



Effect of fixed-dose subcutaneous reslizumab on asthma exacerbations in patients with severe uncontrolled asthma and corticosteroid sparing in patients with oral corticosteroid-dependent asthma: results from two phase 3, randomised, double-blind, placebo-controlled trials

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Summary

Background Reslizumab 3 mg/kg administered intravenously is approved for the treatment of severe eosinophilic asthma. We assessed the safety and efficacy of subcutaneous reslizumab 110 mg in two trials in patients with uncontrolled severe asthma and increased blood eosinophils. The aim was to establish whether subcutaneous reslizumab 110 mg can reduce exacerbation rates in these patients (study 1) or reduce maintenance oral corticosteroid dose in patients with corticosteroid-dependent asthma (study 2).

Methods Both studies were randomised, double-blind, placebo-controlled, phase 3 studies. Entry criteria for study 1 were uncontrolled severe asthma, two or more asthma exacerbations in the previous year, a blood eosinophil count of 300 cells per μL or more (including no more than 30% patients with an eosinophil count <400 cells/ μL), and at least a medium dose of inhaled corticosteroids with one or more additional asthma controllers. Patients in study 2 had severe asthma, a blood eosinophil count of 300 cells per μL or more, daily maintenance oral corticosteroid (prednisone 5–40 mg, or equivalent), and high-dose inhaled corticosteroids plus another controller. Patients were randomly assigned (1:1) to subcutaneous reslizumab (110 mg) or placebo once every 4 weeks for 52 weeks in study 1 and 24 weeks in study 2. Patients and investigators were masked to treatment assignment. Primary efficacy outcomes were frequency of exacerbations during 52 weeks in study 1 and categorised percentage reduction in daily oral corticosteroid dose from baseline to weeks 20–24 in study 2. Primary efficacy analyses were by intention to treat, and safety analyses included all patients who received at least one dose of study treatment. These studies are registered with ClinicalTrials.gov, NCT02452190 (study 1) and NCT02501629 (study 2).

Findings Between Aug 12, 2015, and Jan 31, 2018, 468 patients in study 1 were randomly assigned to placebo ($n=232$) or subcutaneous reslizumab ($n=236$), and 177 in study 2 to placebo ($n=89$) or subcutaneous reslizumab ($n=88$). In study 1, we found no significant difference in the exacerbation rate between reslizumab and placebo in the intention-to-treat population (rate ratio 0.79, 95% CI 0.56–1.12; $p=0.19$). Subcutaneous reslizumab reduced exacerbation frequency compared with placebo in the subgroup of patients with blood eosinophil counts of 400 cells per μL or more (0.64, 95% CI 0.43–0.95). Greater reductions in annual exacerbation risk ($p=0.0035$) and longer time to first exacerbation were observed for patients with higher trough serum reslizumab concentrations. In study 2, we found no difference between placebo and fixed-dose subcutaneous reslizumab in categorised percentage reduction in daily oral corticosteroid dose (odds ratio for a lower category of oral corticosteroid use in the reslizumab group vs the placebo group, 1.23, 95% CI 0.70–2.16; $p=0.47$). The frequency of adverse events and serious adverse events with reslizumab were similar to those with placebo in both studies.

Interpretation Fixed-dose (110 mg) subcutaneous reslizumab was not effective in reducing exacerbation frequency in patients with uncontrolled asthma and increased blood eosinophils (≥ 300 cells/ μL), or in reducing the daily maintenance oral corticosteroid dose in patients with oral corticosteroid-dependent severe eosinophilic asthma. Higher exposures than those observed with 110 mg subcutaneous reslizumab are required to achieve maximal efficacy.

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Introduction

Eosinophils have a key role in the promotion and maintenance of airway inflammation, airway wall

thickening, fibrosis, and angiogenesis in patients with eosinophilic asthma.¹ Baseline counts of blood and sputum eosinophils can be markers of the severity of

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Research in context

Evidence before this study

We searched PubMed for publications from inception to May 3, 2019, using the terms “anti-interleukin-5 antibodies” or “reslizumab” and “asthma” for clinical trials investigating anti-interleukin 5 (IL5) biologic drugs in patients with severe eosinophilic asthma. In two phase 3 trials, weight-based dosing of intravenous reslizumab (3 mg/kg) reduced clinical asthma exacerbation frequency and improved asthma control, lung function, and quality of life. In other reslizumab studies, improvement in lung function was found with intravenous reslizumab (0.3 mg/kg and 3 mg/kg); the greatest improvement in lung function with the higher dose was observed in patients with a blood eosinophil count of 400 cells per μL or more. Clinical trials of other drugs that target the IL5 pathway were also identified. Studies have shown that intravenous or subcutaneous anti-IL5 or anti-IL5 receptor drugs reduce asthma exacerbations and improve lung function, asthma control, and quality of life, and reduce maintenance oral corticosteroid dose in patients with severe eosinophilic asthma.

Added value of this study

To our knowledge, these are the first published studies that have assessed the safety and efficacy of low-dose reslizumab administered as a fixed-dose subcutaneous injection for the treatment of severe eosinophilic asthma. The results of these studies suggest that the lower dose and lower systemic reslizumab concentrations associated with fixed-dose subcutaneous reslizumab, compared with intravenous reslizumab, might not be sufficient to provide robust reductions in exacerbation frequency in patients with uncontrolled asthma

and increased blood eosinophil counts (≥ 300 cells/ μL), or to reduce daily maintenance oral corticosteroid dose in patients with oral corticosteroid-dependent severe asthma. Results indicate that the exposure–response relationships and systemic reslizumab concentration thresholds differ between the endpoints of asthma exacerbations and lung function. Greater effect on asthma exacerbations was observed in the prespecified subgroup of patients with a high blood eosinophil count (≥ 400 cells/ μL), which matched the population in the phase 3 studies of intravenous reslizumab. Regional differences in background asthma exacerbation rate during the study period were also observed.

Implications of all the available evidence

A complete analysis of the effect of body weight on systemic concentrations and a clear understanding of the exposure–response relationships for primary and key secondary asthma endpoints, before initiation of phase 3 studies, would be beneficial to support optimal future study design for biologic drugs in severe asthma. Our results support further assessment of higher doses of weight-based subcutaneous reslizumab. Baseline blood eosinophil counts are a marker of patients who are more responsive to therapies targeting the IL5 pathway, reconfirming the importance of defining the eosinophilic phenotype; however, treatment-induced suppression of blood eosinophils with anti-IL5 therapy is not sufficient to ensure robust clinical efficacy. A reduction in blood eosinophil counts with treatment is a surrogate biomarker, which might not fully reflect changes in eosinophilic airway inflammation in patients with severe asthma. Regional differences in asthma exacerbation rates have been observed and should be considered during future study design.

asthmatic symptoms and independent risk factors for future asthma exacerbations in patients with symptomatic asthma.^{2–4}

Maintenance and activation of eosinophils is dependent on interleukin-5 (IL5), the prototypical eosinophil viability-enhancing factor.⁵ Several monoclonal antibodies that target the IL5 pathway are approved as add-on maintenance treatment for inadequately controlled severe eosinophilic asthma.^{6–8} Reslizumab is an IgG4 κ humanised anti-IL5 monoclonal antibody that is administered as intravenous infusion at a recommended weight-based dose of 3 mg/kg, once every 4 weeks.⁸ Efficacy and safety of intravenous reslizumab have been shown in five phase 3 clinical trials.^{9–12} Weight-based dosing of intravenous reslizumab significantly reduced the risk of asthma exacerbations and improved asthma control, lung function, and quality of life in patients with inadequately controlled asthma, peripheral blood eosinophil counts of 400 cells per μL or more, and a history of asthma exacerbations.⁹ The availability of subcutaneous administration as an alternative to intravenous administration could increase the accessibility of reslizumab treatment, reduce time and

resource requirements associated with intravenous infusion,^{13,14} and simplify administration.

We did two phase 3 clinical trials, which were designed to investigate the safety and efficacy of reslizumab given as a fixed-dose (110 mg) subcutaneous injection once every 4 weeks in patients with uncontrolled asthma and increased blood eosinophils. Study 1 was an asthma exacerbation study that investigated the effect of fixed-dose subcutaneous reslizumab on the rate of clinical asthma exacerbations, and study 2 was a corticosteroid-sparing study that investigated the potential oral corticosteroid-sparing properties of fixed-dose subcutaneous reslizumab in patients with oral corticosteroid-dependent severe asthma.

Methods

Study design

Both studies were randomised, double-blind, placebo-controlled, parallel-group, phase 3 studies. Full details of the study methods are provided in the appendix (p 3). Study 1 consisted of a 2-week screening period, a minimum 3-week run-in period, a 52-week treatment

See Online for appendix

period, and a 12-week follow-up. Study 2 had a 2-week screening period, followed by an oral corticosteroid dose optimisation period of up to 10 weeks, a minimum 2-week run-in period, a 24-week treatment period, and an 8-week follow-up. For study 1, at least one patient was randomly assigned at each of 155 study sites in 20 countries: USA (43 sites), Ukraine (19), Hungary (16), Germany (11), Argentina (10), Russia (8), Israel (8), Poland (6), Romania (5), South Africa (5), Japan (4), Mexico (3), Belgium (3), Czech Republic (3), Turkey (3), Canada (2), Spain (2), New Zealand (2), France (1), and Australia (1). For study 2, at least one patient was randomly assigned at each of 78 study sites in 17 countries: Ukraine (15), the USA (9), Germany (7), Poland (7), Argentina (6), Russia (6), Mexico (5), Israel (5), Spain (3), Australia (2), South Korea (2), France (2), the Netherlands (2), Belgium (2), Hungary (2), Czech Republic (2), and Italy (1).

The subcutaneous reslizumab fixed dose of 110 mg was selected on the basis of clinical data from an intravenous reslizumab phase 3, 16-week, FEV₁ study in patients with eosinophilic asthma,¹¹ in which improvements in lung function and asthma control and reductions in blood eosinophil counts were obtained with intravenous doses of 0·3 mg/kg and 3 mg/kg. Although data on asthma exacerbations were not collected during the treatment period, the similar magnitude of effect on FEV₁ between the 0·3 mg/kg and 3 mg/kg doses suggested that the doses would also have similar effects on asthma exacerbation frequency. A 110 mg subcutaneous dose approximates to a 1 mg/kg intravenous dose for the average 70 kg patient, when adjusting for subcutaneous bioavailability, and was therefore expected to result in clinical efficacy in most patients. The 1 mL volume and presentation in a pre-filled syringe would be convenient for subcutaneous administration.

Both studies were done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All study documents and procedures were approved by the appropriate Institutional Review Board or Ethics Committee at each study site. All patients provided written informed consent before study participation.

Study 1

Participants

We included participants aged 12 years or older with a diagnosis of asthma, an Asthma Control Questionnaire-6 (ACQ-6) score of at least 1·5 at screening, two or more asthma exacerbations requiring the use of systemic corticosteroids in the past year, a blood eosinophil count of 300 cells per μ L or more during screening, and an FEV₁ reversibility of 12% or more to inhaled short-acting β agonist at screening or documentation within 12 months of signing informed consent. Patients were receiving at least a medium dose (>250 μ g/day fluticasone or equivalent) of inhaled corticosteroids for at least 3 months with at least one additional asthma controller

for at least 3 months (or documented failure of a second controller in the past 12 months). For patients using inhaled corticosteroid and long-acting β agonist (LABA) combinations, the mid-strength approved maintenance dose in the local country met this inhaled corticosteroid criterion. Oral corticosteroid use (prednisone 10 mg or less daily, or equivalent) was allowed. Full inclusion and exclusion criteria are summarised in the appendix (p 3).

Randomisation and masking

Patients were randomly assigned (1:1) to receive subcutaneous reslizumab (110 mg) or placebo. Participants were assigned using an interactive web response system (IWRS). Randomisation was stratified by age (12 to <18 years and $\geq$ 18 years) and blood eosinophil count at screening (300 to <400 cells/ μ L and $\geq$ 400 cells/ μ L). A maximum of 30% of patients enrolled could have a blood eosinophil count of between 300 cells per μ L and less than 400 cells per μ L; when this threshold was met, only patients with blood eosinophil counts of 400 cells per μ L or more were enrolled. The inclusion criterion of a baseline blood eosinophil count of 300 cells per μ L or more was based on the available published literature on biologic drugs for treating severe asthma at the time of study design.^{15–17} Anti-IL5 therapies have been shown to reduce asthma exacerbations in patients with baseline blood eosinophil counts of 150 cells per μ L or more¹⁵ or 300 cells per μ L or more.^{16,17} However, data for 3 mg/kg intravenous reslizumab suggested robust effects across multiple asthma endpoints in patients with baseline blood eosinophil counts of 400 cells per μ L or more; therefore, we restricted the enrolment of patients with blood eosinophils between 300 cells per μ L and less than 400 cells per μ L to 30%. Patients and investigators were masked to treatment assignment. The sponsor's personnel involved in the study were also masked to the study drug identity, until the database was locked for analysis and the treatment assignment was revealed.

Procedures

Eligible patients received either one 1·0 mL subcutaneous injection containing 110 mg reslizumab, or one 1·0 mL subcutaneous injection containing sterile placebo solution, once every 4 weeks. Reslizumab and placebo were provided as matching, clear solutions. Treatment continued for 52 weeks, with the last dose administered at week 48 followed by an end-of-treatment visit at week 52. Patients maintained their inhaled asthma controller regimen without change throughout screening, optimisation, run-in, treatment, and follow-up periods (appendix p 3).

Outcomes

The primary efficacy outcome was the frequency of clinical asthma exacerbations per patient during the 52-week treatment period. A clinical asthma exacerbation was defined as a clinically judged deterioration in asthma

	Asthma exacerbation study (study 1)		Oral corticosteroid-sparing study (study 2)	
	Placebo (n=230)*	Subcutaneous reslizumab (n=234)*	Placebo (n=89)	Subcutaneous reslizumab (n=88)
Age, years	44.8 (17.7)	46.9 (17.6)	53.1 (12.0)	55.5 (12.7)
Sex, n (%)				
Men	102 (44%)	90 (38%)	32 (36%)	28 (32%)
Women	128 (56%)	144 (62%)	57 (64%)	60 (68%)
Weight, kg				
Mean (SD)	76.9 (18.3)	78.3 (19.4)	82.7 (18.9)	79.6 (21.4)
Median (IQR)	75.0 (23.6)	77.5 (25.2)	82.0 (20.7)	75.6 (26.2)
BMI, kg/m ²	27.4 (6.1)	28.3 (6.2)	29.9 (6.3)	29.4 (8.0)
FEV ₁ reversibility, %	24.6% (21.3)	22.8% (17.1)	24.6% (20.5)	26.0% (25.9)
Pre-bronchodilator FEV ₁ , L	2.1 (0.9)	2.0 (0.8)	1.7 (0.7)	1.6 (0.7)
FEV ₁ , % predicted	65.0% (19.7)	64.4% (18.3)	58.7% (19.8)	55.2% (16.7)
ACQ-6 score	2.6 (0.8)	2.6 (0.8)	2.4 (1.2)	2.3 (1.1)
AQLQ score	4.4 (1.0)	4.3 (1.0)	4.4 (1.2)	4.4 (1.1)
Blood eosinophil count, cells/μL†	737 (484)	787 (538)	521 (491)	479 (388)
Eosinophil count				
<300 cells/μL	0	1 (<1%)	33 (37%)	28 (32%)
≥300 to <400 cells/μL	42 (18%)	48 (21%)	13 (15%)	19 (22%)
≥400 cells/μL	188 (82%)	185 (79%)	43 (48%)	41 (47%)
Phadiatop test				
Positive	154 (67%)	159 (68%)	47 (53%)	47 (53%)
Missing	12 (5%)	4 (2%)	3 (3%)	1 (1%)
Former smoker	28 (12%)	31 (13%)	13 (15%)	12 (14%)
Age at asthma onset, years	27.5 (19.2)	29.0 (19.9)	32.9 (17.9)	32.8 (17.7)
Time since diagnosis, years	17.5 (13.5)	18.0 (14.0)	20.1 (14.2)	22.3 (16.0)
Asthma exacerbations requiring systemic corticosteroids in the past 12 months	2.3 (0.8)	2.4 (1.0)	1.85 (1.2)	2.1 (1.6)
Inhaled corticosteroid	229 (>99%)‡	232 (>99%)‡	89 (100%)	88 (100%)
High-dose§	98 (43%)	99 (42%)	70 (79%)¶	70 (80%)¶
Medium-dose§	122 (53%)	128 (55%)	17 (19%)	18 (20%)
Long-acting β agonist	218 (95%)	224 (96%)	84 (94%)	87 (99%)
Oral corticosteroid	15 (7%)	15 (6%)	89 (100%)	88 (100%)
Aspirin sensitivity	23 (10%)	26 (11%)	7 (8%)	5 (6%)
Chronic rhinosinusitis with nasal polyps	38 (17%)	37 (16%)	13 (15%)	10 (11%)

Data are mean (SD), or n (%), unless otherwise indicated. ACQ-6=Asthma Control Questionnaire-6. AQLQ=Asthma Quality of Life Questionnaire. BMI=body-mass index. ITT=intention-to-treat. *Two patients in the placebo group and two patients in the reslizumab group were excluded from the ITT analysis. One site was terminated because of recurrent irregularities in data collection and recording. The patients who were randomly assigned at this site were excluded from the ITT analysis set. †Stated baseline eosinophil count reflected the highest value from measurements during screening, run-in, and pre-dose day of randomisation. ‡Three patients presented as not using inhaled corticosteroids at baseline; two (one in each treatment group) were using inhaled corticosteroids at baseline but were counted as non-inhaled corticosteroid users. Of these two patients, the first was using budesonide with formoterol fumarate, which was not coded as an inhaled corticosteroid, and the second was using beclomethasone with formoterol, which was not counted as a baseline medication because of missing dates (the dates were confirmed to be unknown, but were >3 months before screening). The third patient (in the reslizumab group) was not using inhaled corticosteroid at baseline. §High-dose was defined as >500 μg/day fluticasone or equivalent and medium-dose as >250 to ≤500 μg/day fluticasone or equivalent. ¶In regions where the inhaled corticosteroid dose in the highest labelled fixed-dose preparation of inhaled corticosteroid and long-acting β agonist was <500 μg/day fluticasone or equivalent, patients receiving the highest labelled dose in that region were deemed to satisfy the inclusion criterion. ||Self-reported.

