, once-daily LABA and once-daily LAMA use was prohibited within 24 h before spirometry, and short-acting β -agonist or ipratropium use was prohibited within 4 h before spirometry. Patient-reported outcome questionnaires were administered before other assessments and study drug was given after all other assessments had been completed.

Patients were provided with the In2itive e-Diary to record adherence with controller medication, their rescue medication use, and morning peak expiratory flow. Details of these procedures are provided in the [appendix](#).

See Online for appendix

Outcomes

The primary efficacy endpoint was the rate of asthma exacerbations during the 52-week placebo-controlled period in biomarker-high patients (periostin ≥ 50 ng/mL or blood eosinophils ≥ 300 cells per μ L, and including patients high in both). An asthma exacerbation was defined as new or increased asthma symptoms that led to treatment with systemic corticosteroids or to hospital admission. Treatment with systemic corticosteroids was defined as oral, intravenous, or intramuscular corticosteroid treatment for at least 3 days, or an emergency department visit with at least one dose of intravenous or intramuscular corticosteroids.

Secondary efficacy endpoints included: absolute change in pre-bronchodilator FEV₁ from baseline at week 52; time to first asthma exacerbation during the 52-week placebo-controlled period; rate of urgent asthma-related health-care use during the 52-week placebo-controlled period; absolute change in asthma-specific health-related quality of life, as assessed by the overall score of the AQLQ(S), from baseline at week 52; absolute change in asthma rescue medication use from baseline at week 52; and absolute change in asthma control, as measured by the ACQ-5, from baseline at week 52.

Safety assessments consisted of monitoring and recording of adverse events, including serious adverse events and adverse events of special interest. Adverse events of special interest to lebrikizumab included local injection-site reactions, anaphylactic, anaphylactoid and hypersensitivity reactions, infections, and malignancies. Samples were obtained at baseline and after treatment to assess the potential development of immunogenicity to lebrikizumab (anti-therapeutic antibodies) or the hamster phospholipase B-like 2 CHO cell impurity (PLBL2), which was present in the lebrikizumab drug material given to patients in the previous phase 2 trials.^{14,29} A masked anaphylaxis adjudication committee reviewed potential cases of anaphylaxis.

Statistical analysis

We did the efficacy analyses with data from the intention-to-treat population, with patients grouped according to the treatment assigned at randomisation. As prespecified in the protocol, analysis of the primary efficacy and all secondary efficacy endpoints was done separately in the biomarker-high (periostin ≥ 50 ng/mL and blood eosinophils ≥ 300 cells per μ L, periostin ≥ 50 ng/mL and

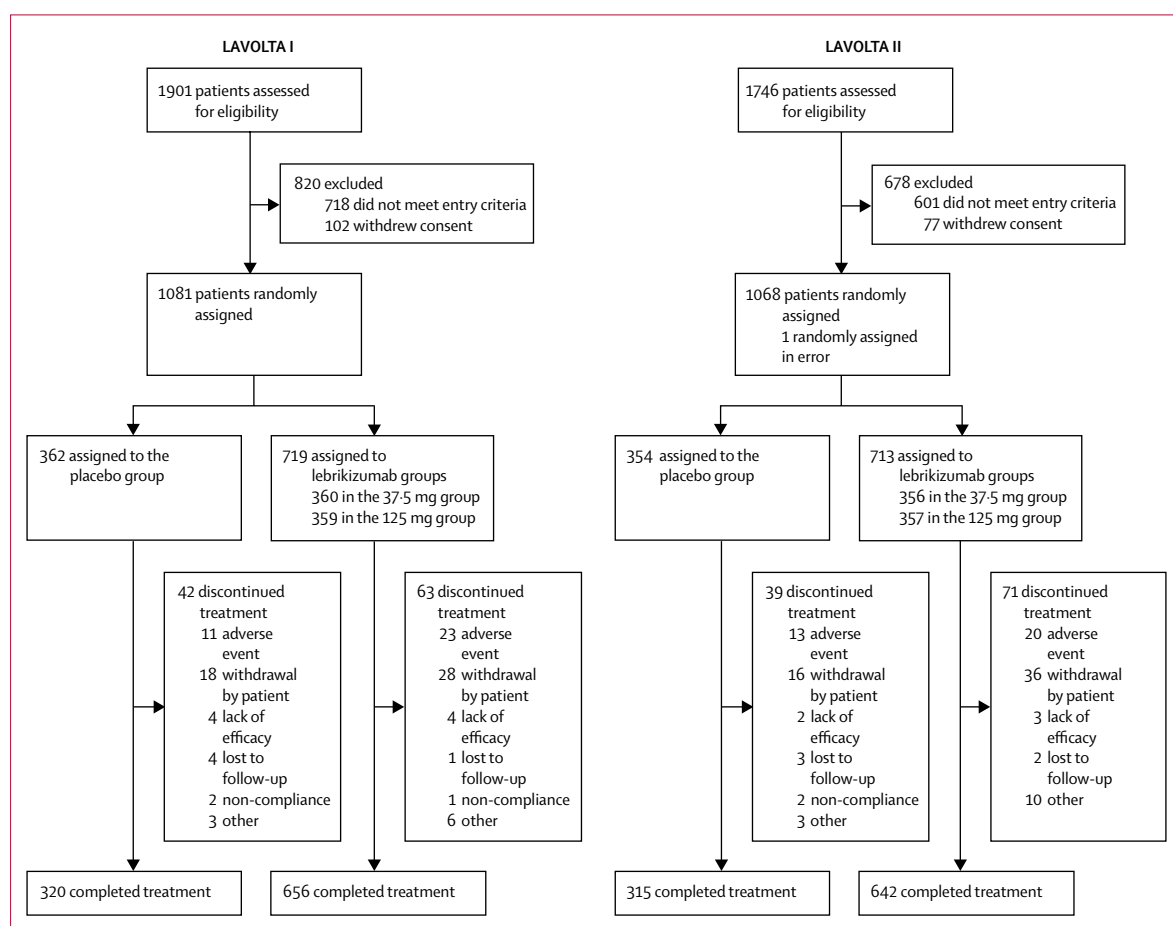


Figure 1: Trial profile

blood eosinophils <300 cells per μL , or periostin <50 ng/mL and blood eosinophils ≥ 300 cells per μL) and biomarker-low (periostin <50 ng/mL and blood eosinophils <300 cells per μL) patient groups.

It was expected that about 64% of enrolled patients would be classified as biomarker high and 36% of enrolled patients would be classified as biomarker low, based on enrolled patients at the time of the protocol amendment. Thus it was calculated that with an overall study sample size of about 1050 patients per study, there would be about 224 patients per treatment group (lebrikizumab 37.5 mg, lebrikizumab 125 mg, or placebo) in the biomarker-high group and 126 patients per treatment group in the biomarker-low group. For each study and within the biomarker-high group, this sample size was calculated to provide greater than 90% power to detect a 50% reduction in the rate of

exacerbations for a given lebrikizumab dose level compared with placebo in an intention-to-treat analysis. If we assume the same detectable reduction rate of exacerbations within the biomarker-low group, the power would be about 84%. Calculations were based on a Poisson regression model and two-sided test at the $\alpha=0.0495$ level, with the assumption of an average rate of 0.6 exacerbations per patient in the placebo group over a 52-week period, a 20% dropout rate by week 52, and 20% Poisson overdispersion. The 50% reduction in exacerbation rate was based on previous phase 2 data; a clinically meaningful reduction and also the rate reduction from a 32-week analysis of phase 2 data.^{13,30}

For the primary endpoint, the time period at risk extended from the day of randomisation to the placebo-controlled period (first day), to the day before randomisation to the active-treatment extension (last

