



Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial

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Summary

Background Interleukin 13 is a central mediator of asthma. Tralokinumab is a human interleukin-13 neutralising monoclonal antibody. We aimed to assess the efficacy and safety of two dosing regimens of tralokinumab in patients with severe uncontrolled asthma.

Methods We did a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 2b study at 98 sites in North America, South America, Europe, and Asia. Patients aged 18–75 years with severe asthma and two to six exacerbations in the previous year were randomly assigned (1:1), via an interactive voice-response or web-response system, to one of two dosing regimen groups (every 2 weeks, or every 2 weeks for 12 weeks then every 4 weeks) and further randomised (2:1), via computer-generated permuted-block randomisation (block size of six), to receive tralokinumab 300 mg or placebo for 1 year. All participants received high-dose fluticasone and salmeterol and continued other pre-study controller drugs. Treatment was administered by an unmasked study investigator not involved in the management of patients; all other study site personnel, patients, the study funder, and data analysts were masked to treatment allocation. The primary endpoint was the annual asthma exacerbation rate at week 52 in the intention-to-treat population. Key secondary endpoints included prebronchodilator forced expiratory volume in 1 s (FEV₁), Asthma Control Questionnaire-6 (ACQ-6), and Asthma Quality of Life Questionnaire–Standardised Version (AQLQ[S]). This trial is registered with ClinicalTrials.gov, number NCT01402986.

Findings Between Oct 4, 2011, and Feb 22, 2014, we randomly assigned 452 patients to receive placebo (n=151) or tralokinumab every 2 weeks (n=150) or every 4 weeks (n=151), of whom 383 (85%) completed the treatment period up to week 52. The annual asthma exacerbation rate at week 52 was similar between patients receiving tralokinumab every 2 weeks (0·91 per patient per year [95% CI 0·76–1·08]) and every 4 weeks (0·97 [0·81–1·14]), and those receiving placebo (0·90 [0·75–1·08]). At week 52, percentage changes in annual asthma exacerbation rate were not significant with tralokinumab every 2 weeks or every 4 weeks versus placebo (6% [95% CI –31 to 33; p=0·709] and –2% [–46 to 29; p=0·904], respectively), with positive changes showing a decrease in exacerbation rate and negative changes showing an increase. Prebronchodilator FEV₁ was significantly increased compared with placebo for tralokinumab every 2 weeks (change from baseline 7·3% [95% CI 2·6–12·0]; p=0·003), but not every 4 weeks (1·8% [–2·9 to 6·6]; p=0·448); however, we did not identify significant changes in the other key secondary endpoints. In a post-hoc subgroup analysis of patients not on long-term oral corticosteroids and with baseline FEV₁ reversibility of 12% or greater, we noted a non-significant improvement in asthma exacerbation rate (44% [95% CI –22 to 74]; p=0·147) and significant improvements in key secondary endpoints (FEV₁ 12·2% [1·7–22·7]; p=0·022; ACQ-6 –0·55 [–1·07 to –0·04]; p=0·036; and AQLQ[S] 0·70 [0·12–1·28]; p=0·019) in patients given tralokinumab every 2 weeks (n=33) compared with placebo (n=48). In patients in this subgroup who also had baseline serum dipeptidyl peptidase-4 (DPP-4) higher than the population baseline median, we noted additional improvements in prebronchodilator FEV₁, ACQ-6, and AQLQ(S), and, in those with periostin concentrations higher than the median, we noted improvements in asthma exacerbation rate, prebronchodilator FEV₁, and ACQ-6. The incidence of treatment-emergent adverse events was similar between the tralokinumab and placebo groups. Treatment-emergent serious adverse events regarded as related to the study drug were pneumonia (one [1%] patient in the placebo group), pneumococcal pneumonia (one [1%] in the tralokinumab every 2 weeks group), angioedema (one [1%] in the placebo group), and worsening asthma (one [1%] in the tralokinumab every 2 weeks group and two [1%] in the tralokinumab every 4 weeks group).

Interpretation In this phase 2b study, both tralokinumab regimens had an acceptable safety and tolerability profile but did not significantly reduce asthma exacerbation rates in patients with severe uncontrolled asthma. Improvement in FEV₁ with tralokinumab given every 2 weeks and results of post-hoc subgroup analyses suggested a possible treatment effect in a defined population of patients with severe uncontrolled asthma. This effect is being further investigated in ongoing phase 3 trials, along with the potential utility of DPP-4 and periostin as biomarkers of interleukin-13 pathway activation.

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Introduction

Asthma is a complex and heterogeneous chronic inflammatory disease of the airways, which presents with variable symptoms of cough, breathlessness, and wheeze, with episodic acute worsening of symptoms known as exacerbations, particularly in severe asthma. Effective treatment of patients with severe asthma is a major unmet clinical need—such patients have a high morbidity¹ and, although representing only 5–10% of adults with asthma,¹ their direct health-care costs are more than twice those of patients with mild or moderate asthma.²

In asthma, interleukin 13, a T-helper-2 (Th2) cytokine, is implicated in driving airway inflammation, remodelling, and hyper-responsiveness,^{3–7} and its expression is substantially increased in patients with severe disease.⁸ Some biological treatments that neutralise interleukin 13 can lead to clinical improvements, mainly in lung function,^{9–11} which are most evident in patients with interleukin-13 pathway activation assessed directly (increased baseline sputum interleukin 13)¹¹ or indirectly (high baseline concentrations of serum periostin).^{9,10}

In this study, we tested the hypothesis that interleukin 13 is important in the pathogenesis of asthma exacerbations by studying the effect of treatment with tralokinumab, a human immunoglobulin-G4 monoclonal antibody that potently and specifically neutralises interleukin 13, on exacerbation frequency in patients with severe uncontrolled asthma.¹² On the basis of findings from a previous phase 2a study¹¹ of an initial 12 week dosing regimen of tralokinumab 300 mg every 2 weeks, we aimed to assess the efficacy and safety of two maintenance dosing regimens of tralokinumab in patients with severe uncontrolled asthma. We did subgroup analyses to examine the response to tralokinumab in individuals with and without interleukin-13 pathway activation and specific baseline clinical characteristics.