Table 1: Demographics and baseline clinical characteristics of the intention-to-treat population in studies 1 and 2

control resulting in at least one of the following: use of systemic corticosteroids (oral or injection), at least a doubling from a stable maintenance oral corticosteroid dose for 3 days or more, or an asthma-specific hospital admission or emergency department visit. A pre-specified, powered subgroup analysis assessed the frequency of clinical asthma exacerbations per patient during the 52-week treatment period in patients who had baseline blood eosinophil counts of 400 cells per μL or more. Secondary outcomes included lung function, as assessed by measurement of change from baseline in pre-bronchodilator FEV₁; patient-reported outcomes (ie, change in ACQ-6 and AQLQ+12 scores at 52 weeks), safety; and immunogenicity (appendix p 13). Blood eosinophil counts at specified timepoints during the treatment period and follow-up visit were assessed (at 12 weeks after end of treatment); the highest value from screening to predose on the day of randomisation was used as baseline.

Serum reslizumab concentrations were determined from blood samples collected at baseline; before study drug administration at weeks 4, 8, 12, 16, 20, 32, 48, and 52; and at early withdrawal or at the follow-up visit. An additional sample was taken at long-term follow-up (appendix p 5).

Study 2

Participants

We included patients aged 12 years or older with a diagnosis of asthma, an FEV₁ reversibility of 12% or more after inhaled reliever medication at screening, or a historical FEV₁ reversibility or a positive methacholine challenge within 24 months, a blood eosinophil count of 300 cells per μL or more within the past 12 months while on at least a medium total daily dose of inhaled corticosteroids, during screening, during oral corticosteroid optimisation, or at the week -2 visit (appendix p 7). Patients required an average daily maintenance dose of oral corticosteroid for asthma (prednisone 5–40 mg, or equivalent) during the 3 months before screening. Patients also required high-dose inhaled corticosteroids (≥880 μg of inhaled fluticasone propionate, or equivalent) plus another controller for at least 6 months before screening. For a fixed-dose preparation of inhaled corticosteroid plus LABA, the highest labelled dose in the local country satisfied this criterion. For patients aged 12 to less than 18 years, at least a medium-dose inhaled corticosteroid plus another controller was required. The dose and regimen needed to have been stable for at least 30 days. Full inclusion and exclusion criteria are summarised in the appendix (p 8).

Randomisation and masking

Patients were randomly assigned (1:1) to receive subcutaneous reslizumab (110 mg) or placebo. The randomisation list and treatment were assigned to the relevant treatment groups using an IWRS. Randomisation

was stratified by optimised average daily oral corticosteroid dose (>10 mg or ≤ 10 mg) and age (12 to <18 years and ≥ 18 years) at baseline. Patients and investigators were masked to treatment assignment. The sponsor's personnel involved in the study were also masked to the study drug identity, until the database was locked for analysis and the treatment assignment was revealed.

Procedures

To achieve the patient's minimal effective oral corticosteroid requirement (appendix p 9), the oral corticosteroid dose was reduced at weekly intervals for up to 10 weeks or until asthma signs and symptoms worsened (minimum 1 day in optimisation). Oral corticosteroid optimisation was considered finished when patients had worsening of asthma signs and symptoms, or if patients optimised to an oral corticosteroid dose of less than 5 mg without worsening of asthma signs and symptoms.

Patients whose minimal effective oral corticosteroid dose remained in the range 5–40 mg prednisone daily at the end of optimisation could advance to run-in, after which patients received either one 1.0 mL subcutaneous injection containing 110 mg reslizumab, or matched placebo, once every 4 weeks. Treatment continued for 24 weeks, with the last dose administered at week 20, followed by an end-of-treatment visit at week 24. Patients maintained an inhaled asthma controller regimen without change throughout the study. The treatment period consisted of a stable-dose induction period of 4 weeks, followed by an oral corticosteroid reduction period. During oral corticosteroid reduction, the oral corticosteroid dose was reduced in accordance with the protocol, based on meeting asthma stability criteria at scheduled monthly clinic visits during weeks 5–20 (appendix p 9).

Outcomes

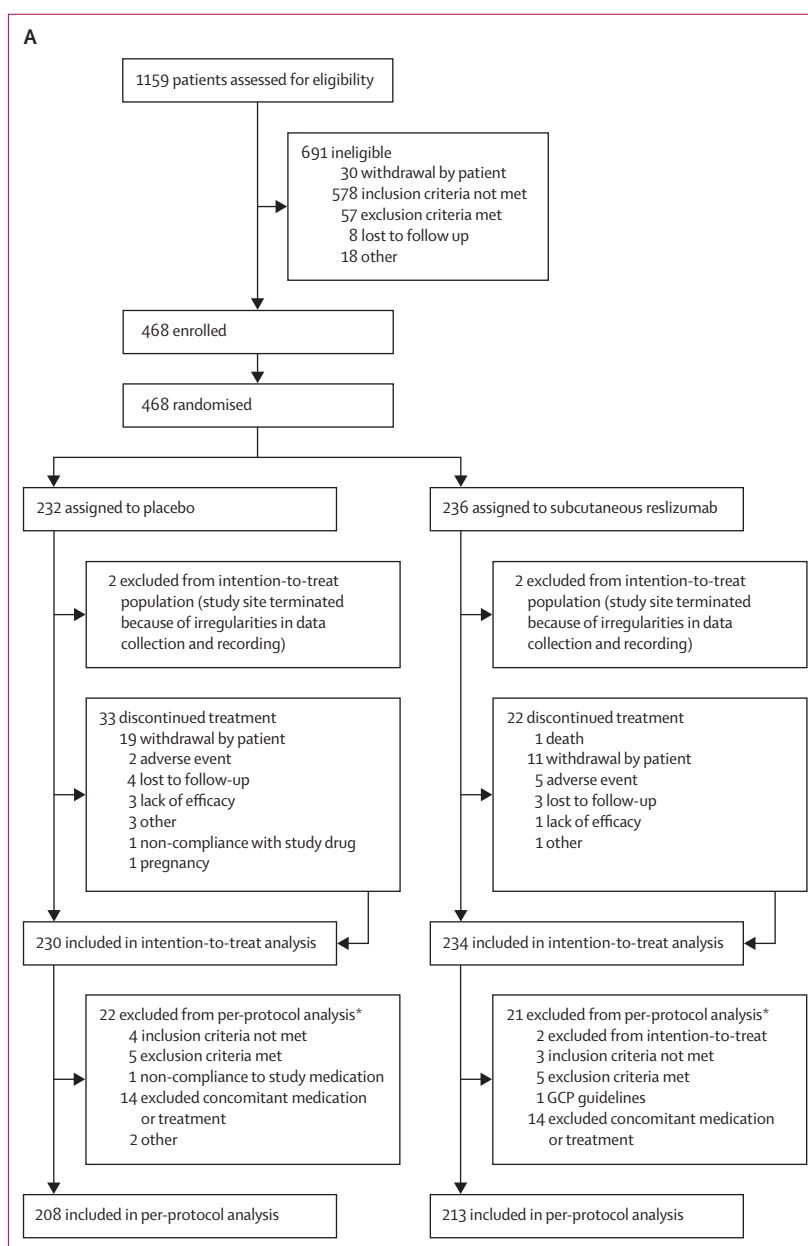
The primary efficacy outcome was categorised percentage reduction in daily oral corticosteroid dose compared with baseline (end of the optimisation phase) during weeks 20–24: 90 to 100%; 75 to $<90\%$; 50 to $<75\%$; >0 to $<50\%$; no decrease in oral corticosteroid dose or loss of asthma control during weeks 20–24; or treatment discontinuation (withdrawal of treatment). Loss of asthma control was defined as FEV₁ less than 80% of baseline at week 24, clinically significant worsening in ACQ-6 score (increase in score ≥ 0.5 points) at week 24 compared with baseline, or clinical asthma exacerbation during weeks 20–24. Patients with missing data or loss of asthma control with reduced oral corticosteroid dose were included in the category reflecting the lowest efficacy.

Secondary outcomes included additional assessments of oral corticosteroid dose reduction, clinical asthma exacerbations, safety, and immunogenicity (appendix p 10). The assessment of blood eosinophil counts was similar to that in study 1; the highest value from screening to week -2 was used as baseline.

Serum reslizumab concentrations were determined from blood samples collected at baseline; before study drug administration at weeks 4, 8, 12, 16, 20, and 24; and at early withdrawal or at the follow-up visit. An additional sample was taken at long-term follow-up (appendix p 7).

Statistical analysis

The primary efficacy analyses used the intention-to-treat (ITT) population of each study, which included all randomly assigned patients. Analyses were also done in the per-protocol populations, defined as all patients from the ITT population without major protocol violations.



(Figure 1 continues on next page)

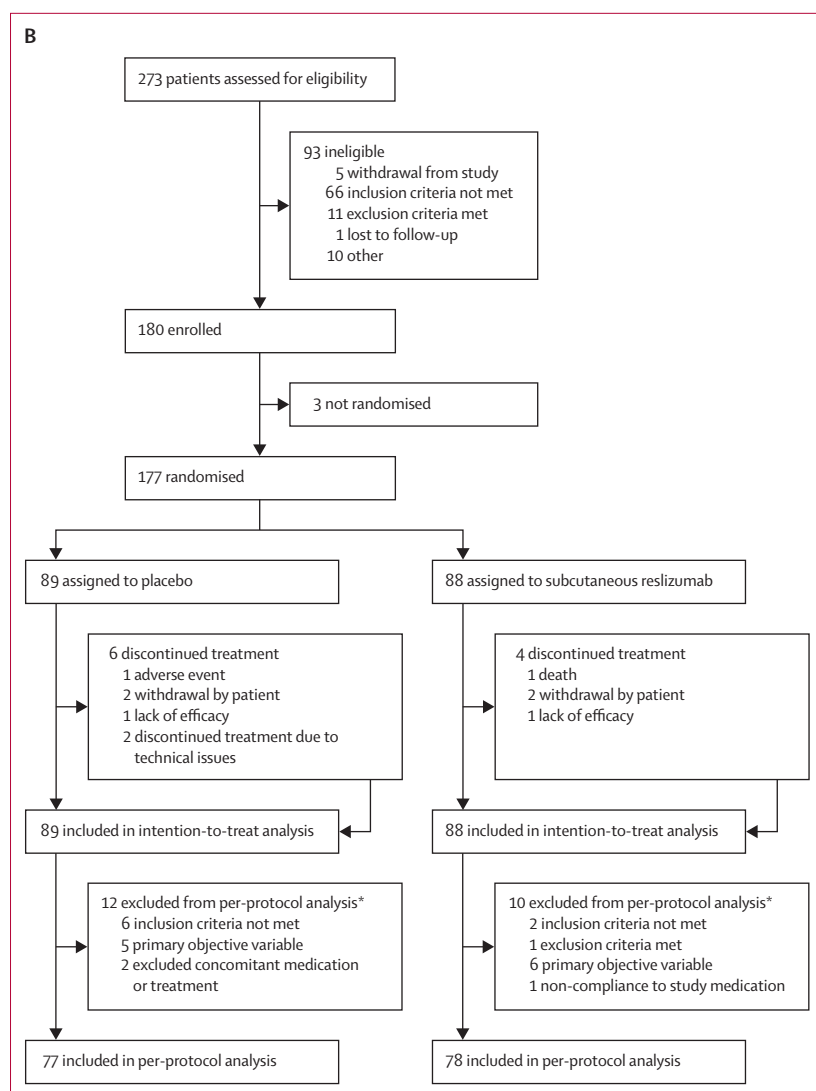


Figure 1: Trial profiles for studies 1 and 2

GCP=good clinical practice. *A patient might have had multiple reasons for exclusion from the per-protocol analysis.

Safety was assessed in the safety population of each study, which included all patients who received at least one dose of study treatment.

Simulation studies were done with SAS (version 9.4) to assess the statistical powers for analysing the frequency of exacerbations using a negative binomial model in study 1, and the power analysis software PASS (version 13.0.7) was used for sample size estimation in study 2. The model assumptions involved in the calculations are described in detail in the appendix (p 11). In brief, power calculations for study 1 were based on a mean of 2.9 exacerbations per patient per year in the placebo group, a dispersion parameter of 1.2 in the negative Binomial model for both treatment groups, and treatment effect of 45% between reslizumab and placebo. On the basis of these assumptions, 225 patients per group would provide more

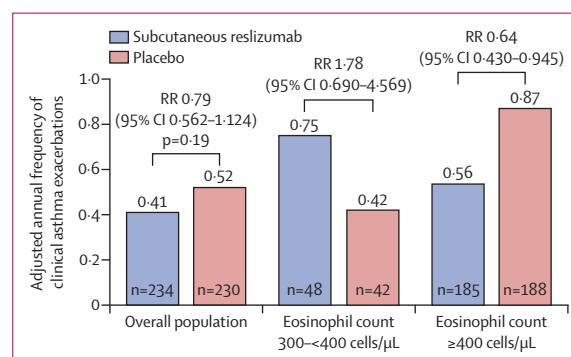


Figure 2: Adjusted frequency of clinical asthma exacerbations during 52 weeks in the intention-to-treat population and in subgroups of patients based on baseline eosinophil counts in study 1

For this analysis, the offset variable is calculated as the logarithm of treatment duration minus the summed duration of exacerbations during the treatment period. RR=rate ratio.

than 90% power to detect a significant treatment effect of reslizumab versus placebo in the reduction of exacerbation rate. For study 2, a sample size of 76 patients per treatment group was chosen to provide 90% power to detect a significant effect of reslizumab over placebo on the probability for a higher categorical reduction of oral corticosteroid dose using a proportional odds model. This was based on the assumption in the placebo group that after 24 weeks of treatment 10.9% of patients have 90–100% reduction, 7.9% have 75 to <90% reduction, 14.8% have 50 to <75% reduction, 10.8% have 0 to <50% reduction, and 55.6% have no reduction, have loss of asthma control, or discontinue; also assuming odds ratio (OR) based on a proportional odds model of 2.63.

For both studies, a fixed-sequence, multiple-testing procedure was implemented to test the primary and secondary outcomes while controlling the overall type I error rate at 0.05. Primary and secondary outcomes were tested sequentially and hierarchically. If the resulting two-sided p value from the primary comparison was less than 0.05, then the next comparison was interpreted inferentially. No multiplicity adjustments were made for other efficacy and exploratory analyses. All statistical analyses were done using SAS (versions 9.1.3 and 9.2).

The frequency of clinical asthma exacerbations was analysed with a generalised linear model for data from the negative binomial regression model. Treatment group, randomisation stratification factors (age and baseline blood eosinophil count for study 1; age and oral corticosteroid dose for study 2), and number of exacerbations in the previous year were model factors. Logarithm of follow-up duration minus the summed duration of exacerbations was an offset variable. Adjusted clinical asthma exacerbation rates, rate ratios (RR), and 95% CIs were calculated. In study 1, multiple imputation was used for missing data in the primary analysis model. Sensitivity analyses were done without imputed data. Because of convergence issues with the primary analysis

model in study 1, a post-hoc data-driven analysis of the effects of subcutaneous reslizumab was done (appendix p 6).

Change from baseline in pre-bronchodilator FEV₁ was analysed with a mixed-model repeated measures model, with fixed effects for treatment, visit, treatment-by-visit interaction, sex, age group, and blood eosinophil group; height and baseline value as covariates; and patient as a random effect. Unstructured covariance was assumed for the repeated measures.

In study 2, categorised percentage reduction in total daily oral corticosteroid dose at weeks 20–24 was analysed with a proportional odds model including factors for treatment group and randomisation strata (age group and oral corticosteroid dose). Baseline oral corticosteroid dose and duration of oral corticosteroid use before study entry were also included as covariates. ORs, 95% CIs, and p values were calculated. A prespecified sensitivity analysis was done with the per-protocol population.