	LAVOLTA I			LAVOLTA II		
	Placebo (n=362)	Lebrikizumab 37.5 mg (n=360)	Lebrikizumab 125 mg (n=359)	Placebo (n=354)	Lebrikizumab 37.5 mg (n=356)	Lebrikizumab 125 mg (n=357)
Age (years)	51.3 (12.3)	51.4 (12.9)	51.0 (12.6)	49.5 (13.3)	50.9 (12.9)	50.2 (12.6)
Sex						
Male	131 (36%)	126 (35%)	111 (31%)	135 (38%)	154 (43%)	120 (34%)
Female	231 (64%)	234 (65%)	248 (69%)	219 (62%)	202 (57%)	237 (66%)
Race						
Asian	41 (11%)	39 (11)	40 (11%)	41 (12%)	43 (12%)	36 (10%)
Black or African American	29 (8%)	19 (5%)	15 (4%)	22 (6%)	25 (7%)	25 (7%)
White	286 (79%)	291 (81%)	295 (82%)	270 (76%)	266 (75%)	272 (76%)
Other	6 (2%)	11 (3%)	9 (3%)	21 (6%)	22 (6%)	24 (7%)
Body-mass index (kg/m^2)	28.7 (5.0)	28.5 (5.0)	28.7 (5.4)	28.0 (4.9)	28.1 (4.9)	27.8 (5.0)
Former smoker	74 (20%)*	62 (17%)	90 (25%)*	64 (18%)	65 (18%)	54 (15%)+
Median (range) duration of asthma (years)	17 (1–68)*	17 (1–69)	17 (1–70)	18 (1–72)	19 (1–69)	16 (1–71)
Baseline ICS ≥ 1000 μg per day (fluticasone propionate DPI or equivalent) and LABA	159 (44%)	161 (45%)	160 (45%)	179 (51%)	165 (46%)	181 (51%)
Mean ICS (fluticasone propionate DPI or equivalent; μg per day)	779.6 (353.8)	773.3 (331.2)	773.3 (322.1)	816.9 (348.7)	810.6 (352.0)	821.8 (364.6)
Pre-bronchodilator FEV ₁						
Absolute (L)	1.850 (0.593)	1.809 (0.532)	1.820 (0.571)	1.886 (0.578)	1.850 (0.541)	1.844 (0.581)
% 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)
Reversibility (%)	24.9 (14.7)	25.6 (15.7)	24.9 (15.5)	27.2 (17.7)	25.2 (13.8)	24.7 (13.6)
ACQ-5 score	2.69 (0.76)	2.61 (0.73)	2.60 (0.74)	2.77 (0.73)	2.72 (0.75)	2.76 (0.70)
Median serum periostin (ng/mL)‡	53.8 (44–66)	53.7 (45–66)	52.7 (45–67)	55.3 (44–69)	54.4 (44–69)	54.2 (44–70)
Median FeNO (ppb)‡	27 (15–50)	27 (15–45)	28 (16–46)	23 (14–42)	24 (15–44)	24 (14–44)
Median blood eosinophil count (cells per μL)‡	230 (170–400)	245 (145–430)	240 (150–380)	240 (150–400)	230 (150–410)	240 (140–390)
Biomarker high (periostin ≥ 50 ng/mL or blood eosinophils ≥ 300 cells per μL)‡	256 (71%)	251 (70%)	255 (71%)	247 (70%)	257 (72%)	251 (70%)
Patients with ≥ 1 exacerbation in previous 12 months	228 (63%)	228 (64%)	226 (63%)	225 (64%)	226 (64%)	237 (66%)

Data are n (%), mean (SD), or median (IQR), unless stated otherwise. ICS=inhaled corticosteroid. DPI=dry-powder inhaler. LABA=long-acting β -agonist. ACQ-5=Five-Item Asthma Control Questionnaire. FeNO=fractional exhaled nitric oxide. ppb=parts per billion. *Plus two current smokers. †Plus one current smoker. ‡Measured at screening.

Table 1: Patient baseline characteristics in the intention-to-treat population

day), inclusive. For patients not randomly assigned to the active-treatment extension, the day of the last study visit on or before study day 379 was used as the last day. All protocol-defined asthma exacerbations with an onset during this time period at risk were included in the primary analysis. For each biomarker group, the rate of asthma exacerbations was compared between each active treatment group and the placebo group with the use of a Poisson regression model corrected for over-dispersion with Pearson χ^2 that included terms for treatment group, number of asthma exacerbations within the 12 months before study entry, baseline asthma medications, and geographic region as covariates. For analyses of the biomarker-high group, additional covariate adjustment was included for screening periostin concentrations and screening blood eosinophil counts (at first screening visit). We also did a prespecified sensitivity analysis of the primary endpoint using a negative binomial regression model including the same covariates as specified for the primary analysis with Poisson regression.

For hypothesis testing of the primary efficacy endpoint within the biomarker-high group, type I error across dose levels was controlled by testing hypotheses sequentially across the two lebrikizumab doses. For each study, the primary endpoint (rate of asthma exacerbations) was tested first in the biomarker-high group comparing the 125 mg lebrikizumab group with the placebo group using

a two-sided α level of 0.0495. If this test was statistically significant, the primary endpoint was to be tested comparing the 37.5 mg lebrikizumab group with the placebo group in the biomarker-high group. For each lebrikizumab dose level found to be statistically different from placebo for the test of the primary endpoint (within the biomarker-high group), sequential testing of the secondary endpoints within that dose level and biomarker-high group was to be done.

The primary and secondary efficacy endpoints were also examined in the biomarker-low patient group, with the aim to characterise the treatment benefit in that population. For these analyses, no control of type I error was applied. Furthermore, efficacy analyses did not include formal comparisons between the two lebrikizumab treatment groups (37.5 mg and 125 mg).

For the secondary endpoints, based on change in pre-bronchodilator FEV₁, AQLQ(S), asthma rescue medication use, and ACQ-5, a mixed-model repeated measures analysis was used. The regression model included terms for treatment group, study visit, treatment group by study visit interaction, the baseline value, and the baseline value by study visit interaction, as well as number of asthma exacerbations within the 12 months before study entry, baseline asthma medications, and geographic region as fixed effects. For analyses of the biomarker-high group, additional covariate adjustment was included for screening