Methods

Study design and patients

We did a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 2b study at 98 sites in North America, South America, Europe, and Asia. The appendix shows details of the study design, which consisted of a 5 week screening and run-in period, a 48 week or 50 week treatment period, and a 22 week safety follow-up period. We enrolled patients aged 18–75 years with severe uncontrolled asthma, consistent with the European Respiratory Society and American Thoracic Society definition,¹³ who were receiving high-dose inhaled corticosteroids (total daily dose >500 µg fluticasone dry powder inhaler or equivalent via metered-dose inhaler) plus a longacting beta agonist (LABA) at least 30 days before visit 1 (run-in day –35), and who had at least two, but no more than six, exacerbations in the previous 12 months. Patients had to have a history of asthma for 1 year or more, and either a documented

increase in post-bronchodilator forced expiratory volume in 1 s (FEV₁) of 12% or greater and 200 mL or more, or a positive methacholine challenge (PC20 ≤8 mg/mL) in the previous 3 years, or an increase in post-bronchodilator FEV₁ of 12% or greater and 200 mL or more at visits 1 or 2 (run-in day –28 plus or minus 3 days). Key exclusion criteria were concomitant respiratory disease, current cigarette smoking, known immune deficiency, or history of cancer. The appendix includes a full list of inclusion and exclusion criteria.

This study was done 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. Details for the full protocol are available in the appendix.

Randomisation and masking

Patients were stratified at screening by the number of asthma exacerbations in the past year (two *vs* three to six), and long-term use of oral corticosteroids (presence *vs* absence). They were randomly assigned (1:1), via an interactive (voice or web) system, to one of two dosing regimen groups (every 2 weeks or every 2 weeks for 12 weeks then every 4 weeks). Within each group, patients were further randomised (2:1), via computer-generated permuted-block randomisation (block size of six) to receive tralokinumab 300 mg or placebo for 1 year (appendix). The investigational product was handled at the site by an unmasked investigational product manager and was given to patients by an unmasked study investigator, neither of whom were involved in the management of patients or per-protocol assessments. An independent, unmasked site investigational product monitor documented investigational product accountability. The patients, all other study site personnel, the study funder, and data analysts were masked to treatment allocation.

Procedures

Treatment was given by subcutaneous injection either every 2 weeks to week 50, or every 2 weeks for 12 weeks followed by every 4 weeks to week 48. From run-in week –4, all patients received fluticasone 500 µg and salmeterol 50 µg twice daily, via dry powder inhaler or equivalent via metered-dose inhaler, for the duration of the study, and continued to receive any additional pre-study asthma controller drugs. Patients receiving an alternative combination of inhaled corticosteroid and LABA before visit 1 were switched at visit 2 to either fluticasone 500 µg and salmeterol 50 µg via dry powder inhaler with one inhalation twice per day, or fluticasone 230 µg and salmeterol 21 µg via metered-dose inhaler with two inhalations twice per day.

We investigated several potential biomarkers of interleukin-13 pathway activation, including serum

See Online for appendix

periostin concentrations;^{9,10} Th2 status, as defined by serum IgE and peripheral blood eosinophil count;^{9,14} and baseline peripheral blood eosinophil count alone. While this study was in progress, we identified *DPP4* as a gene that is highly induced by interleukin 13 in healthy and asthmatic airway epithelial cells (appendix). Dipeptidyl peptidase-4 (DPP-4) was included as a predictive candidate biomarker before the study was unmasked. We measured serum DPP-4 and periostin concentrations with ELISA-based assays (R&D Systems, Minneapolis, MN, USA and Abbott Diagnostics, Abbott Park, IL, USA, respectively).

Outcomes

The primary endpoint was the annual asthma exacerbation rate at week 52. We defined asthma exacerbation as an increase in asthma symptoms resulting in use or increase in dose of systemic corticosteroids for 3 or more consecutive days (appendix). No additional guidance was provided to study sites about the management of patients with deteriorating asthma symptoms, and sites were allowed to follow local treatment practices.

Key secondary endpoints of prebronchodilator FEV₁, Asthma Control Questionnaire-6 (ACQ-6),¹⁵ and Asthma Quality of Life Questionnaire–Standardised Version (AQLQ[S]) at week 52¹⁶ measured the effect of tralokinumab across domains of asthma control and were prioritised during analysis and interpretation of the study outcomes. These key endpoints were not prespecified in the protocol; however, they were prioritised before database lock. Additional secondary endpoints included lung function

endpoints (forced expiratory volume in 6 s [FEV₆], forced vital capacity, inspiratory capacity, peak expiratory flow at home, and FEV₁ at home); patient-reported outcomes, assessed with the EQ-5D; and the effect on asthma symptoms, assessed with the Assessing Symptoms of Moderate-to-severe Asthma (ASMA) diary, which is a 13 item questionnaire developed by MedImmune and the University of British Columbia (Vancouver, BC, Canada).¹⁷

Treatment-emergent and serious adverse events were recorded at every study visit. Standard panels of haematology, chemistry, and urine tests were assessed throughout the study, along with measurement of anti-drug antibodies.