Statistical methods for the secondary efficacy and safety outcomes in both studies are provided in the appendix (pp 6, 11). Prespecified subgroups for the subgroup analyses are detailed in the appendix (pp 7, 12). Model results were only reported if there were 15 patients or more contributing to the analysis in each treatment group; otherwise, descriptive statistics were generated. Eosinophil count (300 to <400 cells/ μ L and $\geq$ 400 cells/ μ L) at baseline was a prespecified stratification factor for study 1, which recruited a sufficient proportion of patients with eosinophil counts of 400 cells per μ L or more (a minimum of 70% of the study population, per protocol). This subgroup analysis was prespecified for the primary analysis and selected secondary efficacy analyses.

The exposure–response analysis was assessed a posteriori using SAS (version 9.4). We identified the relationship between individual reslizumab trough concentrations (C_{trough}) and clinical asthma exacerbation

rate in study 1 using visual graphical analysis with a regression coefficient. Individual C_{trough} was based on the aggregate information for each individual using a model that accounted for the differences in time after the most recent dose and provided a single concentration measure for use in the exposure–response analysis. Patients in the placebo group were assumed to have concentrations of 0 μ g/mL. The underlying hazard for a clinical asthma exacerbation was explored with Kaplan-Meier survival curves of the time to first clinical asthma exacerbation, stratified by tertiles of reslizumab C_{trough} in study 1.

These studies are registered with ClinicalTrials.gov, NCT02452190 (study 1) and NCT02501629 (study 2).

Role of the funding source

Three authors of the report (DAM, MG, and RV) are employees of Teva Branded Pharmaceutical Products R&D, the study funder, and two (JM and LH) are former employees of the study funder. Employees of the study funder had roles in the design of the study, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all of the data outputs, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Aug 12, 2015, and Oct 10, 2016, 1159 patients were recruited in study 1, of whom 468 patients were enrolled and randomly assigned to receive placebo (n=232 [50%]) or subcutaneous reslizumab (n=236 [50%]). The last visit of the last patient occurred on Jan 31, 2018. Between Sept 22, 2015, and Dec 12, 2016, 273 patients were recruited in study 2, of whom 180 were enrolled and 177 were randomly assigned to receive placebo (n=89) or subcutaneous reslizumab 110 mg (n=88). The last visit of the last patient occurred on Dec 4, 2017. Within each study, demographic and baseline disease characteristics were

	ITT population		Eosinophil count 300 to <400 cells/ μ L		Eosinophil count $\geq$ 400 cells/ μ L	
	Placebo (n=230)	Subcutaneous reslizumab (n=234)	Placebo (n=42)	Subcutaneous reslizumab (n=48)	Placebo (n=188)	Subcutaneous reslizumab (n=185)
Adjusted CAEs excluding exacerbation duration from the offset*	0.52	0.41	0.42	0.75	0.87	0.56
RR (95% CI) for reslizumab vs placebo	..	0.79 (0.56 to 1.12)	..	1.78 (0.69 to 4.57)	..	0.64 (0.43 to 0.95)
p value	..	0.19	..	..	..	..
Change in pre-bronchodilator FEV ₁ at 52 weeks, L, LSM (SE)†	0.23 (0.040)	0.37 (0.039)	0.25 (0.093)	0.38 (0.092)	0.26 (0.042)	0.41 (0.041)
Absolute increase (95% CI) vs placebo	..	0.14 (0.057 to 0.23)	..	0.13 (–0.053 to 0.31)	..	0.15 (0.054 to 0.25)
Change in ACQ-6 at 52 weeks, LSM (SE)‡	–1.14 (0.080)	–1.22 (0.078)	–1.36 (0.19)	–1.27 (0.19)	–1.05 (0.084)	–1.18 (0.081)
Absolute change (95% CI) vs placebo	..	–0.09 (–0.27 to 0.10)	..	0.09 (–0.31 to 0.48)	..	–0.12 (–0.32 to 0.083)
Change in AQLQ+12 at 52 weeks, LSM (SE)*§	1.06 (0.089)	1.14 (0.087)	1.25 (0.20)	1.30 (0.20)	1.02 (0.093)	1.11 (0.091)
Absolute increase (95% CI) vs placebo	..	0.08 (–0.11 to 0.27)	..	0.05 (–0.38 to 0.49)	..	0.08 (–0.14 to 0.30)

ACQ-6=Asthma Control Questionnaire-6. AQLQ+12=Asthma Quality of Life Questionnaire for patients aged $\geq$ 12 years. CAE=clinical asthma exacerbation. ITT=intention-to-treat. LSM=least squares mean. RR=rate ratio. *For this analysis, the offset variable was calculated as the logarithm of treatment duration minus the summed duration of exacerbations during the treatment period. †Minimal clinically important difference was a change of 0.1 L. ‡Minimal clinically important difference was change in score of –0.5. §Minimal clinically important difference was change in score of 0.5.

Table 2: Primary and key secondary efficacy outcomes in study 1

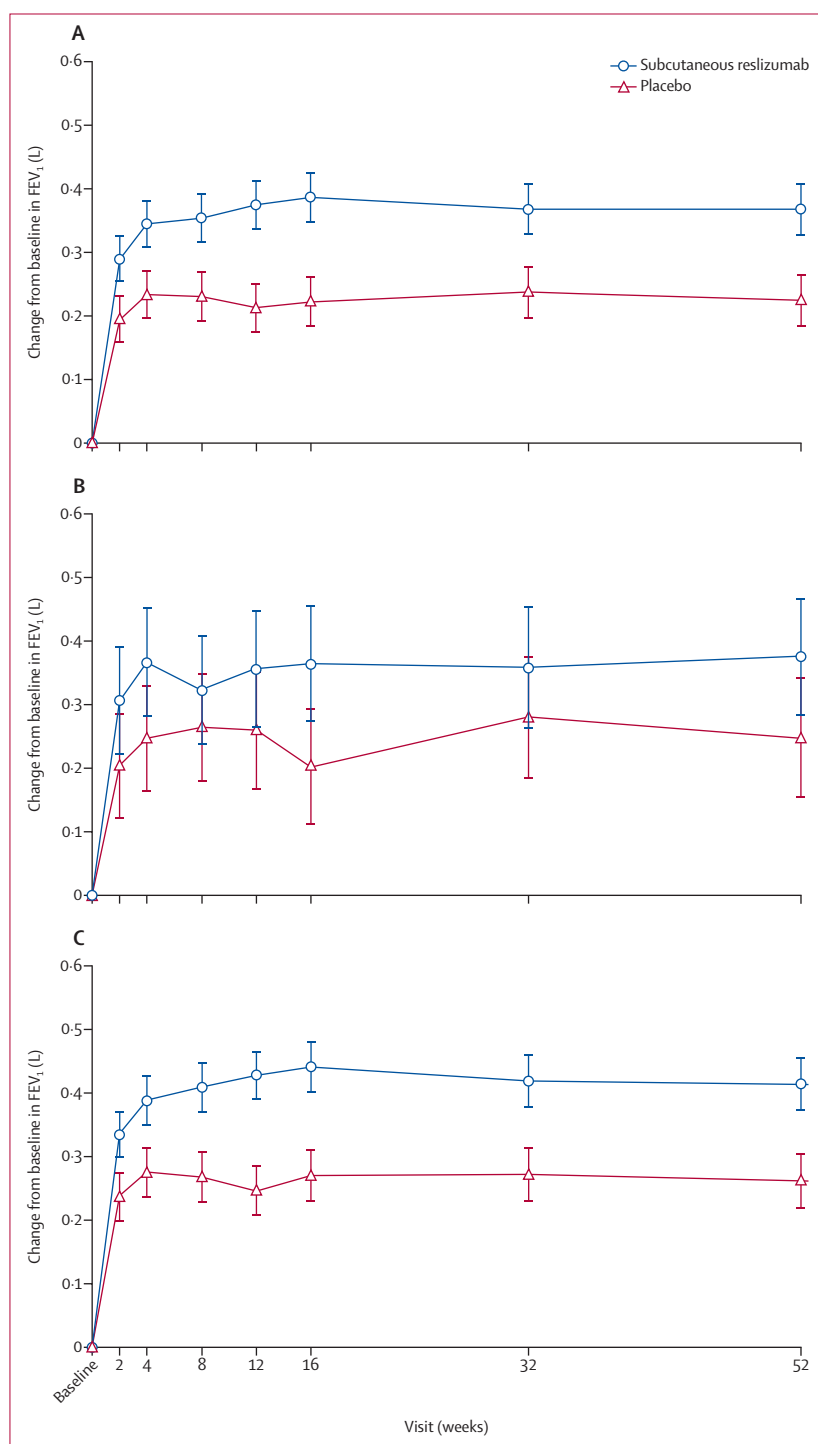


Figure 3: Change in pre-bronchodilator FEV₁ from baseline at each visit by treatment group in study 1
 (A) The intention-to-treat population, (B) patients with baseline eosinophil counts of 300 to <400 cells per µL, and (C) patients with baseline eosinophil counts of ≥400 cells per µL. Least squares mean and SE are given for the change from baseline in FEV₁ at each clinic visit between the first dose of study drug and the end-of-treatment visit for completed patients, and between the first dose of study drug and 4 weeks after the last dose of study drug for patients who discontinued treatment early. Inferential statistics are from a mixed-model repeated measures model with fixed effects for treatment, visit, treatment-by-visit interaction, sex, age group, and blood eosinophil group; height and baseline value as covariates; and patient as a random effect. Unstructured covariance was assumed for the repeated measures.

well balanced across the two treatment groups (table 1). The demographic and baseline disease characteristics for patients in study 1 by baseline eosinophil subgroup are shown in the appendix (p 13). Trial profiles are shown in figure 1. In study 1, 59 (13%) of 468 patients discontinued study treatment (35 [15%] of 232 in the placebo group and 24 [10%] of 236 in the reslizumab group). Seven patients were reported as lost to follow-up (four in the placebo group and three in the reslizumab group). In study 2, 10 (6%) of 177 patients discontinued study treatment (six [7%] of 89 in the placebo group and four [5%] of 88 in the reslizumab group).

In study 1, the frequency of clinical asthma exacerbations did not differ significantly over 52 weeks between fixed-dose subcutaneous reslizumab and placebo in the ITT population (RR 0.79, 95% CI 0.56–1.12; $p=0.19$; figure 2, table 2). As the analysis of the primary efficacy outcome did not meet the criteria for statistical significance, subsequent efficacy outcomes were not interpreted inferentially (figure 2, table 2). Fixed-dose subcutaneous reslizumab reduced clinical asthma exacerbation frequency compared with placebo in the prespecified subgroup of patients with eosinophil counts of 400 cells per µL or more (0.64, 95% CI 0.43–0.95), but not in those with eosinophil counts of between 300 cells per µL and less than 400 cells per µL (figure 2, table 2).

In the prespecified subgroups, patients enrolled in Europe had the smallest treatment effect, and adults aged 65 years or older had a slightly greater reduction in the frequency of clinical asthma exacerbations with fixed-dose subcutaneous reslizumab compared with placebo (appendix p 14). The findings of the other prespecified subgroup analyses were consistent with those of the primary analysis (appendix p 14). In a post-hoc analysis of patients enrolled in eastern Europe (110 [47%] in the reslizumab group and 99 [43%] in the placebo group), the treatment effect was smaller than for the overall results from all of Europe (data not shown), apparently driven by a low frequency of clinical asthma exacerbations in the placebo group (mean of 0.3 [standard error 0.06] exacerbations during the treatment period). Results in the per-protocol sensitivity analysis were similar to those in the primary ITT analysis (data not shown).

In the ITT population, the change from baseline in pre-bronchodilator FEV₁ at week 52 was larger with fixed-dose subcutaneous reslizumab compared with placebo (figure 3, table 2). Improvements in pre-bronchodilator FEV₁ with fixed-dose subcutaneous reslizumab were seen rapidly (ie, at 2 weeks) and were maintained throughout 52 weeks (figure 3). Increases from baseline at week 52 for pre-bronchodilator FEV₁ were larger for fixed-dose subcutaneous reslizumab than placebo in both the prespecified eosinophil subgroups (figure 3, table 2).

Overall ACQ-6 scores decreased from baseline to week 52 in both treatment groups in the ITT population; however, ACQ-6 scores were lower for fixed-dose

subcutaneous reslizumab at all postbaseline timepoints (appendix p 15). The least squares mean change in ACQ-6 score from baseline to week 52 did not differ for fixed-dose subcutaneous reslizumab and placebo (table 2, appendix p 15). ACQ-6 findings for the prespecified eosinophil subgroups are provided in table 2. Increases in Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) were observed with both treatment groups. Changes from baseline in AQLQ+12 scores at 52 weeks were similar for subcutaneous reslizumab and placebo in the ITT population (table 2) and prespecified eosinophil subgroups (table 2). Treatment differences between fixed-dose subcutaneous reslizumab and placebo did not approach the minimal clinically important difference in the ITT population or in either of the prespecified eosinophil subgroups.

We found no meaningful difference between results of the other prespecified subgroup analyses (appendix p 7) and those of the ITT analysis for the key secondary outcomes (data not shown). Results of the other secondary efficacy analyses (Asthma symptom assessment at week 52 [based on a daily asthma control diary]; percentage of asthma control days at week 52 from baseline; change from baseline in St George's Respiratory Questionnaire score at week 32; probability of having a clinical asthma exacerbation by week 52; frequency of clinical asthma exacerbations requiring hospitalisation or emergency

department visit; and frequency of moderate asthma exacerbations, defined as exacerbations requiring additional asthma controlling medication that was not a systemic corticosteroid, and that did not result in an asthma-specific hospitalisation or emergency department visit during the 52-week treatment period) are presented in the appendix (p 7).

In study 2, we found no statistically significant difference between reslizumab and placebo across the five-level categorised percentage reductions in daily oral corticosteroid dose during weeks 20–24 compared with baseline (end of the optimisation phase; OR 1.23, 95% CI 0.70–2.16; $p=0.47$; table 3). Results in the per-protocol sensitivity analysis were similar to those of the primary ITT analysis (appendix p 19). No notable differences between fixed-dose subcutaneous reslizumab and placebo were observed for patients in any of the prespecified subgroup analyses (appendix p 19).

	Placebo (n=89)	Subcutaneous reslizumab (n=88)
Categorised percentage oral corticosteroid dose reduction (5-level response) at weeks 20–24*		
90 to 100%	20 (22%)	18 (20%)
75 to <90%	4 (4%)	8 (9%)
50 to <75%	8 (9%)	13 (15%)
>0 to <50%	9 (10%)	7 (8%)
No decrease†	48 (54%)	42 (48%)
Reslizumab vs placebo	..	1.23 (0.70–2.16)
p value	..	0.47
Categorised oral corticosteroid dose reduction (responder analyses) at weeks 20–24		
At least 50% reduction from baseline	32 (36%)	39 (44%)
Reslizumab vs placebo	..	1.45 (0.79–2.68)
Oral corticosteroid dose ≤5 mg	34 (38%)	37 (42%)
Reslizumab vs placebo	..	1.19 (0.63–2.23)
Oral corticosteroid dose 0 mg	20 (22%)	18 (20%)
Reslizumab vs placebo	..	0.82 (0.37–1.82)
At least 5 mg reduction from baseline	31 (35%)	36 (41%)
Reslizumab vs placebo	..	1.36 (0.72–2.56)

Data are n (%) or OR (95% CI), unless otherwise indicated. OR=odds ratio. *All data were included; missing data were included as non-responders. †No decrease in oral corticosteroid dose, loss of baseline asthma control during weeks 20–24, or discontinuation from study drug.

Table 3: Oral corticosteroid outcomes in the intention-to-treat population in study 2

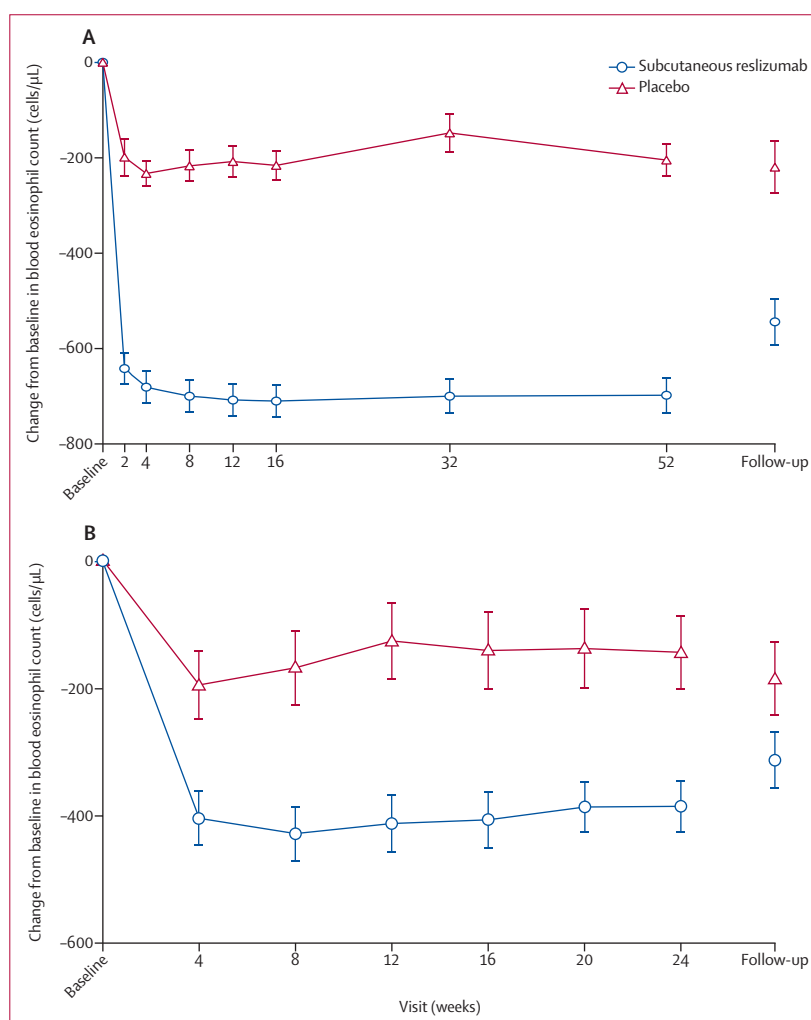


Figure 4: Change in blood eosinophil count from baseline at each visit in the intention-to-treat population in studies 1 and 2

Data are least squares mean and SE for (A) study 1 and (B) study 2. Follow-up was at 12 weeks after the 52-week treatment period in study 1, and at 8 weeks after the 24-week treatment period in study 2.