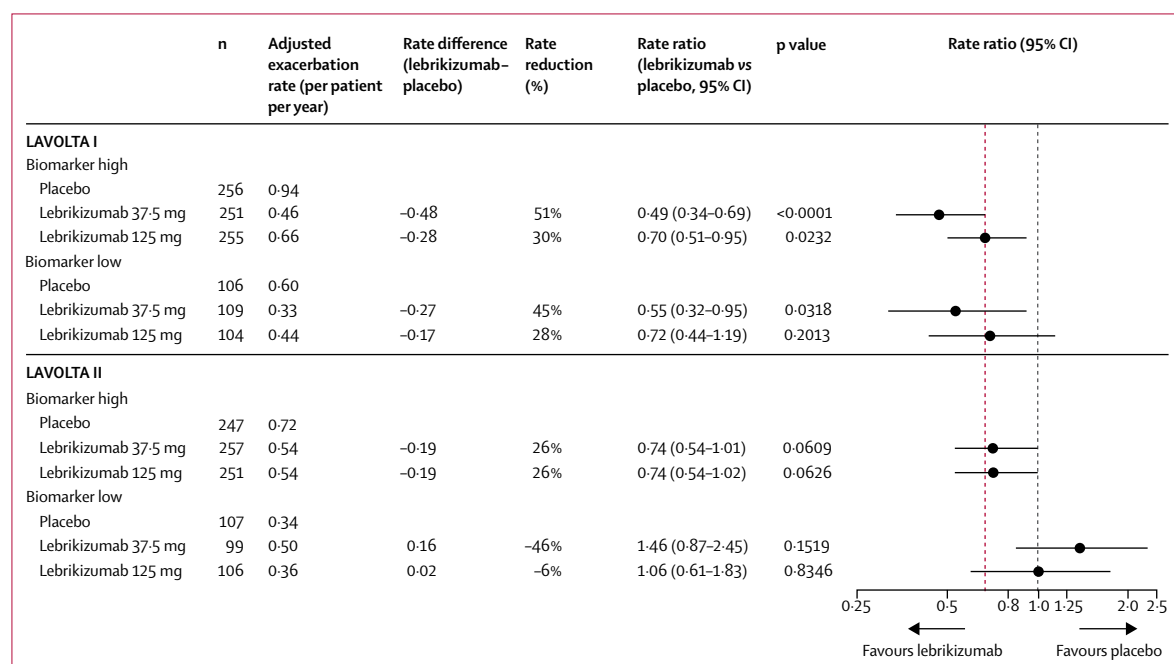


Figure 2: Rate of asthma exacerbations over 52 weeks by biomarker group

Red line shows minimal clinical effect (30% rate reduction). Biomarker high=periostin of at least 50 ng/mL or blood eosinophils of at least 300 cells per μ L. Biomarker low=periostin of less than 50 ng/mL and blood eosinophils less than 300 cells per μ L. Adjusted exacerbation rates and rate ratios are estimates from a Poisson regression model with over-dispersion adjusted for the following covariates in addition to log(patient-years) as an offset: number of asthma exacerbations within the last 12 months, baseline asthma medications, and geographic region. For analysis of the biomarker-high group, a three-level categorical variable (periostin high and eosinophil high, periostin high and eosinophil low, periostin low and eosinophil high) was also included.

periostin concentrations and blood eosinophil counts using a categorical variable with three categories: periostin high and eosinophil high, periostin high and eosinophil low, and periostin low and eosinophil high. For the secondary endpoint based on urgent asthma-related health-care use, an analysis method similar to that for the primary endpoint was used. For the secondary endpoint based on time to first asthma exacerbation, a Cox proportional hazards regression model was used, with covariate adjustment similar to that for the primary endpoint.

Exploratory efficacy analyses included assessment of exacerbations and FEV₁ by biomarker status (periostin and eosinophils combined), and by periostin, eosinophils, or FENO individually as predictive biomarkers. It was also prespecified to do biomarker-by-treatment interaction testing in a hierarchical order and using pooled data from the two studies to increase statistical power. Changes in pharmacodynamics biomarkers with treatment were also assessed over time.

Safety analyses were done with data from all treated patients, with patients grouped according to the treatment they actually received. Safety was assessed through summary of adverse events, laboratory test results, incidence of antibodies against lebrikizumab, and incidence of antibodies against PLBL2. The safety findings presented here are restricted to the placebo-controlled period. Both trials are registered at

ClinicalTrials.gov, LAVOLTA I, number NCT01867125, and LAVOLTA II, number NCT01868061.

Role of the funding source

The funder of the study contributed to study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Enrolment commenced on July 25, 2013, and was completed on Dec 18, 2014. Across both studies, a total of 2149 patients were enrolled at 367 sites in 28 countries (listed in appendix); 1081 patients were randomly assigned in LAVOLTA I and 1068 in LAVOLTA II (one patient in LAVOLTA II, randomly assigned in error, was not treated and not included in the intention-to-treat group); of these patients, 976 (90%) completed treatment in LAVOLTA I and 957 (90%) completed treatment in LAVOLTA II (figure 1). Studies were generally similar with respect to baseline characteristics and enrolment in each of the five regions, and with no meaningful differences between the treatment groups (table 1). The proportion of biomarker-high (periostin ≥ 50 ng/mL or blood eosinophils ≥ 300 cells per μ L) patients was similar across the two studies; however, we recorded higher concentrations of periostin in Asian patients and patients enrolled in Latin America.

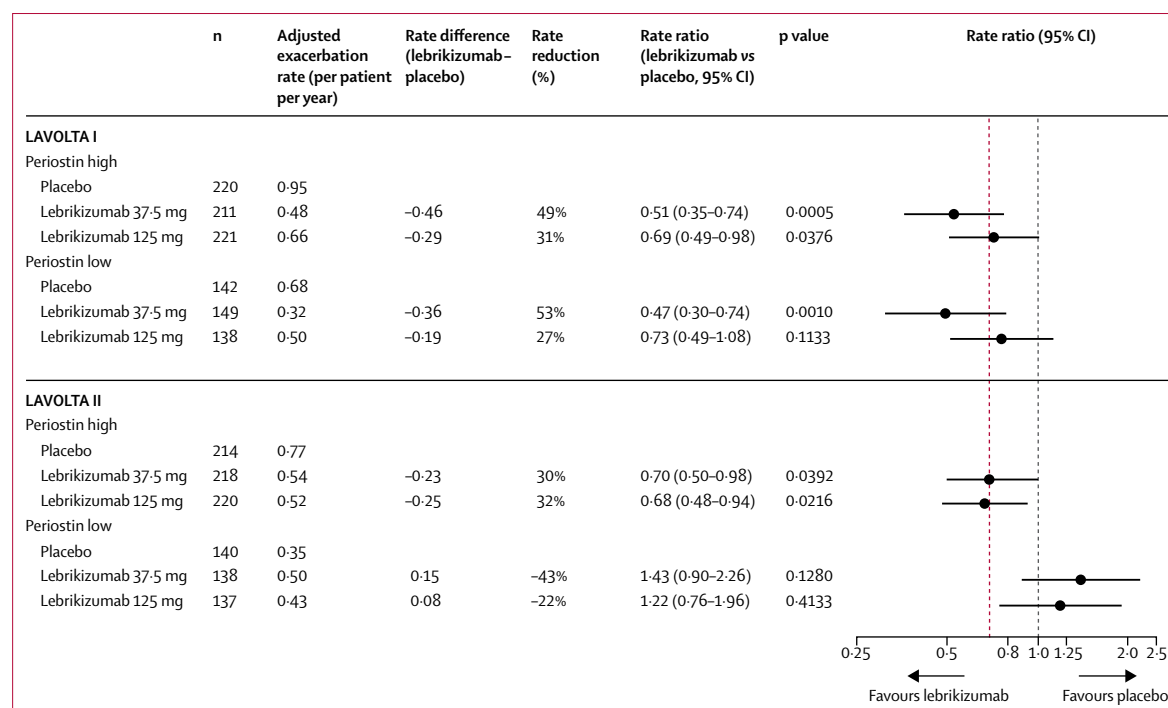


Figure 3: Rate of asthma exacerbations over 52 weeks by periostin group

Red line shows minimal clinical effect (30% rate reduction). Periostin high=periostin of at least 50 ng/mL. Periostin low=periostin of less than 50 ng/mL. Adjusted exacerbation rates and rate ratios are estimates from a Poisson regression model with overdispersion adjusted for the following covariates in addition to log(patient-years) as an offset: blood eosinophil level (high/low), number of asthma exacerbations within the last 12 months, baseline asthma medications, and geographic region.

632 exacerbations were reported in LAVOLTA I (1035 total patient-years of follow-up) and 554 in LAVOLTA II (1023 total patient-years of follow-up). The following adjusted exacerbation rates and rate ratios are estimates from a Poisson regression model described in the statistical analysis section. In the biomarker-high patients, the adjusted rates of exacerbations per patient per year were 0.94 for patients treated with placebo, and 0.46 in the lebrikizumab 37.5 mg group, and 0.66 in the lebrikizumab 125 mg group in LAVOLTA I, and 0.72, 0.54, and 0.54, respectively, in LAVOLTA II (figure 2).