Statistical analysis

The sample size (130 patients per treatment group) was calculated to provide 80% power to detect a 40% reduction in asthma exacerbation rate at week 52 for each tralokinumab group compared with placebo (placebo given every 2 weeks and every 4 weeks were pooled into a single group for the analyses), assuming an annual rate for placebo of 1·2 per patient per year, and that about 50% of enrolled patients had asthma characterised by interleukin-13 pathway activation. The protocol was amended before unmasking to allow for at least 390 patients to be enrolled (appendix). Eligible patients in the 5 week screening and run-in period at the time the enrolment target was met were recruited into the study. The two-sided α was set at 0·10, but was revised in a protocol amendment to 0·15 because the masked estimate of the placebo exacerbation rate during the

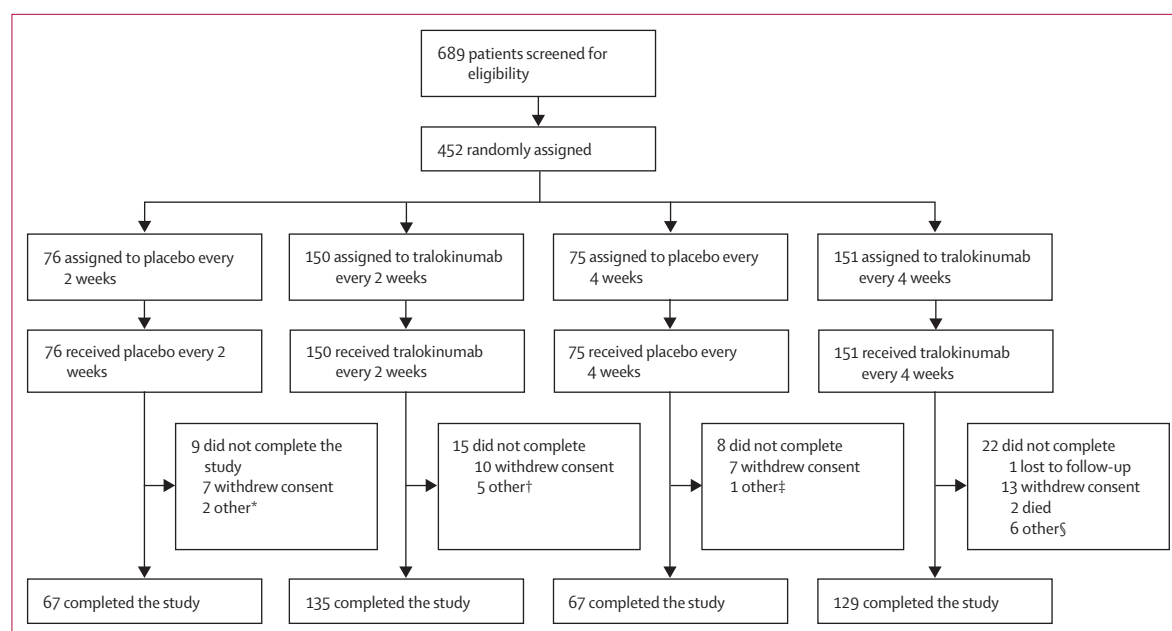


Figure 1: Trial profile

*n=1 adverse event, n=1 did not want to attend further visits. †n=1 changed address, n=1 adverse event, n=1 discontinued at request of patient because of desire for pregnancy, n=1 unable to complete morning diaries within the required timeframe, n=1 working abroad. ‡n=1 discontinued at request of patient. §n=1 adverse event, n=1 low compliance with study visits and asthma exacerbation drugs, n=1 low compliance, n=1 did not meet inclusion criteria, n=1 lost to follow-up, n=1 pregnancy.

study was lower than the initial assumption. All regulatory and ethical approvals were received for these protocol amendments. The final analysis was assessed with a two-sided α of 0.128 adjusted for one interim analysis with O'Brien and Fleming's design;¹⁸ the power was estimated to be 78% after the adjustment. Here, we report nominal p values for each analysis; however, only results with nominal p values less than 0.05 are described as significant, despite the two-sided α being set to 0.15.

Efficacy analyses were done in the intention-to-treat population (all randomly assigned participants) and safety analyses were done in the safety population (all participants who received at least one dose of tralokinumab or placebo and had safety data available). The intention-to-treat and safety populations are identical in this study.

We analysed the primary endpoint using a Poisson regression model adjusted for overdispersion, with treatment group, age, sex, number of asthma exacerbations in the past year, atopic asthma status (defined by the presence or absence of specific IgE to a panel of inhaled allergens), presence or absence of long-term oral corticosteroid use, and geographical region as covariates. We also did a prespecified sensitivity analysis of the primary endpoint with a negative binomial regression model. The annual asthma exacerbation rate is presented as a weighted mean calculated as the total number of exacerbations divided by total person-years of follow-up. Data are presented as percentage changes compared with placebo; a positive change indicates a decrease and a negative change indicates an increase in exacerbation rate.

We analysed secondary endpoints using a mixed-model repeated-measure approach,¹⁹ adjusted for the same covariates listed for asthma exacerbation rate. Change-over-time plots were based on all recorded data. The weekly morning and evening average of FEV₁ and peak expiratory flow at home were summarised by week. We used descriptive statistics to summarise the weekly average and the change from baseline and percentage change from baseline at various timepoints. EQ-5D questionnaire overall scores were summarised by treatment group and visit.

Subgroups were defined to allow investigation of associations between patient characteristics and treatment response. All subgroups except those relating to DPP-4 concentrations were prespecified. Subgroups defined by biomarkers of interleukin-13 pathway activation were baseline serum DPP-4 concentration (median or higher [high] vs less than median [low]), baseline serum periostin concentration (median or higher [high] vs less than median [low]), Th2 status (IgE >100 IU/mL and blood eosinophils $\geq$ 140 cells per μ L [high] vs IgE $\leq$ 100 IU/mL or blood eosinophils <140 cells per μ L [low]), and baseline peripheral blood eosinophil count (<300 vs $\geq$ 300 cells per μ L). Subgroups defined by clinical characteristics were FEV₁ reversibility (reversible [$\geq$ 12% increase] vs not reversible [<12% increase] in post-bronchodilator FEV₁), long-term use of oral