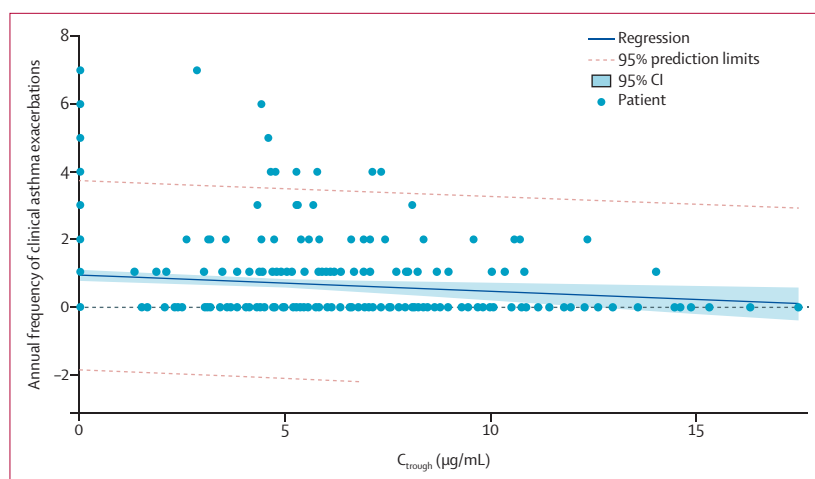


Figure 5: Relationship between trough serum concentration of reslizumab and annual frequency of clinical asthma exacerbations in study 1

C_{trough} =reslizumab trough concentration.

Because the analysis of the primary efficacy outcome did not meet the criteria for statistical significance, secondary efficacy outcomes were not interpreted inferentially. Both treatment groups showed decreases in oral corticosteroid dose over the treatment period (table 3). We found no significant differences in the secondary efficacy analyses for the ITT population (appendix p 20) or subgroup analyses of secondary outcomes (data not shown).

In both studies, blood eosinophil counts decreased in both treatment groups between baseline and first visit and remained below baseline until the end of treatment. Eosinophil counts began to rise towards baseline at the follow-up visits. Mean blood eosinophil counts among patients receiving fixed-dose subcutaneous reslizumab were lower than those of patients receiving placebo at the first post-baseline visit and all subsequent timepoints (figure 4). In study 1, the mean change from baseline to week 52 was $-0.205 \times 10^9/\text{L}$ (SD 0.4709) in the placebo group and $-0.698 \times 10^9/\text{L}$ (0.5356) in the fixed-dose subcutaneous reslizumab group. In study 2, the mean change from baseline to week 24 was $-0.144 \times 10^9/\text{L}$ (0.5040) in the placebo group and $-0.385 \times 10^9/\text{L}$ (0.3570) in the fixed-dose subcutaneous reslizumab group.

Baseline and reslizumab C_{trough} for both studies are reported in the appendix (pp 24–25). Patient body weight and C_{trough} were correlated and higher reslizumab C_{trough} was observed in patients with a lower body weight (appendix p 26).

In study 1, higher C_{trough} values were associated with a lower annual frequency of clinical asthma exacerbations. A regression fit indicated a significant correlation between clinical asthma exacerbation frequency and individual C_{trough} values ($p=0.0035$; figure 5).

The time to first clinical asthma exacerbation analysis indicated the greatest treatment effect (longest time to

first clinical asthma exacerbation) in patients with C_{trough} in the upper tertile (the group with the highest C_{trough} exposures). The C_{trough} exposures were $4.90 \mu\text{g/mL}$ or less for the lowest tertile, between 4.90 and less than $7.46 \mu\text{g/mL}$ for the middle tertile, and more than $7.46 \mu\text{g/mL}$ for the upper tertile, with the placebo group assumed to have an exposure of $0 \mu\text{g/mL}$. The median C_{trough} was $5.99 \mu\text{g/mL}$ (IQR 4.52 – 8.20 ; figure 6).

Within each study, the incidence of adverse events (AEs) was similar across the two treatment groups (table 4). The most common AEs ($\geq 5\%$ in either group) in study 1 were (viral or unspecified) upper respiratory tract infection, allergic rhinitis, acute sinusitis, headache, bronchitis, injection-site erythema, and asthma; and in study 2 were viral upper respiratory tract infection, asthma, bronchitis, headache, influenza, injection-site pain, and allergic rhinitis. Injection-site reactions occurred in 19 (8%) of 231 patients in the placebo group and 27 (11%) of 237 patients in the reslizumab group in study 1, and in two (2%) of 89 patients in the placebo group and five (6%) of 88 patients in the reslizumab group in study 2.

The most common serious AEs (SAEs) across both studies with reslizumab were asthma (table 4). In study 1, SAEs were assessed by investigators as being not related to study treatment, with the exception of two patients in the reslizumab group (respiratory infection and pulmonary embolism in one patient, and benign tracheal and bronchial tumour in another patient). In study 2, no SAEs during the study were assessed as being related to treatment.

One death occurred during the treatment period across both studies. In study 2, an adult man died 7 days after the first dose of reslizumab. The death was reported as sudden death and no autopsy was done. The death was considered by the investigator to be unrelated to treatment. In study 1, one patient from the reslizumab group died from hospital-acquired pneumonia and septicaemia during the follow-up period, more than 1 month after the last subcutaneous reslizumab dose. This event was not considered to be related to the study drug.

One ($<1\%$) patient in the placebo group and five (2%) patients in the fixed-dose subcutaneous reslizumab group discontinued treatment due to AEs in study 1. These AEs were of a diverse nature and, apart from benign tracheal and bronchial tumour and increased liver enzymes, were considered by the investigator to be not related to the study drug. In study 2, one patient in the placebo group discontinued treatment because of an AE.

No hypersensitivity AEs were deemed by the investigator to be causally related to reslizumab (appendix p 27).

Positive anti-drug antibody response in the reslizumab group was noted in 17 (7.2%) of 236 patients in study 1, and 11 (13%) of 88 patients in study 2. Titres of the anti-drug antibody-positive responses were generally low. All titres were transient in study 2 and most were

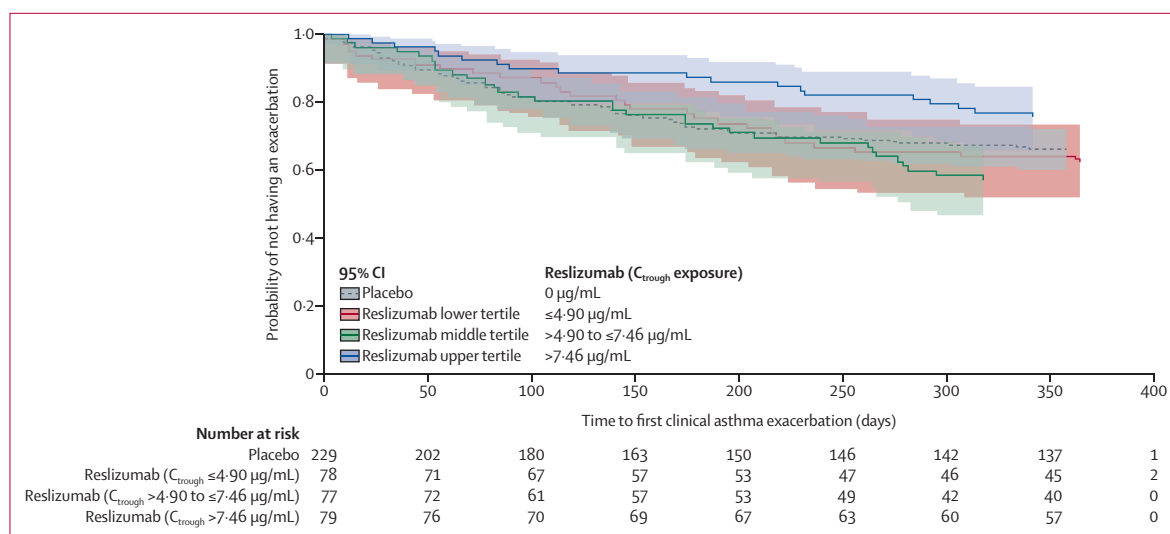


Figure 6: Kaplan-Meier survival curves for time to first clinical asthma exacerbation by tertiles of trough serum concentration of reslizumab in study 1. One patient in the placebo group received reslizumab and was excluded from the analysis. C_{trough} = trough reslizumab concentration.

transient in study 1 (most being single observations that resolved). We found no association between positive anti-drug antibody response and efficacy or safety outcomes (data not shown). All anti-drug antibody-positive samples were analysed using the neutralising antibody assay and none was identified as having neutralising activity.

Discussion

In study 1, 52 weeks of add-on therapy with fixed-dose (110 mg) subcutaneous reslizumab did not result in a significantly different frequency of clinical asthma exacerbations, compared with placebo, in the ITT population; however, our findings indicate that reslizumab treatment was associated with a reduced risk of exacerbations in the prespecified subgroup of patients with eosinophil counts of 400 cells per μL or more. This subgroup was fully powered a priori and aligned with the study population in phase 3 trials of intravenous reslizumab.⁹ The results of the secondary efficacy analyses suggest a clinically significant improvement in lung function, as measured by FEV₁, which was greater with reslizumab compared with placebo at all timepoints. Improvements in lung function were already seen by the first measured timepoint, at week 2, and were sustained over 52 weeks. We observed no effect of subcutaneous reslizumab on the annual rate of clinical asthma exacerbations in the prespecified subgroup of patients with an eosinophil count between 300 cells per μL and less than 400 cells per μL , in whom eosinophilia is less likely to be the major contributor to asthma severity; however, the sample size was too small to draw conclusions for an event-driven endpoint such as asthma exacerbations, as indicated by the high variability in this subgroup. The finding of improvements in clinical asthma exacerbation frequency and lung function with reslizumab in the prespecified subgroup of patients with

	Study 1		Study 2	
	Placebo (n=231)	Subcutaneous reslizumab (n=237)	Placebo (n=89)	Subcutaneous reslizumab (n=88)
Any adverse event	172 (74%)	169 (71%)	47 (53%)	57 (65%)
Adverse events occurring in $\geq 5\%$ of patients by preferred term				
Upper respiratory tract infection	19 (8%)	28 (12%)	5 (6%)	1 (1%)
Viral upper respiratory tract infection	31 (13%)	27 (11%)	5 (6%)	11 (13%)
Allergic rhinitis	12 (5%)	16 (7%)	0	4 (5%)
Acute sinusitis	15 (6%)	14 (6%)	3 (3%)	2 (2%)
Headache	10 (4%)	14 (6%)	3 (3%)	4 (5%)
Bronchitis	17 (7%)	13 (5%)	4 (4%)	6 (7%)
Injection-site erythema	7 (3%)	13 (5%)	0	0
Injection-site pain	9 (4%)	10 (4%)	1 (1%)	4 (5%)
Asthma	21 (9%)	12 (5%)	6 (7%)	8 (9%)
Influenza	7 (3%)	10 (4%)	2 (2%)	4 (5%)
Hypertension	10 (4%)	6 (3%)	5 (6%)	1 (1%)
Any serious adverse events	19 (8%)	19 (8%)	4 (4%)	10 (11%)
Serious adverse events occurring in $\geq 2\%$ of patients by preferred term				
Asthma	5 (2%)	4 (2%)	2 (2%)	3 (3%)
Pneumonia	4 (2%)	2 (<1%)	0	1 (1%)
Cholecystolithiasis	4 (2%)	0	0	0
Adverse events leading to discontinuation from treatment	1 (<1%)	5 (2%)	1 (1%)	0
Deaths	0	0	0	1 (1%)

Data are n (%), based on the number of patients who had at least one adverse event of a particular classification. One patient in the placebo group received reslizumab.

Table 4: Adverse events during treatment by treatment group (safety population) in both studies

high blood eosinophil counts suggests that blood eosinophil counts are a marker of responsiveness to therapies targeting the IL5 pathway,^{15,16} reconfirming the importance of defining the eosinophilic phenotype. Indeed, the findings for reslizumab in the two

prespecified eosinophil subgroups suggest that a baseline threshold of 400 cells per μL or more is an indicator of the efficacy of reslizumab. These results are consistent with the findings of our intravenous reslizumab study,⁹ which showed no further reduction in the frequency of clinical asthma exacerbations with increasing baseline eosinophil counts higher than 400 cells per μL .

The primary outcome findings from study 1 for subcutaneous reslizumab differ from those of previous phase 3 studies of weight-based dosing of intravenous reslizumab,⁹ which showed a 50–59% reduction in clinical asthma exacerbations over 52 weeks, and these differences are probably at least partly due to differences in drug exposure between the two studies. The dose administered with subcutaneous reslizumab 110 mg approximates to a 1 mg/kg intravenous dose for the average 70 kg patient when accounting for bioavailability. Therefore, 110 mg administered subcutaneously was a substantially lower dose than that obtained with 3 mg/kg weight-based dosing for all observed body weights when accounting for bioavailability. For example, the median body weight in study 1 was 76 kg, and patients of this weight would have received a reslizumab dose of approximately 228 mg with 3 mg/kg weight-based dosing compared with the 110 mg subcutaneous dose used in these studies. The 110 mg subcutaneous dose was selected on the basis of previous clinical data for intravenous reslizumab at a lower dose of 0.3 mg/kg in a 16-week FEV₁ study,¹¹ and at the time the effect of exposures at lower doses on clinical asthma exacerbation rates was not as clearly understood. Additionally, for a monoclonal antibody with a soluble target such as IL5, for which clearance of the drug is influenced by body weight, a single fixed dose most likely results in a gradient of concentrations based on the distribution of body weights across a population. Indeed, our correlative data showed reduced drug exposure to fixed-dose reslizumab in patients with higher body weight. By contrast, weight-based dosing of intravenous reslizumab resulted in consistent exposures across body weights, thereby decreasing the risk of lower exposures in heavier patients.^{18,19}

Higher doses of intravenous reslizumab have previously been shown to be associated with larger reductions in blood eosinophil counts and greater improvements in lung function (FEV₁) and patient-reported outcomes,¹¹ compared with lower doses, supporting an exposure–response relationship for reslizumab. This relationship was confirmed in the exposure–response analysis in study 1. The exposures achieved in study 1 with fixed-dose subcutaneous reslizumab were sufficient for improvements in mean change from baseline in FEV₁, but exposures higher than those observed with 110 mg are presumably required to reach maximal efficacy in terms of reducing the exacerbation risk in most patients. Our exposure–response analysis for reductions in the annual frequency of clinical asthma exacerbations in study 1 showed an inverse relationship between exposure and

exacerbation rate, with higher reslizumab exposures associated with lower exacerbation frequencies, suggesting the need for higher exposures to reach the concentration threshold required for maximal efficacy in the greatest proportion of patients. Similar results were observed in the exposure–response analysis of time to first clinical asthma exacerbation.

The effect of body weight on other treatments targeting the IL5 pathway has also been assessed. Body weight was identified as a relevant covariate influencing the pharmacokinetics of other anti-IL5 drugs.^{20,21} The exposure–response relationship and the effect of patient body weight on the efficacy of treatments targeting the IL5 pathway should be explored in more detail in further studies or analyses.

In study 1, annual rates of clinical asthma exacerbations during the treatment period were low with placebo compared with the baseline period (12 months before screening). This finding might be partly due to treatment non-adherence or suboptimal treatment before study enrolment, which minimised treatment differences in the study. Additionally, results from our prespecified subgroup analyses in study 1 suggested that heterogeneity in regional exacerbation rates during the treatment period might have contributed to the size of the treatment effect: patients enrolled from eastern Europe and, to a lesser extent, South America, had a very low frequency of exacerbations during the treatment period, irrespective of treatment group. Similar findings were made in other studies of biologic drugs for the treatment of severe asthma,¹⁷ without clear cause, and additional studies are warranted. Regardless of these regional differences, the relationship between body weight and reslizumab concentrations and the consequent exposure–response relationship were evident across the study population.