In the biomarker-high patients, exacerbation rates were significantly reduced with lebrikizumab treatment compared with placebo in LAVOLTA I; the adjusted rate ratios (RRs) were 0.49 (95% CI 0.34–0.69; $p<0.0001$) for the lebrikizumab 37.5 mg group and 0.70 (0.51–0.95; $p=0.023$) for the lebrikizumab 125 mg dose group compared with placebo (figure 2). However, in the biomarker-high patient group in LAVOLTA II, the adjusted RRs were the same, 0.74 (95% CI 0.54–1.01; $p=0.0609$) for the lebrikizumab 37.5 mg group and 0.74 (0.54–1.02; $p=0.0626$) for the lebrikizumab 125 mg group, compared with placebo. Although these RRs were not statistically significant, the 95% CIs include an RR of 0.70, which is considered to represent a clinically meaningful rate reduction compared with placebo.

In biomarker-low patients, in LAVOLTA I, adjusted RRs were 0.55 (95% CI 0.32–0.95; $p=0.0318$) for the lebrikizumab 37.5 mg group and 0.72 (0.44–1.19; $p=0.0213$) for the lebrikizumab 125 mg dose group; in LAVOLTA II, higher exacerbation rates were observed with adjusted exacerbation rate ratios of 1.46 (95% CI 0.87–2.45; $p=0.1519$) for the lebrikizumab 37.5 mg group and 1.06 (0.61–1.83; $p=0.8346$) for the lebrikizumab 125 mg dose group, compared with placebo (figure 2). In the sensitivity analysis of the primary outcome analysed with a negative binomial regression model, the results were similar to the results of the primary analysis (appendix).

When analysed by quadrants of biomarker status (ie, periostin high–eosinophil high, periostin high–eosinophil low, periostin low–eosinophil high, periostin low–eosinophil low), exacerbations were reduced with both doses compared with placebo in the group of patients with high periostin and high eosinophils in LAVOLTA I and LAVOLTA II. In the high–high biomarker subgroup (626 [29%] patients across both studies), exacerbations were reduced in LAVOLTA I (RR 0.42 [95% CI 0.25–0.70] for the lebrikizumab 37.5 mg group and 0.58 [0.37–0.91] for the lebrikizumab 125 mg dose group) and in LAVOLTA II (0.61 [0.39–0.96] and 0.44 [0.27–0.73]), compared with placebo (appendix).

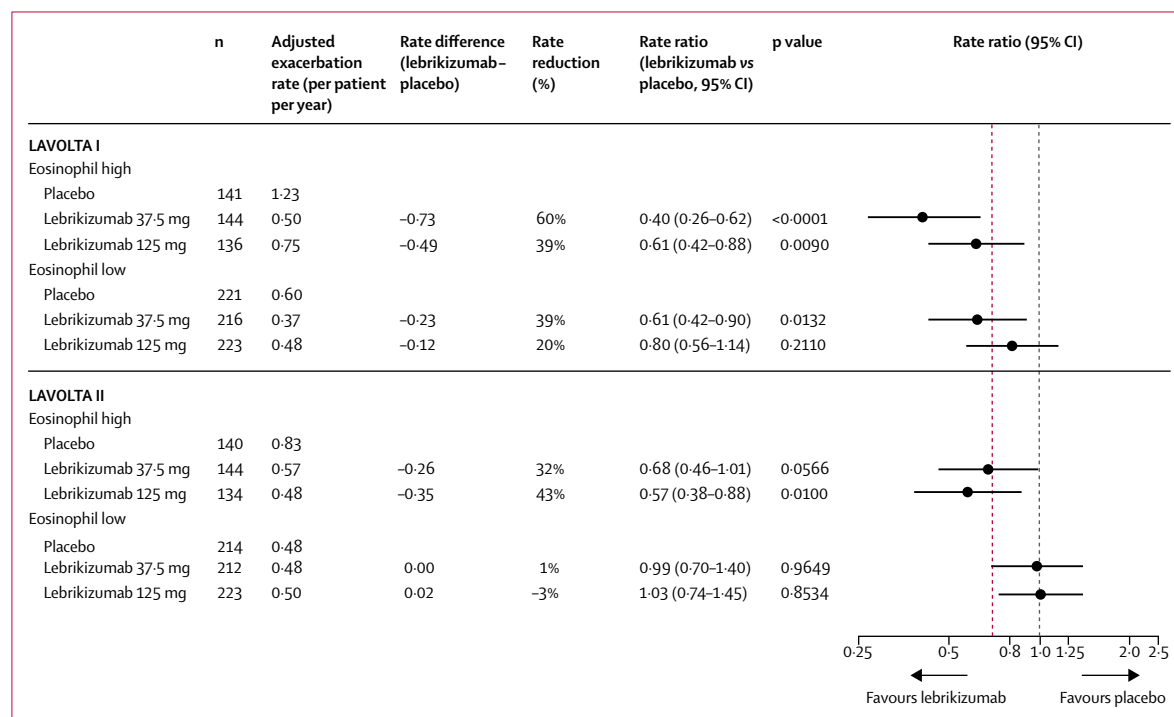


Figure 4: Rate of asthma exacerbations over 52 weeks by eosinophil group

Red line shows minimal clinical effect (30% rate reduction). Eosinophil high=blood eosinophils of at least 300 cells per μL . Eosinophil low=blood eosinophils of less than 300 cells per μL . Adjusted exacerbation rates and rate ratios are estimates from a Poisson regression model with overdispersion adjusted for the following covariates in addition to log(patient-years) as an offset: serum periostin level (high/low), number of asthma exacerbations within the last 12 months, baseline asthma medications, and geographic region.

When analysed by periostin-high-low or eosinophil-high-low patient groups individually, the rate reduction in the periostin-high group as well as in the eosinophil-

high group achieved a nominal p value of less than 0.05 for the 125 mg dose group in both studies (figures 3 and 4). In all-comers (regardless of biomarker status),

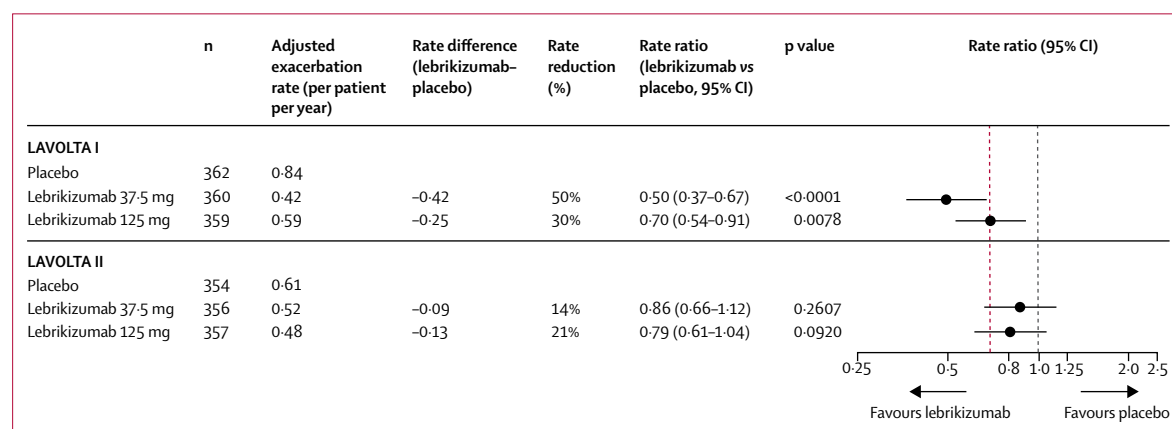


Figure 5: Rate of asthma exacerbations over 52 weeks for all patients

Red line shows minimal clinical effect (30% rate reduction). Adjusted exacerbation rates and rate ratios are estimates from a Poisson regression model with overdispersion adjusted for the following covariates in addition to log(patient-years) as an offset: periostin and eosinophil level (4 categories: periostin high and eosinophil high, periostin high and eosinophil low, periostin low and eosinophil high, periostin low and eosinophil low), number of asthma exacerbations within the last 12 months, baseline asthma medications, and geographic region.