	Placebo group (n=151)	Tralokinumab groups	
		Every 2 weeks (n=150)	Every 4 weeks (n=151)
Age (years)	50.3 (12.9)	49.7 (12.2)	50.5 (11.8)
Sex			
Female	97 (64%)	100 (67%)	100 (66%)
Male	54 (36%)	50 (33%)	51 (34%)
Race			
Asian	52 (34%)	53 (35%)	53 (35%)
White	84 (56%)	83 (55%)	86 (57%)
Other	15 (10%)	14 (9%)	12 (8%)
Prebronchodilator FEV ₁ (L)	1.92 (0.60)	1.92 (0.68)	1.94 (0.71)
Prebronchodilator FEV ₁ (% predicted)	68.0 (16.2)	68.3 (19.6)	69.3 (18.6)
FEV ₁ reversibility (%)	12.9 (16.9)	10.8 (14.4)	10.1 (13.2)
ACQ-6 score	2.54 (0.88)	2.59 (1.07)	2.52 (0.96)
AQLQ(S) score	4.01 (1.03)	3.96 (1.05)	4.02 (1.00)
Blood eosinophil count (10 ³ / μ L)	0.37 (0.58)	0.39 (0.40)	0.34 (0.43)
T-helper-2 status			
Low	73 (51%)	61 (45%)	72 (52%)
High*	70 (49%)	74 (55%)	67 (48%)
Periostin (ng/mL)†	21.85 (17.41–28.70)	23.60 (18.51–30.89)	23.24 (19.41–29.29)
DPP-4 (ng/mL)‡	343 (300–426)	372 (312–447)	375 (311–439)
Asthma history			
Time spent on high-dose inhaled corticosteroids or LABA (months)	12 (6–12)	12 (7–12)	12 (6–12)
Long-term use of oral corticosteroids	27 (18%)	26 (17%)	24 (16%)
Atopic asthma‡	96 (65%)	105 (71%)	92 (63%)
Exacerbations in the past year			
1	0	1 (1%)	0
2	46 (61%)	96 (64%)	51 (68%)
3	22 (29%)	32 (21%)	14 (19%)
4	3 (4%)	11 (7%)	5 (7%)
5	1 (1%)	5 (3%)	4 (5%)
6	4 (5%)	5 (3%)	1 (1%)
Hospital admissions in the past year	27 (18%)	31 (21%)	25 (17%)

Data are mean (SD), n (%), or median (IQR), unless otherwise indicated. FEV₁=forced expiratory volume in 1 s. ACQ-6=Asthma Control Questionnaire-6. AQLQ(S)=Asthma Quality of Life Questionnaire-Standardised Version. DPP-4=dipeptidyl peptidase-4. LABA=longacting beta agonist. *Immunoglobulin (Ig) E >100 IU/mL and blood eosinophils $\geq$ 140 cells/ μ L. †Measured at week 1 before first dose. ‡Defined by the presence of raised IgE specific to any one common aeroallergen on the region-specific ImmunoCap (Thermo Fisher, Uppsala, Sweden) panel tested at baseline.

Table 1: Demographics and baseline characteristics

corticosteroids (presence vs absence), number of exacerbations in the past year (two vs three to six), and baseline percentage of predicted FEV₁ ($\leq$ 60% and $\leq$ 80%). We assessed combinations of subgroups in a post-hoc analysis. We did statistical analyses with SAS (version 9.3).

This trial is registered with ClinicalTrials.gov, number NCT01402986.

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

Between Oct 4, 2011, and Feb 22, 2014, we randomly assigned 452 patients to receive placebo (n=151), tralokinumab every 2 weeks (n=150), or tralokinumab every 4 weeks (n=151). 383 (85%) patients completed the full treatment period up to week 52 and 398 (88%) patients completed the safety follow-up period to week 74 (figure 1). Baseline characteristics were similar between groups and no patients were current smokers (table 1).

The unadjusted annual asthma exacerbation rates at week 52 were similar for patients receiving tralokinumab every 2 weeks (0.91 per patient per year, 95% CI 0.76–1.08), those receiving tralokinumab every 4 weeks (0.97, 0.81–1.14), and those receiving placebo (0.90, 0.75–1.08). At week 52, the percentage changes in annual asthma exacerbation rate were not significant with tralokinumab every 2 weeks or tralokinumab every 4 weeks versus placebo (6% [95% CI –31 to 33; p=0.709] and –2% [–46 to 29; p=0.904], respectively). In the sensitivity analysis of the primary endpoint analysed with a negative binomial regression model, the results were unchanged (appendix). Time to first exacerbation or the number of severe exacerbations did not differ significantly between the tralokinumab groups and the placebo group (appendix).

At week 52, we noted a significant increase in FEV₁ compared with placebo in patients receiving tralokinumab every 2 weeks (7.28%, 95% CI 2.55–12.02; p=0.003), but not in those receiving tralokinumab every 4 weeks (1.84%, 95% CI –2.92 to 6.60; p=0.448; table 2, figure 2). Improvements in ACQ-6 and AQLQ(S) were not significant for either tralokinumab group versus placebo (table 2).

Assessment of other lung function endpoints—FEV₆, forced vital capacity, inspiratory capacity, and peak expiratory flow, and FEV₁ at home—showed no significant improvements, with the exceptions of pre-bronchodilator FEV₆ and morning FEV₁ mean change from baseline in the tralokinumab every 2 weeks group (p=0.034 and 0.037, respectively, vs placebo; appendix). Patient-reported outcomes assessed by EQ-5D and asthma symptoms assessed by the ASMA diary did not differ significantly between either tralokinumab group and placebo (appendix).

Within biomarker-defined subgroups, we noted non-significant reductions in annual asthma exacerbation rate compared with placebo at week 52 in patients receiving tralokinumab every 2 weeks in the high DPP-4 (34%, 95% CI –6 to 59; p=0.083) and high periostin (27%, –17 to 54; p=0.190) subgroups (appendix).

FEV₁ increased significantly from baseline to week 52 in patients with high DPP-4 receiving tralokinumab every 2 weeks versus placebo (10.82%, 95% CI 3.35–18.29; p=0.005); there was no increase in the subgroup with low DPP-4 (3.64%, –2.49 to 9.77; p=0.244; figure 2, appendix). Increases in FEV₁ at week 52 were similar between patients in the high periostin and the low periostin subgroups receiving tralokinumab every 2 weeks versus placebo (6.79% [95% CI –0.21 to 13.79; p=0.057] and 7.37% [0.80–13.95; p=0.028], respectively; figure 2, appendix).