Despite the evidence for pharmacological activity with reslizumab in study 1, we found no significant treatment differences in efficacy outcomes in study 2, which was designed to investigate the oral corticosteroid-sparing effect of reslizumab in patients who had more severe asthma at baseline than did participants in study 1. Patients in study 2 were older, had a longer duration of asthma, worse lung function, and higher body weight than did those in study 1. Because fewer low-weight patients were included in study 2 compared with study 1, reslizumab exposures were lower in study 2. Our findings suggest that the systemic drug concentrations obtained with reslizumab 110 mg were not sufficient to show a quantifiable difference between treatment groups in corticosteroid dose reduction in most patients with severe oral corticosteroid-dependent asthma; as in study 1, higher exposures are probably required to achieve clinically relevant improvements in efficacy outcomes. These results concur with previous studies of the relationship between exposures and clinical efficacy outcomes for anti-IL5 therapies in patients with severe oral corticosteroid-dependent asthma.²² Results from study 2 were not pooled

with study 1 in the exposure–response analysis because of the differences in study design.

Reslizumab rapidly decreased blood eosinophil counts to a low but detectable concentration by the first visit in both studies. Decreases in blood eosinophil counts were not sufficient for clear improvements in clinical outcomes in either study. Although baseline blood eosinophil levels of 400 cells per μL or more are an adequate biomarker to indicate baseline eosinophilic airway inflammation, reduction in blood eosinophils with treatment is a surrogate biomarker, which might not fully reflect changes in eosinophilic airway inflammation. Blood eosinophil counts also decreased in the placebo groups, but to a much smaller extent. This post-baseline decrease in the placebo group might be due to regression to the mean based on the definition used for baseline eosinophil counts, which were assessed as the highest pre-dose value during screening and run-in. The decrease in peripheral blood eosinophils in placebo-treated patients might also indicate better adherence to inhaled corticosteroids during the study compared with pre-study adherence.²³

Subcutaneous reslizumab once every 4 weeks was generally well tolerated. We found few treatment-related AEs and discontinuations due to AEs. The AEs reported during the studies were consistent with the expected profiles for patients with uncontrolled severe asthma in study 1 and with severe oral corticosteroid-dependent asthma in study 2, and with previous experience with intravenous reslizumab.^{9,11} Few patients developed anti-drug antibodies, which were generally transient, low titre, non-neutralising, and not related to efficacy and safety.

These studies had several limitations. The studies were adequately powered, so we believe that the negative findings for the primary endpoints in the overall populations of both studies are meaningful; however, patient numbers for the subgroups were low, which limited the statistical power to detect subgroups that might have benefited from reslizumab. Because of multiple comparisons, a multiple testing procedure was implemented, resulting in only descriptive comparisons for secondary endpoints given that the *p* value was greater than 0.05 for the comparison of the primary endpoint in both studies. The inclusion of patients with a blood eosinophil count between 300 cells per μL and less than 400 cells per μL probably weakened our ability to show a treatment effect in either study, because a blood eosinophil count of 400 cells per μL or more appears to be a better indicator of eosinophil-driven asthma responsive to anti-IL5 therapy. A low asthma exacerbation rate in the placebo group also decreased our ability to show a treatment effect for asthma exacerbation reduction. On the basis of our post-hoc exposure–response analyses, doses of subcutaneous reslizumab higher than 110 mg once every 4 weeks will probably be required to achieve more robust improvements in efficacy outcome measures. Additionally, no long-term safety data beyond 52 weeks for subcutaneous reslizumab are available.

In conclusion, reslizumab given as a fixed-dose (110 mg) subcutaneous injection was not effective in reducing exacerbation rates in patients with uncontrolled asthma and an increased blood eosinophil count (≥ 300 cells/ μL), or in reducing the daily maintenance oral corticosteroid dose in patients with oral corticosteroid-dependent severe eosinophilic asthma. Subcutaneous reslizumab showed evidence of pharmacological activity in study 1, in terms of clinically significant improvements in lung function at 2 weeks, which were sustained until week 52, and clinically important improvements in exacerbation frequency in the subgroup of patients with high blood eosinophil counts (≥ 400 cells/ μL). However, the magnitude of effect of fixed-dose subcutaneous reslizumab on rates of clinical asthma exacerbations was lower than the 50–59% reduction observed with the higher reslizumab exposures associated with weight-based dosing of intravenous reslizumab. Reslizumab was generally well tolerated and no new safety concerns were detected. Exposure-response analyses indicate that to achieve the magnitude of effect on clinical asthma exacerbations observed with intravenous reslizumab 3 mg/kg, systemic reslizumab concentrations higher than those achieved with subcutaneous 110 mg are required. The use of higher, weight-based doses of subcutaneous reslizumab should be assessed in future studies.

Contributors

JCV, MG, and JM contributed to the conception and design of the study. JAB, JCV, KM, JFM, JJ, YA, MH, MC, JM, MG, RV, and GB contributed to the collection of data. JAB, JCV, KM, JFM, JJ, YA, MH, MC, DAM, JM, LH, MG, RV, and GB contributed to the data analysis. All authors contributed to the interpretation of the data and to the development of the first draft of the article. Subsequent drafts were reviewed and approved by all authors.

Declaration of interests

JAB has served as a speaker and consultant for AstraZeneca, BioCryst Pharmaceuticals, CSL Behring, KalVista Pharmaceuticals, Merck, Novartis, Pharming Technologies, Sanofi and Regeneron, and Shire; and has received research grants from AstraZeneca, BioCryst Pharmaceuticals, CSL Behring, Merck, Novartis, Pharming Technologies, Sanofi and Regeneron, and Shire. JCV has served as a speaker and consultant for ALK, Allergopharma, Altana, AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer Ingelheim, Chiesi, Cilag, Cipla, Essex Chemie, GlaxoSmithKline, Hexal-Sandoz, Janssen, Laboratorios Leti, Meda Pharmaceuticals, Merck Sharp & Dohme, Mundipharma, Novartis, Nycomed, Pfizer, Regeneron, The Paul Ehrlich Institute, Revotar Biopharmaceuticals, Sanofi, Schering-Plough, Stallergenes, Takeda, Teva Pharmaceuticals, UCB-Schwarz Pharma, and Zydus Cadila; and has received research grants from Deutsche Forschungsgemeinschaft, Land Mecklenburg-Vorpommern, GlaxoSmithKline, and Merck Sharp & Dohme. KM has served as a speaker and consultant for AstraZeneca, Boehringer Ingelheim, Genentech, Greer, Meda, Merck, Mylan, Novartis, and Teva Pharmaceuticals. JFM has served as a speaker and consultant for AstraZeneca, ImmunoTek, Menarini, Novartis, Sanofi, Teva Pharmaceuticals, and Uriach; and has received research grants from Novartis. JJ has served as a speaker and consultant for AstraZeneca, CSL Behring, Novartis, Regeneron, Sanofi-Genzyme, Shire, and Teva Pharmaceuticals; and has received research grants from BioCryst Pharmaceuticals and Genentech. MH has served as a speaker and consultant for AstraZeneca, GlaxoSmithKline, Novartis, Roche, Sanofi, and Teva Pharmaceuticals. MC has served as a speaker and consultant for AstraZeneca, Genentech, GlaxoSmithKline, Novartis, Regeneron, Sanofi-Aventis, Teva Pharmaceuticals, Theravance Biopharma, and

VIDA; has received research grants from ALA Pharma, AstraZeneca, Chiesi, GlaxoSmithKline, the US National Institutes of Health, Novartis, the Patient-Centered Outcomes Research Institute, and Sanofi-Aventis; and receives royalties from Elsevier. GB has served as a speaker and consultant for AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, Sanofi and Regeneron, Teva Pharmaceuticals, Union Chimique Belge, and Zambon. DAM, MG, and RV are employees of Teva Pharmaceuticals. JM and LH are former employees of Teva Pharmaceuticals. YA declares no competing interests.

Data sharing

Researchers can request access to patient-level data and related study documents including the study protocol and the statistical analysis plan. Requests will be reviewed for scientific merit, product approval status, and conflicts of interest. Patient-level data will be de-identified and study documents will be redacted to protect the privacy of trial participants and to protect commercially confidential information. Please email usmedinfo@tevapharma.com to make your request.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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SUPPLEMENTARY APPENDIX

Results from two phase 3, randomised, double-blind, placebo-controlled trials of fixed-dose subcutaneous reslizumab: an asthma exacerbation study in patients with severe uncontrolled asthma and a corticosteroid-sparing study in patients with oral corticosteroid-dependent asthma

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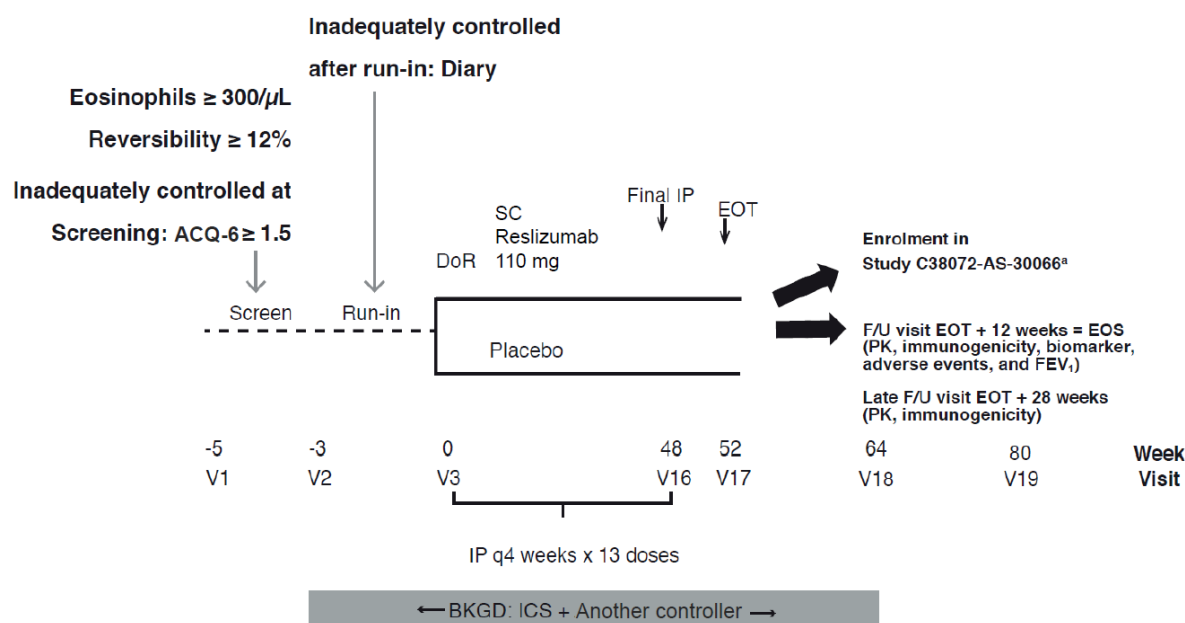
Methods

Asthma Exacerbation Study (Study I)

Study design

Study I was conducted at 201 centres in Argentina, Australia, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Japan, Mexico, New Zealand, Poland, Romania, Russian Federation, South Africa, Spain, Turkey, Ukraine, and the USA.

Supplementary Figure S1: Asthma Exacerbation Study (Study I): study schema



ACQ-6=Asthma Control Questionnaire-6. AE=adverse event. BKGD=background. DoR=day of randomisation. EOS=end of study. EOT=end of treatment. FEV₁=forced expiratory volume in 1 second. F/U=follow-up. ICS=inhaled corticosteroid. IP=investigational product. PK=pharmacokinetic. q4 weeks=every 4 weeks. SC=subcutaneous. V=visit.

Note: A maximum of 30% of the patients (60 patients per treatment group) with blood eosinophil levels of 300–<400 cells/μL were enrolled. When this 30% threshold was reached, only patients with blood eosinophil levels ≥400/μL were enrolled.

^aIf patients elected to enrol in the open-label, long-term Extension Study, they did not complete the early and/or late follow-up visits under the Study I protocol, but instead completed the early and/or late F/U visits at the end of the Extension Study.

For patients who remained in the study after the EOT, two additional F/U visits were performed. The first F/U was for PK, immunogenicity, biomarker, AEs, and FEV₁ and was performed at 12 weeks after the last dose of study drug (approximately week 64).

The second late F/U for immunogenicity and PK testing was performed 24 weeks after the last dose of study drug (approximately week 76).

Patients were deemed to have completed the study once they completed the F/U (EOS) and the database was locked at this last prespecified F/U visit of the study.

Patients

Full inclusion criteria for Study I were:

- Male and female patients aged ≥12 years with asthma. Patients 12–<18 years of age were excluded from participating in South Korea and Argentina, and patients 66 years of age and older were excluded from participating in South Korea
- Written informed consent. A patient 12–<18 years of age was required to provide assent, and their parent(s) or legal guardian(s) was required to provide consent

- At least two documented asthma exacerbations requiring the use of systemic (oral, intramuscular, or intravenous) corticosteroids within 12 months of the patient signing the informed assent form/informed consent form
- Asthma Control Questionnaire-6 (ACQ-6) score ≥ 1.5 at screening (visit 1)
- Blood eosinophil levels ≥ 300 cells/ μ L during screening. A maximum of 30% of the patients enrolled could have blood eosinophil levels of 300–<400 cells/ μ L. When this 30% threshold was reached, only patients with blood eosinophil levels of ≥ 400 / μ L were then enrolled
- Forced expiratory volume in 1 second (FEV₁) reversibility $\geq 12\%$ to inhaled short-acting beta agonist (SABA) at screening according to standard American Thoracic Society (ATS) or European Respiratory Society (ERS) protocol, or documentation within 12 months of signing informed consent
- Receiving at least a medium dose of inhaled corticosteroid (ICS) for ≥ 3 months. For ICS/long-acting beta agonist (LABA) combination preparations, the mid-strength approved maintenance dose in the local country met this ICS criterion
- Receiving at least one additional asthma controller medication(s) (eg, LABA, long-acting muscarinic antagonist [LAMA], leukotriene receptor antagonist, or theophylline preparations) for ≥ 3 months (or documented failure of second controller in the past 12 months)
- Females of childbearing potential (not surgically sterile by hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or 2 years postmenopausal) must have had an exclusively same-sex partner or used a medically acceptable method of contraception, and must have agreed to continue use of this method for the duration of the study and for 5 months after last study drug dose. Acceptable methods of contraception included intrauterine device, steroidal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, bilateral fallopian tube occlusion, and partner vasectomy
- Patients must have been willing and able to comply with study restrictions, perform requisite procedures, and remain at the clinic for the required duration during the study period, and willing to return to the clinic for the follow-up evaluation as specified in the protocol
- Patients must have maintained their usual asthma controller regimen without change throughout the screening and run-in periods. A patient who experienced an asthma exacerbation during this time that required additional medication, beyond increased SABA use, was considered to have failed screening/run-in and could not undergo randomisation. A patient may have been rescreened for this reason one time only. The duration between the date of screen failure and the rescreening must have been >30 days

In order to be randomised, a patient must have demonstrated the following:

- Inadequate asthma control at baseline/day of randomisation (DoR) as evidenced by one of the four criteria below:
 - Daytime asthma symptom score >0 on >2 of the previous 7 days based on the asthma control diary received at run-in, or
 - Need for reliever SABA use on >2 of the previous 7 days, or
 - ≥ 1 nighttime awakening due to asthma over the previous 7 days, or
 - Pre-bronchodilator FEV₁ $<80\%$ predicted at baseline/DoR

and

- Completion of at least 4 days of diary entries or equivalent during the last 7 days of run-in. A patient may be rescreened for this reason one time only

Full exclusion criteria in Study I were:

- Clinically significant, uncontrolled medical condition (treated or untreated) that would have interfered with the study schedule or procedures, interpretation of efficacy results, or compromised the patient's safety
- Another underlying lung disorder (eg, chronic obstructive pulmonary disease, interstitial lung disease, bronchiectasis eosinophilic granulomatosis with polyangiitis [EGPA, also known as Churg-Strauss syndrome], or allergic bronchopulmonary aspergillosis [ABPA])
- Known hypereosinophilic syndrome
- Diagnosis of malignancy within 5 years of the screening visit, except for treated and cured non-melanoma skin cancers
- The patient was a pregnant or lactating woman, or intended to become pregnant during the study or within 5 months after the last dose of study drug. Any woman who became pregnant during the study was withdrawn from the study

- Required treatment for an asthma exacerbation within 4 weeks of screening or during the screening/run-in period
- Current smoker (ie, has smoked within the last 6 months before screening) or had a smoking history ≥ 10 pack years
- Currently using any systemic immunosuppressive or immunomodulatory biologic (eg, anti-immunoglobulin E monoclonal antibody [mAb] or other mAb [eg, mepolizumab] or soluble receptors) or non-biologic (eg, methotrexate or cyclosporine), except maintenance oral corticosteroid (OCS) for the treatment of asthma (up to and including 10 mg of prednisone daily or equivalent). Note: Previous use of such agents that occurred >5 half-lives from the initial screening visit may have been allowed, if approved by the medical monitor
- Participation in a clinical trial within 30 days or five half-lives of the investigational drug before screening, whichever is longer
- Previously exposed to benralizumab within 12 months of screening
- Previously exposed to reslizumab
- A history of an immunodeficiency disorder including human immunodeficiency virus (HIV)
- Current or suspected drug and alcohol abuse
- Active helminthic parasitic infection or was treated for one within 6 months of screening
- A history of allergic reaction or hypersensitivity to any component of the study drug
- A history of latex allergy (the current prefilled syringe device has a natural rubber component to the needle shield)

Procedures

At the start of the run-in period, patients began daily self-monitoring at home using an asthma control diary and peak expiratory flow (PEF) meter, while taking their usual asthma medications, in order to establish their baseline level of asthma control based on the frequency of symptoms, use of reliever (SABA), nighttime awakenings due to asthma, and ambulatory lung function measurement. Improvement in asthma control during the treatment period was primarily assessed by a reduction in the rate of clinically significant asthma exacerbations with reslizumab versus placebo during the 52-week treatment period. Pulmonary function; Asthma Quality of Life Questionnaire for patients aged ≥ 12 years (AQLQ+12), ACQ, and St George's Respiratory Questionnaire (SGRQ) scores; asthma symptoms; use of reliever (SABA); nighttime awakenings due to asthma; safety measures; pharmacokinetics (PK); and immunogenicity were assessed periodically; final assessments for the treatment period were made at the end of treatment (EOT) visit (week 52) or at early withdrawal. Patients who withdrew from the study before completing the 52-week evaluation period had visit 17 (week 52 or early withdrawal) procedures and assessments performed at their final visit. Patients returned 12 weeks after the EOT visit for follow-up haematology, PK, immunogenicity, and safety assessments. If a patient elected to withdraw (or was discontinued from treatment by the investigator), every attempt was made to continue the assessments subsequent to their withdrawal from the study drug.