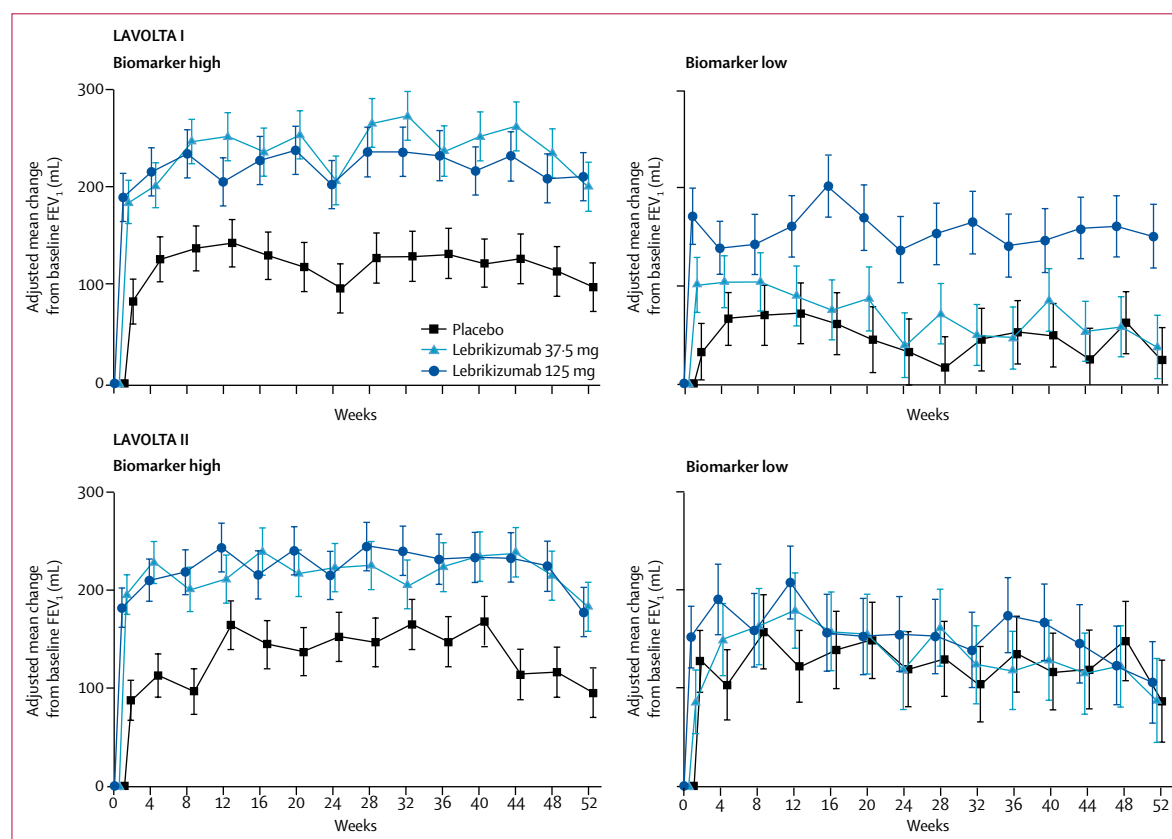


Figure 6: Change from baseline in FEV₁ over 52 weeks

Adjusted mean changes are based on a mixed model repeated measures (MMRM) analysis which included terms for treatment, visit, treatment*visit, baseline FEV₁, baseline FEV₁*visit, number of asthma exacerbations within the last 12 months, baseline asthma medications, and geographic region. For analysis of the biomarker-high group, a three-level categorical variable (periostin high and eosinophil high, periostin high and eosinophil low, and periostin low and eosinophil high) was also included.

lebrikizumab reduced exacerbation rates with a nominal p value of less than 0·05 for both doses in LAVOLTA I but not in LAVOLTA II (figure 5).

Exploratory analyses by FENO, another potential type 2 biomarker, showed that efficacy was greater in patients with FENO greater than 30 ppb versus those with FENO less than 30 ppb (appendix).

In the placebo groups of the trials, mean exacerbation rates were higher in biomarker-high patients (0·94 per patient per year) compared with biomarker-low patients (0·60 per patient per year) in LAVOLTA I and 0·72 per patient per year compared with 0·34 per patient per year in LAVOLTA II.

Treatment-by-biomarker interaction testing included a comparison of the treatment benefit (reduction in the

annual rate of asthma exacerbations) for biomarker-high versus biomarker-low, periostin-high versus periostin-low, eosinophil-high versus eosinophil-low, and FENO-high versus FENO-low patient groups in a prespecified testing order (appendix). Although the first ranked treatment-by-biomarker interaction test did not reach significance, a nominal p value of 0·03 was recorded for the treatment-by-biomarker interaction test for the eosinophil-high versus eosinophil-low comparison in the 125 mg dose group, but was not considered statistically significant based on the prespecified hierarchical testing order.

In biomarker-high patients in LAVOLTA I, the adjusted mean change from baseline at week 52 in pre-bronchodilator FEV₁ was 98 mL (SE 25) for patients treated with placebo, 201 mL (25) in the lebrikizumab

	Biomarker high			Biomarker low		
	Placebo	Lebrikizumab 37·5 mg	Lebrikizumab 125 mg	Placebo	Lebrikizumab 37·5 mg	Lebrikizumab 125 mg
Change from baseline in FEV₁ (mL)						
LAVOLTA I						
Adjusted mean (SE)	98 (25)	201 (25)	211 (25)	25 (33)	38 (32)	150 (33)
Difference in means (95% CI)		103 (34 to 172)	113 (44 to 182)		13 (−78 to 104)	126 (35 to 217)
p value		0·0034	0·0013		0·7792	0·0070
LAVOLTA II						
Adjusted mean (SE)	96 (25)	184 (25)	179 (25)	87 (41)	88 (43)	107 (41)
Difference in means (95% CI)		88 (18 to 158)	82 (12 to 152)		1 (−117 to 118)	19 (−96 to 135)
p value		0·0139	0·0217		0·9889	0·7442
Time to first exacerbation						
LAVOLTA I						
Patients with event (n, %)	99 (39%)	74 (30%)	78 (31%)	35 (33%)	22 (20%)	30 (29%)
Median time to event (weeks)	..	..	..	..	..	..
Hazard ratio (95% CI)		0·58 (0·42 to 0·79)	0·65 (0·47 to 0·89)		0·52 (0·30 to 0·89)	0·59 (0·35 to 0·98)
p value		0·0007	0·0071		0·0183	0·0435
LAVOLTA II						
Patients with event (n, %)	94 (38%)	75 (29%)	72 (29%)	27 (25%)	32 (32%)	25 (24%)
Median time to event (weeks)	..	..	..	..	..	..
Hazard ratio		0·77 (0·56 to 1·06)	0·73 (0·53 to 1·01)		1·37 (0·80 to 2·37)	0·95 (0·54 to 1·66)
p value		0·1151	0·0550		0·2536	0·8544
Asthma-related health-care use						
LAVOLTA I						
Health-care use rate (per year)	0·61	0·25	0·62	0·29	0·41	0·20
Rate difference (events/year)		−0·36	0·01		0·12	−0·09
Rate ratio (95% CI)		0·41 (0·23 to 0·72)	1·01 (0·65 to 1·57)		1·41 (0·77 to 2·59)	0·69 (0·33 to 1·41)
p value		0·0022	0·9669		0·2701	0·3054
LAVOLTA II						
Health-care use rate (per year)	0·45	0·34	0·42	0·30	0·56	0·41

(Table 2 continues on next page)