We noted significant improvements in ACQ-6 and AQLQ(S) in patients in the high DPP-4 subgroup (–0.50 [95% CI –0.86 to –0.14; p=0.007] and 0.69 [0.30 to 1.08; p<0.001], respectively; appendix); these improvements were not significant in the low DPP-4 subgroup (appendix). No significant improvements in ACQ-6 and AQLQ(S) were recorded in the subgroups with high or low periostin (appendix).

Of the clinical characteristics assessed, presence or absence of airway reversibility at baseline and long-term

	Placebo group (n=151)	Tralokinumab groups	
		Every 2 weeks (n=150)	Every 4 weeks (n=151)
Prebronchodilator FEV ₁ (n)	125	130	122
Percent change from baseline (%)	1.32% (–2.39 to 5.02)	8.60 (4.88 to 12.32)	3.16 (–0.62 to 6.94)
Difference from placebo (95% CI; p value)	..	7.28 (2.55 to 12.02; 0.003)	1.84 (–2.92 to 6.60; 0.448)
Prebronchodilator FEV ₁ (n)	125	130	122
Mean change from baseline (L)	0.00 (–0.06 to 0.07)	0.13 (0.07 to 0.20)	0.05 (–0.02 to 0.11)
Difference from placebo (95% CI; p value)	..	0.13 (0.05 to 0.21; 0.002)	0.04 (–0.04 to 0.12; 0.321)
ACQ-6 (n)	118	115	112
Mean change from baseline	–0.65 (–0.84 to –0.47)	–0.84 (–1.03 to –0.65)	–0.78 (–0.97 to –0.59)
Difference from placebo (95% CI; p value)	..	–0.19 (–0.43 to 0.06; 0.131)	–0.13 (–0.37 to 0.12; 0.306)
AQLQ(S) (n)	107	109	101
Mean change from baseline	0.70 (0.50 to 0.91)	0.91 (0.70 to 1.12)	0.90 (0.69 to 1.11)
Difference from placebo (95% CI; p value)	..	0.21 (–0.05 to 0.46; 0.110)	0.20 (–0.06 to 0.46; 0.132)

Data in parentheses are 95% CI, unless otherwise indicated. FEV₁=forced expiratory volume in 1 s. ACQ-6=Asthma Control Questionnaire-6. AQLQ(S)=Asthma Quality of Life Questionnaire-Standardised Version.

Table 2: Secondary efficacy endpoints at week 52 in the intention-to-treat population

use of oral corticosteroids were associated with treatment response (appendix). In patients who had post-bronchodilator reversibility of 12% or more at baseline, we recorded non-significant reductions in annual asthma exacerbation rate (34%, -32 to 67; $p=0.245$ vs placebo), with improvements in FEV₁ and AQLQ(S) at week 52; however, these improvements were not shown in patients with less than 12% reversibility (appendix). FEV₁ at week 52 did not increase in patients with long-term oral corticosteroid use; however, in patients without long-term use of oral corticosteroids, FEV₁ was significantly improved compared with placebo (appendix). Other baseline biomarker and clinical characteristics had unimportant, or inconsistent, predictive effects on clinical response to tralokinumab (appendix).

Findings from subgroup analyses led us to further investigate patients receiving tralokinumab every 2 weeks with airway reversibility at baseline, but not receiving long-term oral corticosteroids ($n=33$) in a post-hoc analysis (table 3). In this post-hoc subgroup, we recorded a non-significant reduction in annual asthma exacerbation rate versus placebo ($n=48$), and significant improvements in FEV₁, ACQ-6, and AQLQ(S) (table 3). We noted further improvements in efficacy in patients in this subgroup who also had raised serum DPP-4 or periostin at baseline (table 3).

The incidence of treatment-emergent adverse events was similar between patients in the placebo group and those in the tralokinumab groups (table 4). Most treatment-emergent adverse events were mild or moderate in severity, and were not regarded as related to the study drug. The most common grade 3 treatment-emergent adverse events were worsening asthma (12 [8%] of 150 patients in the tralokinumab every 2 weeks group, 16 [11%] of 151 in the tralokinumab every 4 weeks group, and 20 [13%] of 151 for the placebo group), injection-site pain (one [1%] in the tralokinumab every 4 weeks group and four [3%] in the placebo group), bronchitis (two [1%] in the tralokinumab every 4 weeks group, and four [3%] in the placebo group), and sinusitis (four [3%] in the placebo group). The most common drug-related treatment-emergent adverse events (reported in >5% of patients in any treatment group) were injection-site pain, injection-site erythema, and injection-site pruritus.

Treatment-emergent serious adverse events were similar between the placebo and tralokinumab groups (table 4). Serious adverse events regarded as related to the study drug, as assessed by the investigator, were pneumonia (in one patient receiving placebo), pneumococcal pneumonia (in one patient receiving tralokinumab every 2 weeks), angioedema (in one patient receiving placebo), and worsening asthma (in one patient receiving tralokinumab every 2 weeks and two receiving tralokinumab every 4 weeks).

Two patients died (cardiac failure and septic shock) in the group receiving tralokinumab every 4 weeks; neither death was regarded as related to the study drug (table 4).