Study drug was administered by qualified study personnel, who ensured that the study drug was administered in accordance with the protocol, as a subcutaneous (SC) injection every 4 weeks (q4w) for a total of 13 doses. Patients within each treatment group (placebo and 110 mg) were randomly allocated to a particular sequence of injection sites:

- a. upper arm (A)→abdomen (B)→thigh (C)
- b. abdomen (B)→thigh (C)→upper arm (A)
- c. thigh (C)→upper arm (A)→abdomen (B)

Study drug was administered as a single SC injection containing either placebo (1.0 mL) or 110 mg of reslizumab (1.0 mL).

Outcomes

Secondary efficacy outcomes included:

- Change from baseline/DoR in pre-bronchodilator FEV₁ at week 52
- Change from baseline/DoR in AQLQ+12 (restricted to the subset of the intention-to-treat [ITT] analysis set within the specified age range [12–70 years] at baseline) at week 52

- Change from baseline/DoR in ACQ-6 at week 52
- Asthma symptom assessment at week 52 (based on a daily asthma control diary)
- Percentage of asthma control days at week 52 from baseline/DoR
- Change from baseline/DoR in SGRQ at week 32
- Probability of having a clinical asthma exacerbation (CAE) by week 52
- Frequency of CAEs requiring hospitalisation or emergency department (ED) visit
- [Frequency of moderate asthma exacerbations, defined as exacerbations requiring additional asthma controlling medication that was not a systemic corticosteroid, and that did not result in an asthma-specific hospitalisation or emergency department visit during the 52-week treatment period.](#)

Other prespecified efficacy outcomes were:

- Change from baseline/DoR in pre-bronchodilator forced vital capacity (FVC) and forced expiratory flow at 25–75% of FVC (FEF_{25–75%}) throughout the study

Eosinophil counts were assessed at DoR/baseline; weeks 2, 4, 8, 12, 16, 32, and 52 or early withdrawal; and the follow-up visit (approximately week 64). Serum reslizumab concentrations were determined from blood samples collected at baseline/DoR; weeks 1 (patients in US study centres only) and 2, and prior to study drug administration at weeks 4, 8, 12, 16, 20, 32, 48, and 52 or early withdrawal; and the follow-up visit (approximately week 64). An additional PK sample was taken at long-term follow-up (approximately week 76) at the same time as anti-drug antibody (ADA) sample collection. Reslizumab concentration data are provided for samples received at the testing laboratory by January 25, 2018.

Immunogenicity outcomes comprised the development of ADAs. Samples were obtained before the administration of the study drug at DoR; prior to study drug administration at weeks 4, 16, 32, and 52 or early withdrawal; and the follow-up visit (approximately week 64). Additional samples were collected at the late follow-up visit (approximately week 76). Additionally, a neutralising antibody (NAb) assay was performed for samples with a positive ADA result. ADA data are provided for samples received at the testing laboratory by December 20, 2017.

The safety outcomes for this study were as follows:

- Adverse events (AEs) throughout the study
- Vital signs (pulse, respiratory rate, and blood pressure [BP]) throughout the study
- Concomitant medication usage throughout the study
- Physical examination findings throughout the study
- Clinical laboratory evaluations at screening, baseline/DoR, and periodically throughout the study
- Electrocardiogram (ECG) evaluation at screening and weeks 24, 36, and 52 or early withdrawal

Statistical analysis

Power calculations conducted for Study I were based on a mean number of 2.9 exacerbations per patient per year in the placebo group, a dispersion parameter of 1.2 in the negative Binomial model for both treatment groups, and treatment effect of 45% between reslizumab and placebo. Based on these assumptions, 225 patients per group (450 total) would provide >90% power to detect significant treatment effect of reslizumab versus placebo in the reduction of exacerbation rate. The sample size was increased beyond that required to provide 90% power in order to allow a sufficient number of patients to assess safety and immunogenicity and to ensure adequate enrolment in the adolescent subset. The protocol permitted up to 30% of the patients enrolled to have blood eosinophil levels of 300–<400 cells/ μ L, and the rest were required to have baseline levels $\geq$ 400 cells/ μ L. Due to issues with convergence observed in the primary analysis model that affected the pre-planned multiple imputation, a post-hoc data-driven analysis was conducted to further assess the effect of reslizumab on CAE rates. This revised analysis assumed that the number of imputed events for all reslizumab patients was equal to 0, based on observed data from four reslizumab patients who discontinued treatment early but remained in the study (and reported no CAEs after treatment discontinuation).

For the secondary outcomes, only observed data from the patients were used in the statistical analyses (ie, there was no plan to estimate missing data). Analysis of pulmonary function tests, AQLQ+12, ACQ-6, asthma symptom assessment (determined from the asthma control diary), and SGRQ used a mixed-model repeated measures (MMRM) model with treatment, visit, treatment-by-visit interaction, baseline value, and stratification

factors as fixed effects, and patient as a random effect. Unstructured covariance was assumed for the repeated measures. The asthma symptom score was determined from the information recorded in the asthma control diary. A Likert-style scale was used to quantify symptomatology, with higher scores indicating more severe symptoms. Every AM and PM, patients indicated how much they were bothered by their asthma symptoms. An analysis of variance model was used to analyse percentage of asthma control days with treatment group and stratification factors. Kaplan-Meier survival curves were used to estimate and compare the distributions of time to first CAE between treatment groups. Differences were compared using a log-rank test adjusting for the stratification factors. The frequency of exacerbations requiring hospitalisation or ED visits were examined separately. The analysis used similar methodology to that described for the primary analysis.

A fixed sequence multiple testing procedure was implemented to test the primary and secondary variables while controlling the overall Type I error rate at 0.05. If the resulting two-sided p value from the primary comparison was ≤ 0.05 , then the next comparison of interest (first secondary variable) would be interpreted inferentially at 0.05. This process would continue through the secondary variables until either all comparisons of interest were interpreted inferentially, or until the point at which the resulting two-sided p value for a comparison of interest was > 0.05 . At the point where $p > 0.05$, no further comparisons would be interpreted inferentially. The prespecified hierarchy of secondary efficacy outcomes followed the order in the list of secondary efficacy variables.

For blood eosinophil counts, summary statistics of actual values, change from baseline, and percent change from baseline to each scheduled visit were provided by treatment group using the ITT population.

For the immunogenicity outcomes, the number of patients with positive/negative results was summarised at each scheduled visit. Samples from placebo-treated patients were not analysed for this study. The assessment of safety was based on measurements and events recorded during the treatment period (on-treatment). On-treatment assessments were defined as events and measurements occurring between the first dose of study drug and the EOT (week 52) visit, for patients who completed treatment and between the first dose of study drug and the last dose of study drug +4 weeks for patients who discontinued treatment early. Safety data were summarised using descriptive statistics by timepoint and/or treatment group, as appropriate.

Selected efficacy outcomes, including CAEs (primary), pre-bronchodilator FEV₁, AQLQ+12, ACQ-6, and blood eosinophils were examined for categorical subgroups. Subgroups used for the efficacy analyses were:

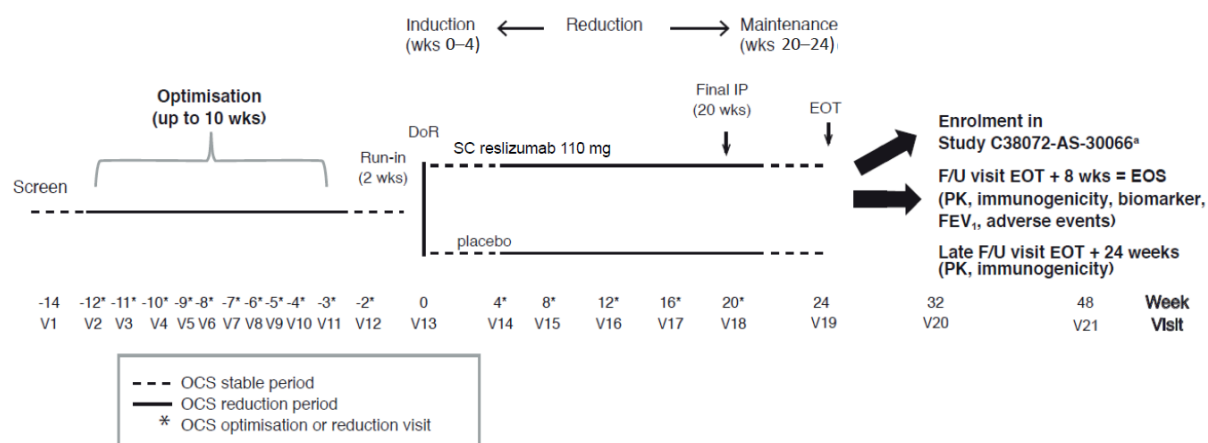
- Eosinophil count (300–<400 cells/ μ L and ≥ 400 cells/ μ L) was a prespecified stratification factor according to the study design, which recruited a sufficient proportion of patients with eosinophil levels $\geq 400/\mu$ L
- Age group (12–<18 years and ≥ 18 years; 12–<18 years, 18–<65 years, and ≥ 65 years)
- Patients with a history of nasal polyps and abnormal Sinonasal Outcome Test-22 score (> 0.318) at baseline/DoR
- Patients with a history of nasal polyps
- Asthma background medication at baseline based on Global Initiative for Asthma (GINA) guidelines: GINA 4: high-dose or medium-dose ICS/LABA; GINA 5: OCS
- Race (white, black, Asian, other; black and non-black)
- Region (US/Canada, Europe, other; US and non US)
- Sex (male and female)
- Age at asthma onset (< 40 and ≥ 40 years)
- Body mass index (< 30 and ≥ 30 kg/mg²)
- Phadiatop result (positive and negative)
- Post-baseline ADA status (positive and negative)

OCS-Sparing Study (Study II)

Study design

Study II was conducted at 92 centres in Argentina, Australia, Belgium, Czech Republic, France, Germany, Hungary, Israel, Italy, Korea, Mexico, the Netherlands, Poland, Russia, Spain, Ukraine, and the USA.

Supplementary Figure S2: OCS-Sparing Study (Study II): study schema



DoR=day of randomisation. EOS=end of study. EOT=end of treatment. FEV₁=forced expiratory volume in 1 second. F/U=follow-up. OCS=oral corticosteroid. IP=investigational product. PK=pharmacokinetic. SC=subcutaneous. V=visit. Wks=weeks.

For patients who remained in the study after the EOT, two additional follow-up visits were performed. The first follow-up was for PK, immunogenicity, biomarker, adverse events, and FEV₁ and was performed at 8 weeks after the last dose of study drug (approximately week 32).

An additional, late follow-up for immunogenicity and PK testing was performed 24 weeks after the last dose of study drug (ie, approximately week 48).

Patients were deemed to have completed the study once they completed the first follow-up (EOS) and the database was locked at this last prespecified follow-up visit of the study.

Patients

Full inclusion criteria in Study II were:

- Male and female patients aged ≥ 12 years with asthma. Patients 12–<18 years of age were excluded from participating in South Korea, the Netherlands, and Argentina, and patients 66 years of age and older were excluded from participating in South Korea
- Written informed consent. During the screening period, a signed and dated informed consent form (and an assent form for children 12–<18 years of age in accordance with local standards) was obtained before a diagnosis of asthma was confirmed on the basis of patient history and by demonstration of airway reversibility
- Required an average daily maintenance dose of OCS for asthma of 5–40 mg of prednisone or equivalent during the 3 months before screening. Patients on an OCS dose of >40 mg at screening who the investigator believed may be able to decrease OCS dose to ≤ 40 mg during the optimisation period could also be enrolled. Note: every-other-day dosing that was within this daily average (ie, 10–80 mg) was allowed
- Documented blood eosinophil level of ≥ 300 cells/ μ L during the previous 12 months while on at least a medium total daily dose of ICS, or ≥ 300 cells/ μ L at screening while on chronic OCS or during the OCS optimisation period or at the week –2 visit (end of optimisation period/beginning of run-in period)
- Required at least 880 μ g of inhaled fluticasone propionate or equivalent daily, plus another controller(s) (eg, LABA, LAMA, leukotriene inhibitor, or theophylline), or documented intolerance to another controller for ≥ 6 months before the screening visit. For a fixed-dose ICS/LABA preparation, the highest labelled dose in that region would satisfy this criterion. For patients 12–<18 years of age, the ICS dose must have corresponded to at least a medium total daily ICS dose. Note: the dose and regimen of asthma controllers and any allergen immunotherapy should have been stable during the 30 days before signing the informed assent form/informed consent form
- FEV₁ reversibility $\geq 12\%$ after administration of inhaled reliever medication according to the standard ATS or ERS protocol. Given the refractory nature of the disease in this population and the influence of high background controller medications on reversibility testing, documented FEV₁ reversibility 12% or a provocation concentration producing a 20% fall in FEV₁ for methacholine of ≤ 8 mg/mL within 24 months of the screening visit, and performed according to the standard ATS/ERS procedures, would fulfill this

criterion. Patients could be screened again if they did not meet spirometry/reversibility criteria initially. The duration between the date of screen failure and the rescreening must have been >30 days

- Females of childbearing potential (not surgically sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, or 2 years postmenopausal) must have had exclusively same-sex partners or used medically acceptable methods of birth control and must have agreed to continue use of this method for the duration of the study and for 5 months after the last study drug dose. Acceptable methods of birth control included intrauterine device, systemic hormonal contraceptive (oral, implanted, transdermal, or injected), barrier method with spermicide, abstinence, bilateral fallopian tube occlusion, and partner vasectomy
- The patient must have been willing and able to comply with study restrictions, willing and able to perform requisite procedures and remain at the clinic for the required duration during the study period, and willing to return to the clinic for the follow-up evaluation as specified in the protocol
- Except for OCS, which was adjusted per protocol, the patient must have maintained their usual asthma controller regimen without change throughout the screening, optimisation, run-in, and treatment periods

Full exclusion criteria in Study II were:

- Clinically significant, uncontrolled medical condition (treated or untreated) that would interfere with the study schedule or procedures and interpretation of efficacy results or would compromise the patient's safety
- Another underlying lung disorder (eg, chronic obstructive pulmonary disease, interstitial lung disease, bronchiectasis, EGPA, or ABPA)
- Known hypereosinophilic syndrome
- A history of any malignancy within 5 years of the screening visit, except for treated and cured non-melanoma skin cancers
- The patient was pregnant or intended to become pregnant during the study or within 5 months from last dose of study drug or was lactating. Any woman becoming pregnant during the study was to be withdrawn from the study
- Required treatment for an asthma exacerbation within 4 weeks of screening
- Current smoker (ie, had smoked within the last 6 months before screening) or had a smoking history ≥ 10 pack-years
- Currently using any systemic immunosuppressive or immunomodulatory biologic (eg, anti-immunoglobulin E mAb or other mAb [eg, mepolizumab] or soluble receptor) or non-biologic (eg, methotrexate or cyclosporine), except maintenance OCS for the treatment of asthma. Previous use of such agents that occurred more than 5 half-lives from the screening visit could be allowed if approved by the medical monitor
- Participation in a clinical study within 30 days or five half-lives of the investigational drug before screening, whichever was longer
- Previously exposed to benralizumab within 12 months of screening
- Previously exposed to reslizumab
- A history of immunodeficiency disorder, including HIV
- Current suspected drug and/or alcohol abuse
- An active helminthic parasitic infection or was treated for one within 6 months of screening
- A history of allergic reactions or hypersensitivity to any component of the study drug
- A history of latex allergy (the prefilled syringe device had a natural rubber component to the needle shield)

Procedures

During the optimisation period, the patient's minimal effective OCS requirement was determined. The patient's previous OCS was standardised to an equivalent dose and regimen of prednisone to the nearest 2.5 mg daily. The patient's previous non-OCS background asthma controller medications were to be continued unchanged throughout the pre-randomisation period and the entire study. At the beginning of the optimisation period, asthma symptom diary and electronic PEF meter were distributed, on which the patient recorded asthma symptoms, number of reliever bronchodilator inhalations, nighttime awakenings due to asthma requiring rescue inhaler, and AM and PM PEF. For optimisation, the OCS dose was reduced at 1-week intervals for up to 10 weeks or until there was a worsening of asthma signs and symptoms (minimum 1 day in optimisation). When either a lung function or symptomatic deterioration occurred, the patient was to be returned to the previously effective OCS level, which would then constitute the minimally effective dose for the purpose of run-in. If this

previously effective dose was no longer effective, the investigator could determine the clinically appropriate, minimally effective dose for the purpose of run-in. The optimisation period was considered finished when patients experienced a worsening of asthma signs and symptoms, or if patients optimised to an OCS dose of <5 mg without a worsening of asthma signs and symptoms. Patients could enter run-in (visit 12) on the same day as optimisation ended if the patients were on the minimally effective prednisone dose (did not require a prednisone burst at end optimisation).