Biomarker high				Biomarker low		
	Placebo	Lebrikizumab 37.5 mg	Lebrikizumab 125 mg	Placebo	Lebrikizumab 37.5 mg	Lebrikizumab 125 mg
(Continued from previous page)						
Rate difference (events/year)		-0.11	-0.03		0.26	0.11
Rate ratio (95% CI)		0.76 (0.49 to 1.19)	0.94 (0.62 to 1.43)		1.89 (0.98 to 3.64)	1.38 (0.69 to 2.77)
p value		0.2343	0.7726		0.0558	0.3654
Change from baseline in AQLQ(S) score						
LAVOLTA I						
Adjusted mean (SE)	0.78 (0.064)	0.93 (0.063)	0.91 (0.064)	0.85 (0.098)	0.73 (0.096)	0.86 (0.097)
Difference in means (95% CI)		0.14 (-0.03 to 0.32)	0.13 (-0.05 to 0.30)		-0.12 (-0.38 to 0.15)	0.01 (-0.26 to 0.28)
p value		0.1098	0.1623		0.4015	0.9293
LAVOLTA II						
Adjusted mean (SE)	0.80 (0.065)	0.81 (0.064)	1.05 (0.064)	0.70 (0.102)	0.80 (0.105)	0.62 (0.100)
Difference in means (95% CI)		0.01 (-0.16 to 0.19)	0.25 (0.07 to 0.43)		0.10 (-0.18 to 0.39)	-0.08 (-0.36 to 0.20)
p value		0.8704	0.0061		0.4808	0.5857
Change from baseline in rescue medication use (puffs per day)						
LAVOLTA I						
Adjusted mean (SE)	-0.6 (0.1)	-1.1 (0.1)	-1.1 (0.1)	-0.8 (0.2)	-0.8 (0.2)	-1.2 (0.2)
Difference in means (95% CI)		-0.5 (-0.9 to -0.1)	-0.5 (-0.9 to -0.1)		0.0 (-0.6 to 0.7)	-0.4 (-1.0 to 0.3)
p value		0.0256	0.0121		0.9337	0.2696
LAVOLTA II						
Adjusted mean (SE)	-0.6 (0.2)	-1.0 (0.2)	-1.1 (0.2)	-0.3 (0.2)	-0.7 (0.2)	-0.5 (0.2)
Difference in means (95% CI)		-0.4 (-0.9 to 0.0)	-0.6 (-1.0 to -0.1)		-0.3 (-0.8 to 0.2)	-0.1 (-0.6 to 0.3)
p value		0.0478	0.0100		0.1849	0.5231
Change from baseline in ACQ-5 score						
LAVOLTA I						
Adjusted mean (SE)	-0.8 (0.07)	-0.9 (0.06)	-0.9 (0.07)	-0.8 (0.09)	-0.8 (0.09)	-0.8 (0.09)
Difference in means (95% CI)		-0.1 (-0.3 to 0.1)	-0.1 (-0.3 to 0.1)		0.0 (-0.3 to 0.3)	0.0 (-0.2 to 0.3)
p value		0.2497	0.4236		0.9787	0.9293
LAVOLTA II						
Adjusted mean (SE)	-0.8 (0.07)	-0.8 (0.06)	-1.0 (0.07)	-0.7 (0.09)	-0.8 (0.10)	-0.7 (0.09)
Difference in means (95% CI)		0.0 (-0.2 to 0.2)	-0.2 (-0.3 to 0.0)		-0.1 (-0.4 to 0.1)	0.0 (-0.2 to 0.3)
p value		0.9260	0.0855		0.3466	0.8885
AQLQ=Asthma Quality of Life Questionnaire. ACQ-5=Five-Item Asthma Control Questionnaire. -- =not evaluable (since less than 50% of the patients had an exacerbation, the median time to the first event could not be determined).						
Table 2: Secondary efficacy outcomes at 52 weeks						

Table 2: Secondary efficacy outcomes at 52 weeks

37.5 mg group, and 211 mL (25) in the lebrikizumab 125 mg group; in LAVOLTA II the corresponding FEV₁ values were 96 mL (25), 184 mL (25), and 179 mL (25). The resulting placebo-corrected mean change from baseline at week 52 was 103 mL ($p=0.0034$) in the lebrikizumab 37.5 mg group and 113 mL ($p=0.0013$) in the lebrikizumab 125 mg group of LAVOLTA I, and 88 mL ($p=0.0139$) in the 37.5 mg group and 82 mL ($p=0.0217$) in the 125 mg group of LAVOLTA II. Improvement in mean FEV₁ was evident after 1 week of treatment and was generally sustained throughout the study (figure 6). In biomarker-low patients, lebrikizumab

treatment did not show improvement over placebo (37.5 mg group: LAVOLTA I, 13 mL; LAVOLTA II, 1 mL; 125 mg group: LAVOLTA II, 19 mL) except for a mean 126 mL improvement with 125 mg in LAVOLTA I (table 2).

In biomarker-high patients, time to first asthma exacerbation was improved with lebrikizumab treatment in LAVOLTA I (hazard ratio [HR] 0.58 [95% CI 0.42–0.79] in the 37.5 mg group and 0.65 [0.47–0.89] in the 125 mg group) with a similar trend in LAVOLTA II (HR 0.77 [0.56–1.06] in the 37.5 mg group and 0.73 [0.53–1.01] in the 125 mg group) compared with placebo (since less

than 50% of the patients had an exacerbation, the median time to the first event could not be determined; table 2, appendix).

In biomarker-high patients, rate of urgent health-care use at the 37.5 mg dose was reduced compared with placebo (RR 0.41 [95% CI 0.23–0.72] and 0.76 [95% CI 0.49–1.19]) in LAVOLTA I and LAVOLTA II, respectively, but RRs in the 125 mg group compared with placebo were 1.01 (95% CI 0.65–1.57) in LAVOLTA I and 0.94 (95% CI 0.62–1.43) in LAVOLTA II (table 2).

In biomarker-high patients, there was no clinically meaningful improvement in AQLQ(S) score with lebrikizumab compared with placebo in either LAVOLTA I or LAVOLTA II (table 2). Asthma rescue medication use was lower among lebrikizumab-treated patients than placebo patients in biomarker-high patients. From a mean baseline of 2.7–3.0 puffs per day in LAVOLTA I and 3.0–3.5 puffs per day in LAVOLTA II, mean rescue medication use was reduced by 0.5 puffs per day on average in LAVOLTA I and by 0.4–0.6 puffs per day in LAVOLTA II in biomarker-high patients (table 2).

Despite reductions in rescue medication use, there were no corresponding placebo-corrected improvements in asthma control as measured by ACQ-5 score in either study (table 2).

Following lebrikizumab treatment, there was a trend towards a dose-dependent increase in median blood eosinophil count in both studies, primarily in patients who were biomarker high at screening. The increase in blood eosinophils persisted throughout the treatment period (appendix). FeNO and periostin concentrations were reduced as early as 1 week after the first dose. FeNO reached a maximum decrease around week 1 and

periostin around week 12. Both biomarkers remained decreased throughout the treatment period in both LAVOLTA I and LAVOLTA II. The median percentage decrease was greater in biomarker-high patients than in biomarker-low patients. There was no dose response observed for either FeNO or periostin (appendix).

Serum lebrikizumab trough concentrations were similar in LAVOLTA I and LAVOLTA II (appendix) and consistent with those observed in previous phase 2 studies for both the 37.5 mg and 125 mg dose groups.¹⁴

Positive anti-lebrikizumab antibodies were reported in 202 (14%) of 1426 patients treated with lebrikizumab and 15 (2%) of 713 patients treated with placebo, in LAVOLTA I and LAVOLTA II. Antibodies against PLBL2 were detected in 238 (19%) of 1278 patients treated with lebrikizumab and 18 (3%) of 621 patients treated with placebo in the LAVOLTA studies (appendix).

Discontinuations and exposure times were similar across treatment groups (appendix). Pooling both studies, the proportion of patients who experienced treatment-emergent adverse events (combined lebrikizumab doses, 1125 [79%] of 1432 patients vs placebo, 576 [80%] of 716 patients), serious adverse events (115 [8%] patients vs 65 [9%] patients), and adverse events leading to study drug discontinuation (49 [3%] patients vs 31 [4%] patients) were similar between lebrikizumab and placebo (table 3). Treatment groups were balanced on the key safety events of anaphylaxis, malignancy, and serious infections. In analyses of pooled data, injection-site reactions were similar across groups (combined lebrikizumab doses, 117 [8%] patients vs placebo, 55 [8%] patients).