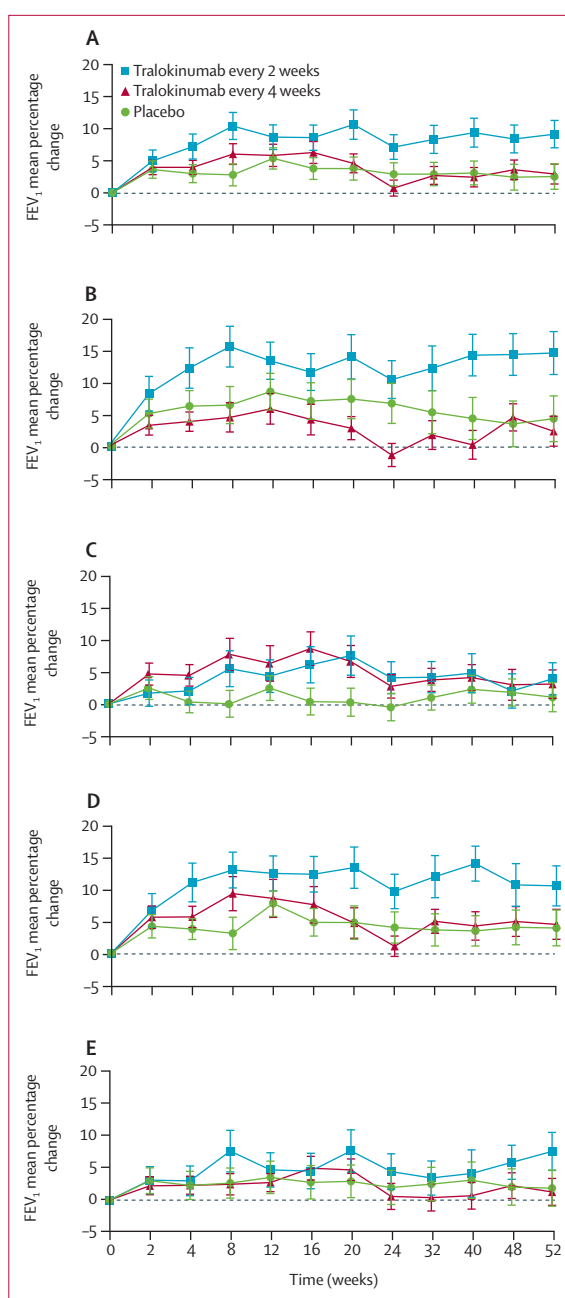


Figure 2: Mean percentage change from baseline in FEV₁ over time
Error bars show SEs. Figure shows results for the intention-to-treat population (A), and for patients with high dipeptidyl peptidase-4 (B), low dipeptidyl peptidase-4 (C), high periostin (D), and low periostin (E) at baseline. FEV₁=forced expiratory volume in 1 s.

Blood eosinophil counts at week 52 were raised in patients in both tralokinumab groups compared with placebo (appendix). We noted no association between this increase and treatment-emergent adverse events. No other clinically relevant changes in haematology, chemistry, or urine measures were noted (data not shown). We detected anti-drug antibodies in two (1%)

	All (n=33)	DPP-4-high group (n=24)	DPP-4-low group (n=8)	Periostin-high group (n=18)	Periostin-low group (n=15)
Primary endpoint					
Asthma exacerbation rate					
Percent reduction versus placebo (95% CI; p value)	44% (-22 to 74; 0.147)	57% (-30 to 86; 0.134)	-7% (-88.6 to 88; 0.950)	67% (2 to 89; 0.046)	-32% (-7.04 to 53; 0.597)
Secondary endpoints (difference from placebo)					
Prebronchodilator FEV ₁					
Percent change from baseline (95% CI; p value)	12.21% (1.74 to 22.67; 0.022)	20.41% (1.30 to 39.52; 0.037)	-0.94% (-15.35 to 13.47; 0.897)	15.14% (0.35 to 29.92; 0.045)	8.00% (-7.04 to 23.04; 0.294)
ACQ-6					
Mean change from baseline (95% CI; p value)	-0.55 (-1.07 to -0.04; 0.036)	-0.89 (-1.63 to -0.14; 0.020)	-0.43 (-1.41 to 0.56; 0.390)	-0.68 (-1.31 to -0.06; 0.033)	-0.23 (-1.10 to 0.64; 0.596)
AQLQ(S)					
Mean change from baseline (95% CI; p value)	0.70 (0.12 to 1.28; 0.019)	1.26 (0.48 to 2.04; 0.002)	0.24 (-0.87 to 1.35; 0.663)	0.64 (-0.11 to 1.39; 0.095)	0.71 (-0.23 to 1.65; 0.138)

DPP-4=dipeptidyl peptidase-4. FEV₁=forced expiratory volume in 1 s. ACQ-6=Asthma Control Questionnaire-6. AQLQ(S)=Asthma Quality of Life Questionnaire-Standardised Version.

Table 3: Asthma exacerbation rate, FEV₁, ACQ-6, and AQLQ(S) for tralokinumab every 2 weeks versus placebo in patients who were reversible at baseline and not receiving long-term oral corticosteroids

patients receiving placebo, no patients receiving tralokinumab every 2 weeks, and two (1%) patients receiving tralokinumab every 4 weeks.

Discussion

In this phase 2b study, tralokinumab 300 mg given either every 2 weeks or every 4 weeks did not significantly reduce asthma exacerbation rates in patients with severe uncontrolled asthma. However, FEV₁ was significantly increased in patients receiving tralokinumab every 2 weeks, which is consistent with phase 2a data¹¹ and studies of other monoclonal antibodies that target interleukin 13, such as lebrikizumab.^{9,10} Increases in FEV₁ with tralokinumab given every 4 weeks did not differ significantly from placebo, suggesting that dosing every 2 weeks is most efficacious. Both tralokinumab regimens showed an acceptable safety and tolerability profile over the 52 week treatment period and during the 22 week follow-up period.

Findings from post-hoc subgroup analyses showed that, although the asthma exacerbation rate did not differ significantly between the placebo and tralokinumab groups, improvements in lung function were greatest in patients given tralokinumab every 2 weeks who had a combination of raised biomarker concentrations, post-bronchodilator reversibility, and were not receiving long-term oral corticosteroids.