Patients whose minimal effective OCS dose remained between ≥ 5 and ≤ 40 mg of prednisone daily at the end of optimisation could advance to run-in. During run-in, patients continued to keep their daily asthma control diary and PEF meter to perform daily self-monitoring of asthma symptoms while maintaining their minimally effective OCS dose and previous background asthma medications unchanged. The frequency of symptoms, use of inhaled reliever bronchodilator, nighttime awakenings due to asthma requiring a rescue inhaler, and ambulatory lung function during the last 7 days of the run-in period constituted the baseline level of control for analysis and the basis for the OCS reduction algorithm used during the treatment period.

After completion of the optimisation/run-in period, patients could continue in the study if they met all of the following criteria after OCS optimisation:

- The patient was using an average daily dose of ≥ 5 mg of prednisone
- The patient was using an average daily dose of ≤ 40 mg of prednisone
- The patient had not had/reported an asthma exacerbation during the run-in period, defined as requiring a burst of systemic corticosteroid for an asthma worsening (injection or, if oral, at least a doubling from the current OCS dose for ≥ 3 days); an asthma-specific hospital admission; or an asthma-specific ED visit
- The patient must have completed ≥ 4 days of diary entries (or any combination of four morning and four evening recordings) during the last 7 days of the run-in period

The post-randomisation period consisted of the treatment period, follow-up visit, and late follow-up visit. During the treatment period, the patients continued their usual non-OCS background asthma medication without change; the OCS dose was tapered per protocol. The treatment period consisted of an induction period and an OCS reduction period. During the induction period, the minimally effective dose of OCS was maintained and unchanged during the first 4 weeks of the treatment period. During the OCS reduction period, the minimally effective OCS dose was reduced per protocol at scheduled clinic visits from the beginning of week 5 (ie, end of the induction period) through week 20. If the OCS dose could not be decreased, it was to be held constant or could be increased to a previous level at the investigator's discretion until the next study visit at which dose reduction criteria were met. This dose was maintained for the final 4 weeks of the treatment period.

Study drug was administered by qualified study personnel, who ensured that the study drug was administered in accordance with the protocol, as an SC injection in the upper arm q4w for a total of six doses.

Outcomes

Secondary efficacy outcomes included:

- Proportion of patients achieving $\geq 50\%$ reduction in OCS dose at weeks 20–24 relative to the OCS dose at DoR/baseline, while maintaining asthma control
- Proportion of patients achieving dose reduction to ≤ 5 mg daily dose at weeks 20–24, while maintaining asthma control
- Proportion of patients achieving <5 mg decrement in OCS dose (ie, the minimal and non-responders) at weeks 20–24, compared with the OCS dose at DoR/baseline, while maintaining asthma control
- Proportion of patients discontinuing OCS at weeks 20–24, while maintaining asthma control
- Percent change from DoR/baseline in OCS dose at weeks 20–24
- Annualised rate of CAEs requiring a burst of systemic corticosteroid (injection or, if oral, at least a doubling from the current OCS dose for ≥ 3 days), an asthma-specific hospital admission, or an asthma-specific ED visit during the treatment period (weeks 0–24)

Other prespecified efficacy outcomes were:

- Probability of having a CAE by week 24
- Change from DoR/baseline in pre-bronchodilator FEV₁ to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- Change from DoR/baseline in ACQ-6 to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal
- Change from DoR/baseline in AQLQ+12 to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal

Eosinophil counts were assessed at DoR/baseline; weeks 4, 8, 12, 16, 20, and 24 or early withdrawal, and at the follow-up visit (approximately week 32). Serum reslizumab concentrations were determined from blood samples collected from each patient at DoR/baseline; prior to study drug administration at weeks 4, 8, 12, 16, 20, and 24 or early withdrawal; and at the follow-up visit (approximately week 32). An additional PK sample was obtained at the late follow-up visit (approximately week 48).

Immunogenicity outcomes comprised the development of ADAs. The drug-emergent ADA response was identified by analysing ADA in serum samples obtained before the administration of study drug at DoR/baseline; prior to study drug administration at weeks 4, 8, 12, and 24 or early withdrawal; and at the follow-up visit (approximately week 32). An additional sample was obtained at the late follow-up visit (approximately week 48). A titre was determined for samples that tested positive for ADA. Additionally, a NAb assay was performed for samples with a positive ADA result.

The safety outcomes for this study were as follows:

- Occurrence of AEs throughout the study, including the week 32 follow-up visit
- Clinical laboratory evaluations of serum chemistry at screening, DoR, and periodically throughout the study
- Clinical laboratory evaluations of haematology throughout the study
- Vital signs (pulse, body temperature, respiratory rate, and BP) measurements throughout the study
- ECG evaluation at screening and at week 24 or early withdrawal
- Physical examination findings, including body weight measurements, throughout the study
- Signs and/or symptoms of adrenal insufficiency (OCS withdrawal effects) throughout the study
- Concomitant medication usage throughout the study, including the week 32 follow-up visit

Statistical analysis

A sample size of 76 patients per treatment arm was chosen to provide 90% power to detect a significant effect of reslizumab over placebo on the probability for a higher categorical reduction of OCS dose using a proportional odds model. This was based on the assumption in the placebo group that after 24 weeks of treatment 10·9% of patients have 90–100% reduction, 7·9% have 75–<90% reduction, 14·8% have 50–<75% reduction, 10·8% have 0–<50% reduction, and 55·6% have no reduction, have loss of asthma control, or discontinue; also assuming odds ratio (OR) based on a proportional odds model of 2·63.

As for Study I, a fixed-sequence, multiple-testing procedure was implemented to control for overall type I error rate. The hierarchy of secondary outcomes in this study was assessed as follows:

- Proportion of patients achieving $\geq 50\%$ reduction in OCS dose at weeks 20–24 relative to the OCS dose at DoR/baseline, while maintaining asthma control
- Proportion of patients achieving dose reduction to ≤ 5 mg daily dose at weeks 20–24, while maintaining asthma control
- Percent change from DoR/baseline in OCS dose at weeks 20–24
- Proportion of patients achieving < 5 mg decrement in OCS dose (ie, the minimal and non-responders) at weeks 20–24, compared with the OCS dose at DoR/baseline, while maintaining asthma control
- Annualised rate of CAEs requiring a burst of systemic corticosteroid (injection or, if oral, at least a doubling from the current OCS dose for ≥ 3 days), an asthma-specific hospital admission, or an asthma-specific ED visit during the treatment period (weeks 0–24)
- Proportion of patients discontinuing OCS at weeks 20–24, while maintaining asthma control

Analysis of change from baseline in OCS dose to each scheduled visit was performed using a MMRM model including fixed effects for treatment, visit, treatment-by-visit interaction, age (12–<18 years and ≥ 18 years), and OCS dose at baseline (> 10 and ≤ 10 mg); baseline OCS dose and duration of OCS use prior to study entry as covariates; and patient as a random effect. An unstructured covariance matrix was used for the within-patient correlation modelling. Unstructured covariance was assumed for the repeated measures. Based on the MMRM model, the treatment effect, difference from placebo, and associated 95% confidence intervals (CIs) were presented together with the corresponding p value. Each of the categorical secondary outcomes based on the total daily dose at weeks 20–24 were analysed using a binary logistic regression model, incorporating the same covariates as the primary outcome. The estimated OR, 95% CI, and p value were presented. Patients who were unable to maintain asthma control or who withdrew treatment prematurely were counted as non-responders and analysed as part of the lowest category of response.

The annualised rate of CAEs was analysed using the generalised linear model for data from the negative binomial regression model. Treatment group, randomisation strata (age and OCS dose), number of exacerbations in the previous year, and an offset variable were model factors. The offset variable was calculated as the logarithm of follow-up duration minus the summed duration of exacerbations during the follow-up. The ratio of CAE rate between the treatment groups and its 95% CIs were determined. Kaplan-Meier survival curves were used to estimate and compare the distributions of time to first CAE between treatment groups. The hazard ratio (HR), 95% CIs, and p value were estimated using a Cox proportional hazards regression model adjusting for the stratification factors.

Analysis of pulmonary function tests, AQLQ+12, and ACQ-6 used a MMRM model with treatment, visit, treatment-by-visit interaction, and stratification factors (age group and OCS dose) as fixed effects; sex and height (pulmonary function tests only), and baseline value as covariates; and patient as a random effect. Unstructured covariance was assumed for the repeated measures. The treatment effect, difference from placebo, 95% CIs, and p value were presented.

For blood eosinophil counts, summary statistics of actual values, change from baseline, and percent change from baseline to each scheduled visit were provided by treatment group using the ITT analysis set.

For the immunogenicity outcomes, the number of patients with positive/negative results was summarised at each scheduled visit. The assessment of safety was based on measurements and events recorded during the treatment period (on-treatment). On-treatment assessments were defined as events and measurements occurring between the first dose of study drug and the EOT (week 24) visit, for patients who completed treatment and between the first dose of study drug and the last dose of study drug +4 weeks for patients who discontinued treatment early. Safety data were summarised using descriptive statistics by timepoint and/or treatment group, as appropriate.

Selected efficacy outcomes, including OCS dose (primary), pre-bronchodilator FEV₁, AQLQ+12, ACQ-6, blood eosinophils, and overall AE categories were analysed for categorical subgroups. Subgroups used for the efficacy analyses were:

- Age strata (12–<18 years and ≥18 years; 12–<18 years, 18–<65 years, ≥65 years)
- OCS strata (optimised baseline dose of OCS >10 and ≤10 mg)
- Sex (male, female)
- Race (white, black, Asian, other; black, non-black)
- Region (US/Canada, Europe, other; US, non-US)
- Phadiatop result (positive, negative)
- Duration of OCS use (<5 years, ≥5 years)
- Post-baseline ADA status (positive, negative) – for reslizumab-treated patients only

Results

Supplementary Table S1: Demographics and baseline clinical characteristics of the prespecified eosinophil subgroups in the Asthma Exacerbation Study (Study I)

	Eosinophil levels 300–<400 cells/ μ L		Eosinophil levels $\geq$ 400 cells/ μ L	
	Placebo	SC reslizumab 110 mg	Placebo	SC reslizumab 110 mg
	(N=42)	(N=48)	(N=188)	(N=185)
Mean (SD) age, years	45.1 (17.1)	48.7 (16.2)	44.8 (17.9)	46.4 (18.0)
Sex, male, n (%)	14 (33)	18 (38)	88 (47)	72 (39)
Mean (SD) weight, kg	81.8 (21.4)	84.7 (19.2)	75.8 (17.4)	76.6 (19.2)
Mean (SD) BMI, kg/m ²	29.3 (7.3)	29.7 (6.7)	27.0 (5.7)	27.9 (6.1)
Mean (SD) FEV ₁ reversibility, %	26.6 (18.9)	21.0 (15.8)	24.1 (21.8)	23.2 (17.4)
Mean (SD) pre-bronchodilator FEV ₁ , L	2.0 (0.8)	2.2 (0.9)	2.1 (0.9)	1.9 (0.8)
Mean (SD) FEV ₁ % predicted	63.3 (19.1)	66.9 (18.4)	65.3 (19.9)	63.7 (18.3)
Mean (SD) ACQ-6 score	2.6 (0.8)	2.7 (0.9)	2.6 (0.8)	2.5 (0.7)
Mean (SD) blood eosinophils, $1 \times 10^9/L^*$	0.34 (0.03)	0.35 (0.03)	0.82 (0.49)	0.90 (0.55)
Phadiatop test, n (%)				
Positive	31 (74)	35 (73)	123 (65)	124 (67)
Missing	2 (5)	1 (2)	10 (5)	3 (2)
Former smoker, n (%)	6 (14)	7 (15)	22 (12)	24 (13)
Mean (SD) age at asthma onset, years	24.1 (21.5)	28.5 (21.1)	28.3 (18.6)	29.1 (19.7)
Mean (SD) time since diagnosis, years	21.1 (15.0)	20.2 (15.5)	16.7 (13.1)	17.4 (13.6)
Mean (SD) number of asthma exacerbations requiring SCS in the past 12 months	2.3 (1.3)	2.3 (0.9)	2.3 (0.7)	2.4 (1.1)
ICS, n (%)	42 (100)	47 (98)	187 (>99)	184 (>99)
High-dose ICS [†]	19 (45)	25 (52)	79 (42)	73 (39)
Medium-dose ICS [†]	22 (52)	21 (44)	100 (53)	107 (58)
LABA, n (%)	40 (95)	46 (96)	178 (95)	177 (96)
OCS, n (%)	1 (2)	3 (6)	14 (7)	12 (6)
Aspirin sensitivity, n (%) [‡]	2 (5)	5 (10)	21 (11)	21 (11)
CRSwNP, n (%) [‡]	0	4 (8)	38 (20)	33 (18)

*Stated baseline eosinophil level reflects the highest value from measurements during screening, run-in, and pre-dose day of randomisation.

[†]High-dose ICS defined as >500 μ g/day fluticasone or equivalent; medium-dose ICS defined as >250– $\leq$ 500 μ g/day fluticasone or equivalent.

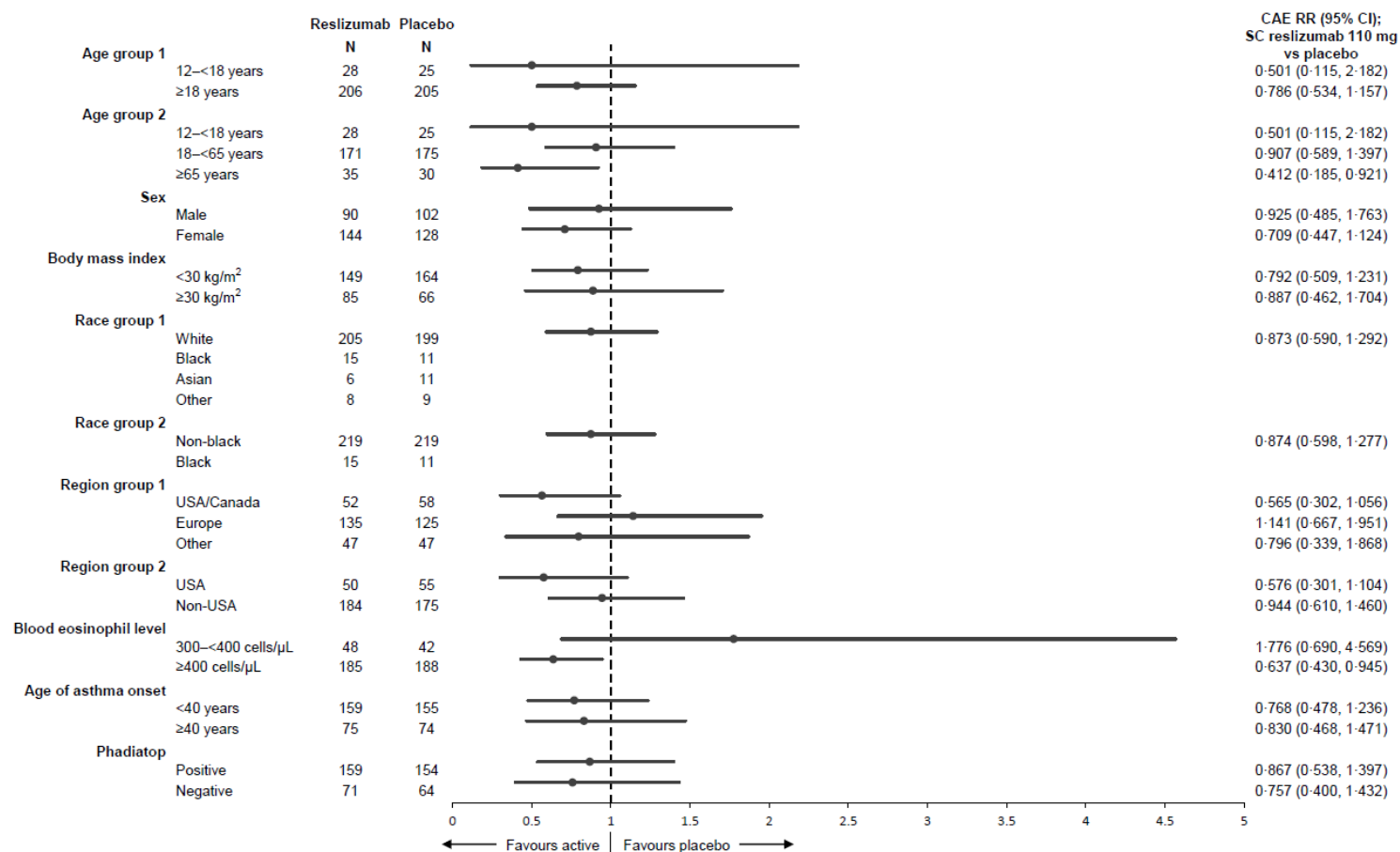
[‡]Self-reported.