However, the following serious adverse events of note were recorded in patients treated with lebrikizumab during the placebo-controlled period: one event of aplastic anaemia (125 mg dose) and five serious adverse events related to elevated levels of eosinophils. One serious adverse event of eosinophil count increase was reported in a patient in the 37.5 mg lebrikizumab group and occurred at the time of a mild asthma exacerbation; this patient had a reported history of Churg-Strauss syndrome before randomisation. Four eosinophil-related serious adverse events were reported in three patients randomly assigned to the 125 mg lebrikizumab group. One patient was diagnosed with eosinophilic pneumonia and Churg-Strauss syndrome and had no previous history of eosinophil-related events before randomisation. A second patient was admitted to hospital twice for assessment of eosinophilia (two separate serious adverse events) and also had frequent exacerbations during the clinical trial; this patient had a history of eosinophilia before study entry. A third patient in the 125 mg lebrikizumab group was admitted to hospital for assessment of eosinophilia and leucocytosis and had a history of hospital admissions for similar laboratory abnormalities before study entry. In addition to the five serious adverse events related to eosinophilia in lebrikizumab-treated patients, one event of eosinophilic

	Placebo (n=716)	Lebrikizumab 37.5 mg (n=716)	Lebrikizumab 125 mg (n=716)
Number of adverse events	2474	2407	2477
Number of serious adverse events	93	70	72
Number of deaths	1 (<1%)	0	0
Patients with at least one adverse event	576 (80%)	567 (79%)	558 (78%)
Patients with at least one adverse event assessed as related to study drug by investigator	116 (16%)	79 (11%)	116 (16%)
Patients with at least one serious adverse event	65 (9%)	56 (8%)	59 (8%)
Patients with adverse events leading to discontinuation from study treatment	31 (4%)	15 (2%)	34 (5%)
Patients with adverse events of special interest			
Injection-site reaction	55 (8%)	42 (6%)	75 (10%)
Anaphylaxis per Sampson's criteria	3 (<1%)	1 (<1%)	0
Assessed as related to study drug	2 (<1%)	0	0
Infection (broad)	366 (51%)	364 (51%)	369 (52%)
Infection (narrow)*	1 (<1%)	1 (<1%)	2 (<1%)
Malignancy	5 (1%)	5 (1%)	2 (<1%)

*Medical Dictionary for Regulatory Activities High Level Group Term (MedDRA HLT) for helminthic disorders, mycobacterial infectious disorders, and protozoal infectious disorders or MedDRA HLT of listeria infections.

Table 3: Adverse events in LAVOLTA I and LAVOLTA II

pneumonia was reported in a patient in the placebo group. This patient had a history of eosinophilic otitis media before randomisation.

An imbalance in the incidence of herpes zoster was observed for the lebrikizumab groups: combined lebrikizumab doses (16 [1%] patients) compared with placebo (two [$<1\%$] patients).

Discussion

In these replicate trials, LAVOLTA I met its primary endpoint and significantly reduced asthma exacerbation rates in biomarker-high (periostin ≥ 50 ng/mL or blood eosinophils ≥ 300 cells per μL) patients. Although LAVOLTA II did not achieve statistically significant reductions on the same endpoint, clinically meaningful treatment effects could not be ruled out. Whereas FEV₁ showed improvement in biomarker-high patients in both trials, there were no differences between lebrikizumab and placebo in other secondary endpoints such as AQLQ(S) and ACQ-5 scores. In LAVOLTA I there was not a clear distinction in efficacy between biomarker-high and biomarker-low patient groups, whereas in LAVOLTA II biomarker-high patients showed greater treatment benefit than the biomarker-low group. Pharmacokinetics and pharmacodynamics in these phase 3 trials were consistent with findings in phase 2, indicating that exposures were similar at the same doses and the interleukin-13 pathway was inhibited.

The reasons for the absence of consistent efficacy are speculative. In both LAVOLTA I and LAVOLTA II the placebo groups had improvements in endpoints such as AQLQ(S) score, ACQ-5 score, and rescue medication use. This is common in trials involving patients with uncontrolled asthma. However, we would expect to see an additive improvement with lebrikizumab therapy on top of standard of care. It is possible that, as was seen in phase 2 studies and as has been reported with other interleukin-13 targeted treatments, anti-interleukin-13 therapy might have more effect on airflow obstruction than on the reduction of exacerbations, suggesting that the role of interleukin-13 in asthma exacerbations could be limited. The anti-interleukin-4R α treatment, dupilumab, which binds to the interleukin-4R α receptor and blocks interleukin-4 and interleukin-13 signalling, has recently shown improvement on both exacerbations and lung function in a phase 2b study.³¹ Whether it is blocking both cytokine pathways or whether there is another aspect of the trial design or study population that is important for efficacy against both endpoints remains to be fully determined.

In these phase 3 trials, the biomarker strategy was amended before the primary analysis to include blood eosinophil counts or serum periostin to define the type 2 inflammation-high population assessed as part of the primary efficacy endpoint. The strategy was revised after post-hoc analyses of phase 2 data, which showed that in addition to periostin, blood eosinophils could identify a responder population with regard to exacerbation

frequency and FEV₁ improvement. It was also noted that the classification of patients as eosinophil high or eosinophil low based on a cutoff of 300 cells per μL was similar to that of periostin classification based on a cutoff of 50 ng/mL.

Although the treatment-by-biomarker interaction analysis failed to achieve statistical significance, the strongest treatment-by-biomarker interaction was observed for blood eosinophils. Overall, patients who were both periostin high and eosinophil high showed better efficacy in both studies.

Type 2 biomarkers correlate with one another but do not completely overlap, suggesting that they might identify different aspects of type 2 inflammation or that type 2 biomarkers are increased for reasons other than asthma (eg, comorbidities). Therefore, using multiple biomarkers might provide more confidence that type 2 inflammation is indeed the driver of the disease. However, the more stringent criteria that are required to define the eligible population would also result in a smaller sub-population and potentially exclude patients who could benefit from the treatment. Raised blood eosinophils might correlate better with serum interleukin-13 than serum periostin because eosinophils produce interleukin-13. However, both biomarkers are peripheral and are probably not specific for interleukin-13 activity in the airway.

Whereas periostin is increased following induction by interleukin-13 in epithelial cells, its ability to predict response to anti-interleukin-13 therapy might have been overestimated in phase 2 trials. Although serum interleukin-13 and serum periostin concentrations have been shown to correlate, correlation with airway tissue concentrations of interleukin-13 has not been extensively studied. Periostin from sources other than the airway might also restrict clinical use.

The biomarker classifications assessed were prognostic for exacerbations, with increased exacerbation rates in placebo groups of biomarker-high patients compared with biomarker-low patients (eg, pooled placebo data from both studies: eosinophil high, 1.03 vs eosinophil low, 0.54; periostin high, 0.86 vs periostin low, 0.52). This prognostic effect was even more pronounced in patients who were high for both eosinophil counts and periostin concentrations (pooled data: eosinophil high and periostin high, 1.15 vs eosinophil low and periostin low, 0.47; see appendix for the rate of asthma exacerbations in placebo groups for all biomarker classifications).

The greater clinical benefit seen in the phase 2 studies and the absence of consistent results across the dose levels tested in these two replicate phase 3 LAVOLTA studies are difficult to explain. The baseline characteristics were generally similar across lebrikizumab phase 2b and phase 3 studies and are unlikely to account for the findings. The LAVOLTA I and LAVOLTA II studies had more patients with a history of at least one exacerbation

in the 12 months before the study (48% in the pooled 2b study population *vs* about 63% in LAVOLTA I and 65% in LAVOLTA II).