There is increasing evidence that severe asthma is a heterogeneous disease that might therefore have variable treatment responses to specific cytokine-neutralising monoclonal antibody treatments. Recognition of this heterogeneity and identification of the subgroups most likely to respond to these treatments is an important goal (panel). This stratified medicine approach has been applied to Th2-directed biological

drugs with anti-interleukin-5 and anti-interleukin-5 receptor treatments showing particular benefits in patients with evidence of eosinophilic inflammation.²²⁻²⁵ Failure to identify the subgroup of patients with the potential to benefit from interleukin-13-targeted therapies is one potential reason for the absence of efficacy reported with other anti-interleukin-13 treatments, including IMA-638 (anrukizumab)²⁰ and GSK679586.²¹ Direct measurement of interleukin 13 in the sputum has previously been used to identify patients with enhanced responses to tralokinumab;¹¹ however, alternative biomarkers of interleukin-13 activation are needed because of limitations in obtaining reliable sputum samples and low concentrations of interleukin 13. Serum periostin has been identified as a blood biomarker that indicates interleukin-13 activation of the epithelium, with previous reports suggesting that raised serum periostin can be used to identify patients with favourable clinical outcomes to lebrikizumab.^{9,10} Consistent with these reports of an association between high pretreatment periostin concentrations and improvements in lung function in bronchodilator-reversible patients with asthma receiving lebrikizumab,^{9,10} we noted that patients who were bronchodilator-reversible, not receiving long-term oral corticosteroids, and who had raised pretreatment periostin concentrations showed improvements in lung function when receiving tralokinumab every 2 weeks. We also report the novel finding that serum concentration of DPP-4, a multifunctional enzyme with expression that is highly induced by interleukin 13 in airway epithelial cells and that has been implicated in asthma,^{26,27} allergic rhinitis,²⁸ and in the activation of T cells,²⁹ is also potentially predictive of response to tralokinumab.

In addition to inducing expression of DPP-4 and periostin in airway epithelial cells, interleukin 13 promotes airway smooth muscle contractility and airway hyper-responsiveness.⁶ Bronchodilator reversibility is associated with airway hyper-responsiveness³⁰ and probably reflects interleukin-13 activation of airway smooth muscle. In the present study, we noted that post-bronchodilator reversibility was associated with response to tralokinumab. Importantly, an enhanced clinical response was seen in patients with a combination of bronchodilator reversibility and either raised serum DPP-4 or periostin, suggesting that benefits could be related to blockade of interleukin-13 activation of both airway smooth muscle and bronchial epithelium. Furthermore, although increased concentrations of interleukin 13 in the sputum of patients with severe asthma who were receiving oral corticosteroids have been reported previously,⁸ we noted no benefit in patients receiving long-term oral corticosteroids, suggesting that interleukin 13 might not have been the main mediator of poor asthma control in these patients. These findings were pursued in a post-hoc analysis, in which we identified a population of patients with post-bronchodilator reversibility who were not receiving long-term oral corticosteroids, in whom significant improvements were noted in several secondary endpoints representing different domains of asthma control. The findings from this analysis directly informed both the patient population and the key endpoints to be assessed in the ongoing phase 3 studies of tralokinumab, STRATOS 1 and STRATOS 2 (ClinicalTrials.gov numbers NCT02161757 and NCT02194699, respectively). These trials will provide the opportunity to further explore the use of DPP-4 and periostin as surrogate biomarkers of interleukin-13 pathway activation in a larger study population. The increase in blood eosinophil counts at week 52 in patients receiving both tralokinumab regimens compared with those receiving placebo in the present study is in line with that reported for lebrikizumab, an anti-interleukin-13 monoclonal antibody,⁹ and dupilumab, an anti-interleukin-4 receptor monoclonal antibody.³¹ This increase has previously been suggested to be a result of reduced migration of eosinophils from the blood to the lungs due to inhibition of eosinophil-attracting chemokines.⁹

Several limitations should be considered in the interpretation of the results of this study. The sample size of some prespecified and post-hoc subgroups was insufficient to detect significant differences in efficacy outcomes; furthermore, we did not control for multiple comparisons in these subgroup analyses. Notably, the post-hoc subgroup analyses, although following a clear biological rationale, were not prespecified, and were underpowered because of the small number of patients; they should be regarded as hypothesis-generating analyses that need to be validated in larger phase 3 studies.

In conclusion, tralokinumab did not significantly reduce asthma exacerbation rates in all patients with severe uncontrolled asthma, although significant

	Placebo group (n=151)	Tralokinumab groups	
		Every 2 weeks (n=150)	Every 4 weeks (n=151)
Treatment-emergent adverse events			
One or more adverse event	129 (85%)	134 (89%)	128 (85%)
One or more drug-related adverse event	45 (30%)	46 (31%)	44 (29%)
One or more serious adverse event	21 (14%)	18 (12%)	25 (17%)
One or more drug-related serious adverse event	2 (1%)	1 (1%)	2 (1%)
Discontinuations due to adverse events	8 (5%)	4 (3%)	7 (5%)
Deaths	0	0	2 (1%)
Treatment-emergent adverse events reported in >5% of patients in any treatment group			
Asthma	74 (49%)	71 (47%)	62 (41%)
Nasopharyngitis	40 (27%)	35 (23%)	26 (17%)
Bronchitis	22 (15%)	27 (18%)	20 (13%)
Upper respiratory tract infection	18 (12%)	20 (13%)	20 (13%)
Headache	17 (11%)	17 (11%)	17 (11%)
Injection-site pain	15 (10%)	7 (5%)	11 (7%)
Influenza	13 (9%)	11 (7%)	14 (9%)
Diarrhoea	12 (8%)	5 (3%)	7 (5%)
Gastroenteritis	10 (7%)	8 (5%)	6 (4%)
Sinusitis	10 (7%)	5 (3%)	8 (5%)
Urinary tract infection	9 (6%)	11 (7%)	8 (5%)
Back pain	9 (6%)	8 (5%)	10 (7%)
Pharyngitis	9 (6%)	6 (4%)	11 (7%)
Rhinitis	9 (6%)	5 (3%)	8 (5%)
Dizziness	9 (6%)	2 (1%)	3 (2%)
Abdominal pain	9 (6%)	1 (1%)	1 (1%)
Vomiting	8 (5%)	4 (3%)	1 (1%)
Arthralgia	6 (4%)	11 (7%)	9 (6%)
Hypertension	6 (4%)	8 (5%)	9 (6%)
Cough	6 (4%)	7 (5%)	8 (5%)
Pain in extremity	5 (3%)	2 (1%)	8 (5%)
Rhinitis allergic	3 (2%)	11 (7%)	3 (2%)
Injection-site erythema	1 (1%)	12 (8%)	7 (5%)
Myalgia	1 (1%)	6 (4%)	8 (5%)
Injection-site pruritus	1 (1%)	8 (5%)	1 (1%)
Treatment-emergent adverse events that resulted in permanent discontinuation of study drug			
Urticaria	2 (1%)	0	0
Angioedema	1 (1%)	1 (1%)	0
Gastroenteritis	1 (1%)	0	0
Pneumonia	1 (1%)	0	0
Lipase increased	1 (1%)	0	0
Abortion spontaneous	1 (1%)	0	0
Asthma	0	0	2 (1%)
Eosinophilic pneumonia	0	0	1 (1%)
Myocarditis	0	1 (1%)	0
Gastric disorder	0	0	1 (1%)
Injection-site erythema	0	1 (1%)	0
Injection-site rash	0	0	1 (1%)
Injection-site urticarial	0	1 (1%)	0
Pyrexia	0	0	1 (1%)
Rheumatoid arthritis	0	0	1 (1%)

Table 4: Treatment-emergent adverse events in the safety population

Panel: Research in context**Systematic review**

We searched PubMed for reports published up to June 23, 2015, using the search term “interleukin-13”. The most relevant clinical trials were of the anti-interleukin-13 treatments lebrikizumab,⁹ IMA-638 (anrukizumab) and IMA-026,²⁰ and GSK679586.²¹ Mitchell and colleagues’ review⁷ provides a comprehensive assessment of the clinical role of interleukin 13 in asthma and various anti-interleukin-13 targeted treatments.

Interpretation

In this phase 2b study, tralokinumab 300 mg given every 2 weeks or every 4 weeks did not reduce asthma exacerbation rates in patients with severe uncontrolled asthma compared with placebo, although improvements in forced expiratory volume in 1 s (FEV₁) were noted in patients receiving the drug every 2 weeks. However, both tralokinumab regimens had an acceptable safety and tolerability profile. Our findings confirm that selection of patients to benefit from anti-interleukin-13 treatment is crucial; the results of post-hoc subgroup analyses suggested a possible broader treatment effect, which is being investigated in ongoing phase 3 trials. Dipeptidyl peptidase-4 was identified as a potential novel surrogate biomarker of interleukin-13 pathway activation. Our findings add to growing evidence that surrogate biomarkers of enhanced interleukin-13 pathway activation can be used to identify patients with enhanced response to anti-interleukin-13 treatments. Dependent on the results of ongoing phase 3 studies, tralokinumab might represent an add-on treatment option for patients with severe uncontrolled asthma and enhanced interleukin-13 pathway activation, identified through a combination of biomarkers and clinical characteristics.

improvements were shown in FEV₁ in those given tralokinumab every 2 weeks. In post-hoc analyses of patients with bronchodilator reversibility and raised concentrations of blood biomarkers associated with interleukin-13 pathway activation, treatment-related effects were noted in additional secondary endpoints of asthma control. Phase 3 studies investigating the efficacy and safety of tralokinumab in patients with uncontrolled asthma are underway (ClinicalTrials.gov, numbers NCT02161757 and NCT02194699).

Contributors

CEB and RL contributed to study design; data collection, analysis, and interpretation; and preparation and review of the report. PC contributed to protocol design, analysis and discussion of the findings, and writing and review of the report. PMO'B and SK contributed to data analysis and interpretation, and preparation and review of the report. EP contributed to study design, data analysis and interpretation, and preparation and review of the report. DS contributed to study design, data analysis and interpretation, and writing of the report. RDM contributed to study design, data analysis and interpretation, and preparation and review of the report. KS contributed to assay development, data collection, and preparation and review of the report. KR contributed to data collection, analysis and interpretation, and to preparation and review of the report.

Declaration of interests

CEB received a grant for this study from MedImmune (a subsidiary of AstraZeneca); grants for other work from GlaxoSmithKline, Genentech (Roche), Novartis, and Chiesi; and consultancy fees paid to his institution from GlaxoSmithKline. PC received grants from MedImmune during the conduct of the study; grants and personal fees from Almirall, Boehringer Ingelheim, Centocor, GlaxoSmithKline, Merck, AstraZeneca, Novartis, Teva, and Chiesi; personal fees from Takeda; and grants from Boston Scientific unrelated to this work. RL received personal fees from Almirall, AstraZeneca, and Forest; personal fees and non-financial support from GlaxoSmithKline; and non-financial support from Amgen, AstraZeneca, Genentech, Novartis, Ono Pharma, and Teva unrelated to this work. PMO'B received personal fees and non-financial support from AstraZeneca and GlaxoSmithKline; personal fees from Boehringer Ingelheim, Forest, Merck, Verona, Chiesi, and Takeda; and non-financial support from Amgen, Axican, Genentech, Novartis, and Sanofi, unrelated to this work. SK received grants and personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Takeda; grants from Teva and MedImmune; and personal fees from Almirall and Grifols, unrelated to this work. DS, RDM, KS, KR, and EP are employees of MedImmune. RDM, KS, KR, and EP are named inventors on a pending patent application (international patent application number PCT/US2015/12885) assigned to MedImmune related to this study, including, for example, methods of asthma diagnosis and treatment with tralokinumab with DPP-4 used as a predictive biomarker. RDM is also a named inventor on a pending patent application (international patent application number PCT/EP2011/067947) assigned to MedImmune related to another study (ClinicalTrials.gov, number NCT00873860), which includes methods of asthma diagnosis and treatment with tralokinumab.

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