Pharmacokinetics and pharmacodynamics data were consistent with previous findings, and drug product quality attributes, including potency, were comparable between phase 2 and phase 3 clinical materials. The PLBL2 concentration in the drug used in the phase 3 trial was significantly lower (<1 ng/mg drug) than the phase 2 material (about 30–300 ng/mg drug), due to targeted manufacturing process changes. Although the incidence of anti-lebrikizumab antibodies was 14·2% and anti-PLBL2 antibody was 18·6%, this did not appear to affect overall drug exposure or have a meaningful effect on efficacy or safety.

Although baseline demographics and characteristics were generally balanced between the trials, there were some differences between the studies. Most noteworthy was that LAVOLTA II had a lower exacerbation rate in biomarker-high patients in the placebo group compared with LAVOLTA I. Mean inhaled corticosteroid dose across all three treatment groups in each study was higher in LAVOLTA II (816 µg per day) than LAVOLTA I (775 µg per day). Higher inhaled corticosteroid doses might potentially be associated with lower exacerbation rates during the study despite other baseline characteristics being similar and might have affected the estimate of benefit of lebrikizumab treatment. The differences in sex ratio between LAVOLTA I and LAVOLTA II are small and unlikely to explain the differences in the results.

The proportion of biomarker-high patients was similar between the two studies; however, periostin concentrations were higher in Asian patients and patients enrolled in South America. Exploratory analyses excluding these patients did not change the interpretation of overall efficacy (data not shown).

A deficiency of the LAVOLTA I and II studies was the failure to show a clear dose response, although the studies were not powered to detect a difference between the 37·5 mg and 125 mg doses. The 37·5 mg dose was included to provide a lower exposure that was not overlapping with the 125 mg dose, but overall showed similar exacerbation rate reduction to the higher 125 mg dose. The 37·5 mg dose appeared to be numerically better for exacerbation rate reduction in LAVOLTA I; however, the exacerbation endpoint is relatively imprecise. Although the point estimates for the two doses differed by 21% in LAVOLTA I and were identical in LAVOLTA II, the CIs were overlapping. In the previous phase 2 LUTE/VERSE studies,¹⁴ the greatest treatment benefit on exacerbation rate reduction was in the lowest dose group (37·5 mg). However, these trials were stopped early and had a small number of exacerbation events, which might have resulted in a suboptimal estimate of the exacerbation rate reduction. Overall, the discrepancies across the studies preclude a definitive conclusion on dose response with respect to treatment benefit on exacerbations.

Although the dose–response relationship for exacerbations was not clear in the phase 2 or 3 studies, FEV₁ might be a more sensitive endpoint for differentiation of the 37·5 mg and 125 mg doses. In the LUTE/VERSE studies, the improvement in FEV₁ was less pronounced for the 37·5 mg dose compared with the 125 mg dose, suggesting it was a partly effective dose.¹⁴ Although the improvement in mean FEV₁ in LAVOLTA I was slightly lower in biomarker-high patients for the 37·5 mg dose at week 52, the two doses were generally overlapping at earlier timepoints in both studies. An exposure–response quartile analysis for FEV₁ in the LAVOLTA studies showed a trend of improvement between the first and second exposure quartiles, suggesting that 37·5 mg had not reached the maximum response.

Lebrikizumab decreased biomarkers of type 2 inflammation (FENO and periostin), suggesting interleukin-13 pathway inhibition; however, it is possible that maximal blockade of interleukin-13 was achieved but remained insufficient to substantially affect clinical endpoints in this population of asthma patients. Although phase 2 data did not show correlation between on treatment periostin reduction and response to treatment, to complete this analysis using the larger dataset from the LAVOLTA studies would potentially be useful; however, this action was not prespecified and has not been assessed here.

Lebrikizumab treatment caused a clinically modest mean increase in blood eosinophil counts. This effect has been observed with lebrikizumab,¹⁴ tralokinumab,³² and the anti-interleukin-4Rα blocker dupilumab,³¹ and is thought to relate to induction by interleukin-13 of adhesion molecules like P-selectin and chemokines with a CC motif that bind to CCR3. These chemokines and adhesion molecules can serve as chemoattractants for eosinophils.^{33,34} Blocking interleukin-13 might prevent upregulation of these chemokines and thereby reduce eosinophil migration from the blood to the airway and result in accumulation of eosinophils in the peripheral blood.

Three other asthma studies with lebrikizumab (NCT01875003, NCT01987492, and NCT02099656) have terminated dosing because of the absence of efficacy in the LAVOLTA studies, and the assessment of the data from these still-blinded studies is pending. These clinical studies will inform the efficacy and safety of lebrikizumab treatment in patients with severe asthma on chronic maintenance corticosteroids, in adolescent patients with severe asthma, and provide further data on airway effects of lebrikizumab.

Our study had limitations. The study population did not select for patients with a history of exacerbations as trials of other biological agents in asthma have done.^{31,35} However, phase 2 trials with lebrikizumab that showed greater benefit with lebrikizumab treatment than the LAVOLTA trials did not have a requirement for history of exacerbations either. Although patients who self-reported a history of exacerbations had a higher rate of exacerbations during the study compared with patients

with no reported exacerbations, post-hoc analyses did not suggest that efficacy was greater as a percentage reduction in patients with a self-reported history of two exacerbations or more in the preceding year (LAVOLTA I, 56% and 26% reduction; LAVOLTA II, 33% and 27% reduction, with 37.5 mg and 125 mg lebrikizumab, respectively; appendix).

These trials were powered assuming an absolute rate of 0.6 events per patient per year in the placebo group and should have been able to detect a 50% reduction associated with treatment if it existed. The observed exacerbation rates in the placebo groups confirm that each trial was well powered to detect the target effect size. One assumption was that all exacerbation events could be potentially inhibited by blocking interleukin-13. However, studies that have defined exacerbation events based on sputum cell counts show that a number of events might not be driven by type 2 mechanisms.³⁶

The heterogeneity of severe asthma means that identifying and targeting the mechanism driving an individual's disease is important to improve outcomes. These trials assessed the efficacy of an anti-interleukin-13 therapy in patients with uncontrolled asthma and high concentrations of type 2 biomarkers and suggest that benefit on exacerbations was improved by selecting biomarker-high patients. However, the studies did not provide consistently significant results for the primary endpoint or a clear dose response. The overall efficacy of lebrikizumab in these trials did not meet the exacerbation rate reduction or FEV₁ improvement expected from the phase 2 results in this patient population. The lack of efficacy on patient-reported symptoms was a notable lack of efficacy seen in earlier phase 2 studies, and so the longer duration of treatment in the phase 3 trials did not improve on this observation. The biomarker strategy, which focused on patients high for either blood eosinophil counts or periostin concentrations, did not consistently identify those who achieved benefit from lebrikizumab treatment. Overall, these data suggest that the underlying biology of lung function and asthma exacerbations might differ and interleukin-13 might play a less prominent role in the latter. Targeting interleukin-13 alone might not be sufficient to provide clinically meaningful improvement in exacerbations and symptoms measured by ACQ-5 in these patients.

Contributors

All authors have contributed to the conception or design of the work, the acquisition, analysis, or interpretation of data for the work, and have been involved in drafting the work or revising it critically for important intellectual content. All authors provided approval of the final version to be published.

Declaration of interests

NAH has received honoraria for serving as a consultant or an advisory board for Boehringer Ingelheim, Roche, Mylan, Sunovion, Astra Zeneca and Novartis. His institution received research grant support on his behalf from Roche, GSK, Mylan, Boehringer Ingelheim, Astra Zeneca and Chiesi. PKor reports personal fees from Genentech as a consultant, fees to his employer for this clinical trial and previously for performing clinical trials in asthma for AstraZeneca, GSK, Regeneron and Sanofi-Aventis.

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