ACQ-6=Asthma Control Questionnaire-6. BMI=body mass index. CRSwNP=chronic rhinosinusitis with nasal polyps. FEV₁=forced expiratory volume in 1 second. ICS=inhaled corticosteroid. LABA=long-acting beta agonist. OCS=oral corticosteroid. SC=subcutaneous. SCS=systemic corticosteroids. SD=standard deviation.

Asthma Exacerbation Study (Study I) efficacy outcomes

CAEs

Supplementary Figure S3: CAEs during the 52-week treatment period: Treatment effect by prespecified subgroups (ITT population)

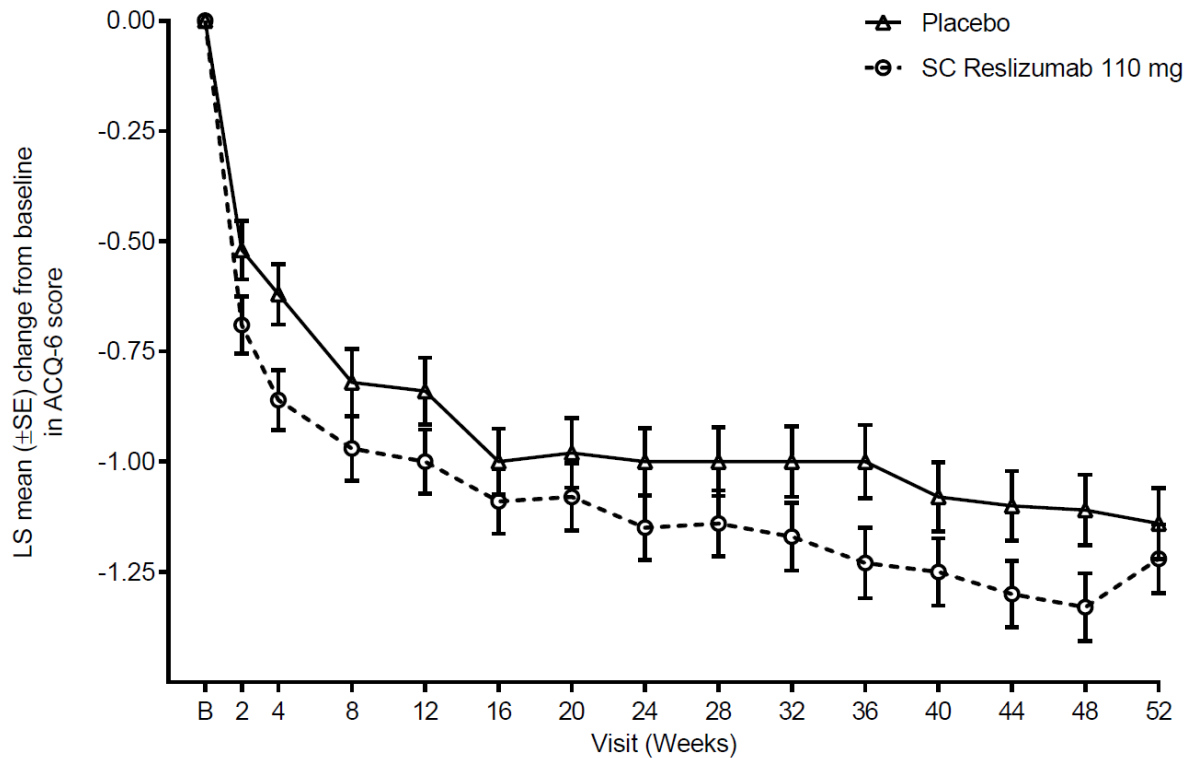


Model results were reported only if there are at least 15 patients contributing to the analysis in each treatment group. Analysis of CAEs excludes exacerbation duration from the offset. BMI=body mass index. CAE=clinical asthma exacerbation. CI=confidence interval. ITT=intention-to-treat. RR=rate ratio. SC=subcutaneous

ACQ-6 score

Overall ACQ-6 scores decreased from baseline to week 52 in both treatment groups in the ITT population (supplementary figure S4); however, ACQ-6 scores were lower for fixed-dose SC reslizumab at all post-baseline timepoints. The least squares mean (LSM) change in ACQ-6 score from baseline to week 52 did not differ for fixed-dose SC reslizumab and placebo: LSM difference -0.09 , 95% CI -0.266 to 0.095 .

Supplementary Figure S4: ACQ-6 overall score: LS mean (SE) change from baseline to each visit by treatment group in the ITT population

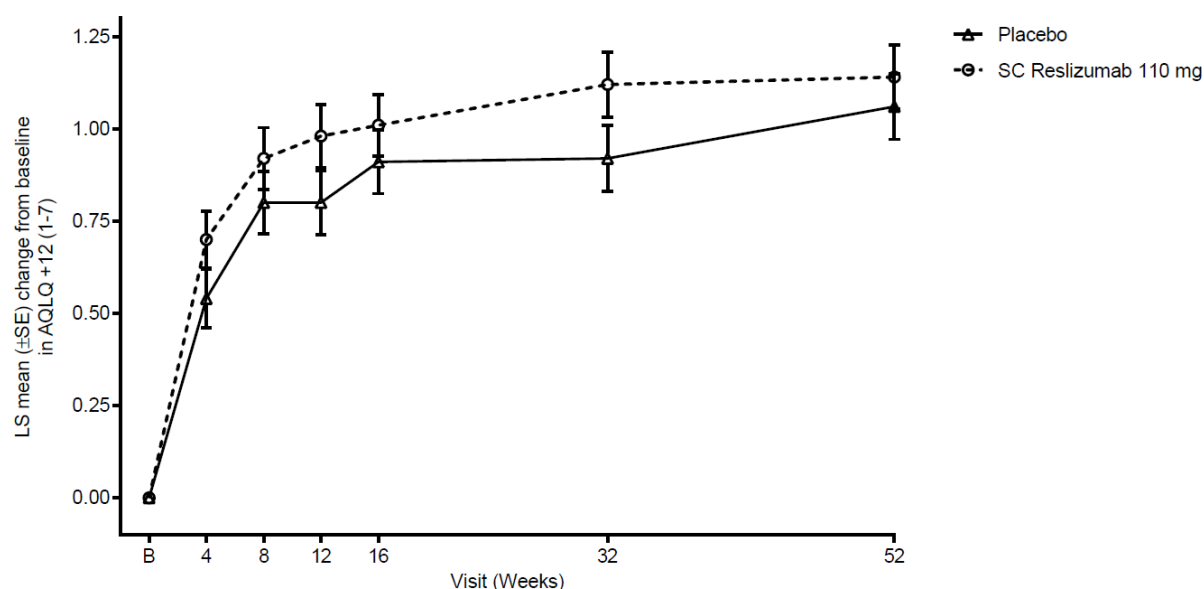


Data are included between the first dose of study drug and the end-of-treatment visit for completed patients and between the first dose of study drug and 4 weeks after the last dose of study drug for patients who discontinued treatment early. Inferential statistics are from a mixed-model repeated measures model with fixed effects for treatment, visit, treatment-by-visit interaction, age group, and blood eosinophil group; baseline value as a covariate; and patient as a random effect. Unstructured covariance was assumed for repeated measures. ACQ-6=Asthma Control Questionnaire-6. ITT=intention-to-treat. LS=least square. SC=subcutaneous. SE=standard error.

AQLQ+12 score

Increases in overall AQLQ+12 scores were observed in both treatment groups (supplementary figure S5). LSM (standard error [SE]) change from baseline in AQLQ+12 scores at 52 weeks was similar for placebo and reslizumab: 1.06 (0.089) versus 1.14 (0.087), respectively; LSM difference 0.08 , 95% CI -0.113 to 0.271 .

Supplementary Figure S5: AQLQ+12 (1–7) overall score: LS mean (SE) change from baseline to each visit by treatment group (ITT population [patients aged 12–70 years])



The analysis of AQLQ+12 is restricted to the subset of the ITT population within the specified age range (12–70 years) at baseline. AQLQ+12=Asthma Quality of Life Questionnaire for patients aged ≥ 12 years. B=baseline. ITT=intention-to-treat. LS=least squares. SC=subcutaneous. SE=standard error.

SGRQ score

At the prespecified timepoint of week 32, the LSM (SE) change from baseline in SGRQ score was -13.1 (1.38) in the placebo group and -16.4 (1.32) in the reslizumab group; LSM difference -3.3 , 95% CI -6.02 to -0.66 . This difference was not sustained at week 52 (data not shown).

Frequency of CAEs requiring hospitalisation/ED visit

Adjusted rates of CAEs requiring hospitalisation/ED visit were similar for reslizumab and placebo. Exacerbations excluding exacerbation duration from the offset: reslizumab 0.05 versus placebo 0.05 ; CAE RR 0.94 , 95% CI 0.430 to 2.069 (supplementary table S2).

Frequency of Moderate Asthma Exacerbations

The mean frequencies of moderate asthma exacerbations were 0.1 for both groups; the numbers of patients (%) with at least one moderate asthma exacerbation were 27 (12%) for the placebo group and 25 (11%) for the reslizumab group.

Supplementary Table S2: Frequency of CAEs requiring hospitalisation and/or ED visits during the 52-week treatment period (ITT population)

	Placebo (N=230)	SC reslizumab 110 mg (N=234)	CAE RR reslizumab – placebo (95% CI)
Analysis: excluding exacerbation duration from the offset*			
Adjusted CAE rate (95% CI)	0.05 (0.016 – 0.169)	0.05 (0.015 – 0.158)	0.94 (0.430 – 2.069)

*For this analysis, the offset variable is calculated as the logarithm of treatment duration minus the summed duration of exacerbations during the treatment period. Adjusted CAE rates, CAE RR, and 95% CIs are based on negative binomial regression model adjusted for stratification factors (age group, blood eosinophil group) and number of prior exacerbations, and an offset variable. CAE=clinical asthma exacerbation. CI=confidence interval. ED=emergency department. ITT=intention-to-treat. RR=rate ratio. SC=subcutaneous.

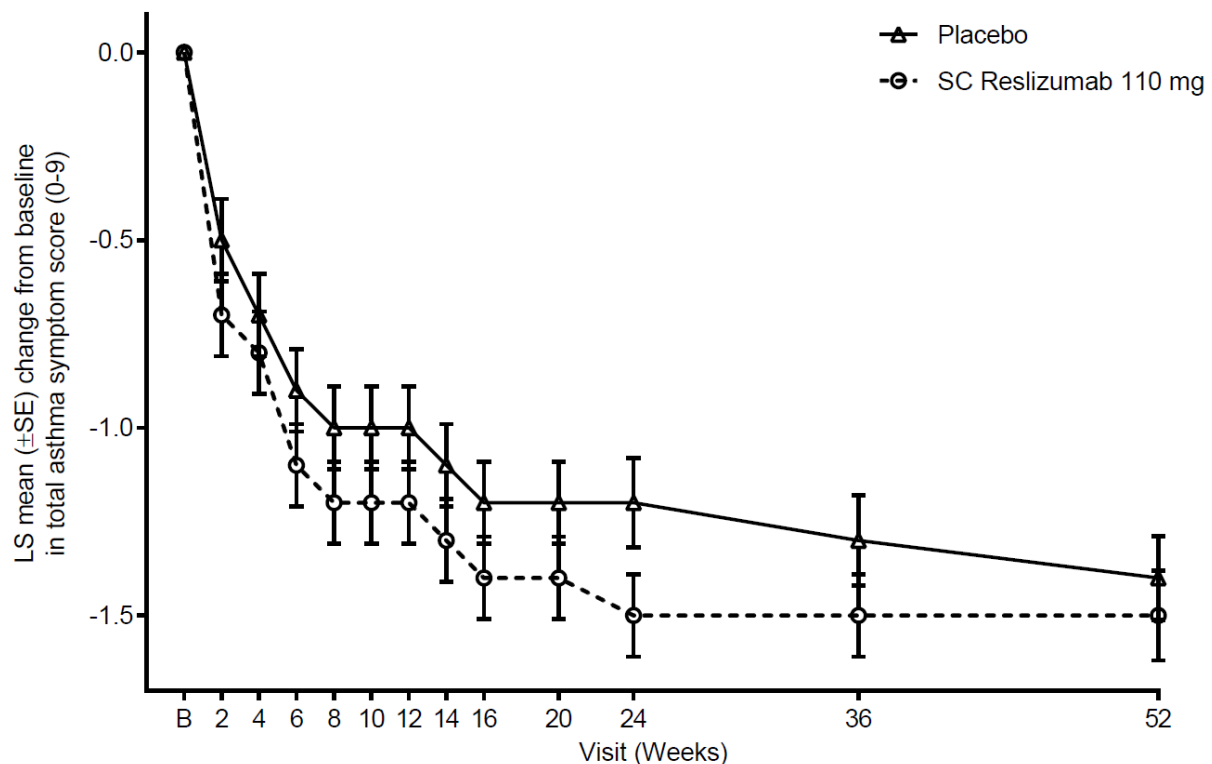
Probability of having a CAE

The Kaplan-Meier estimate of the probability of not experiencing a CAE by week 52 was 0·66 (95% CI 0·59–0·72) for the placebo group and 0·66 (95% CI 0·59–0·71) for the reslizumab group: HR 0·97, 95% CI 0·708 to 1·335.

Asthma symptom assessment

Asthma symptom scores from baseline decreased at each visit during the study for both treatment groups (supplementary figure S6). The LSM (SE) change in asthma symptom score at week 52 was –1·4 (0·12) in the placebo group and –1·5 (0·12) in the reslizumab group: LSM difference –0·1, 95% CI –0·35 to 0·15.

Supplementary Figure S6: Total asthma symptom score (0–9): LS mean (SE) change from baseline to each week by treatment group (ITT population)



B=baseline. ITT=intention-to-treat. LS=least squares. SC=subcutaneous. SE=standard error.

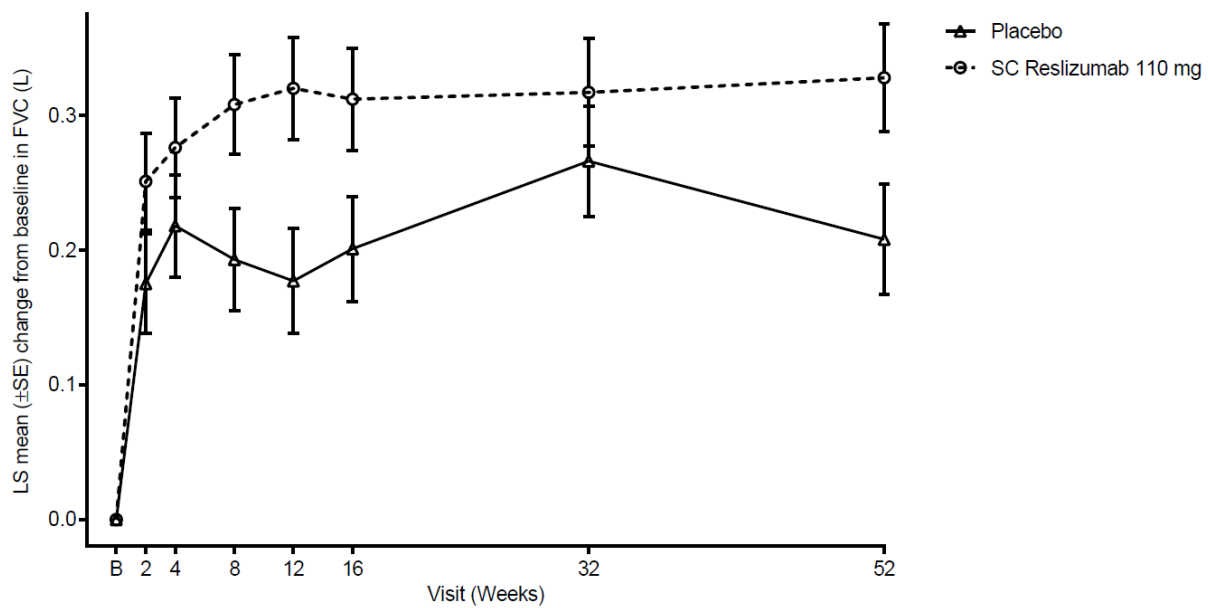
Percentage of asthma control days

The mean percentage of asthma control days over the 52 weeks of treatment was 6·7 for the placebo group and 7·6 for the reslizumab group. The LSM (SE) change in percentage of asthma control days at week 52 was 7·1 (1·27) in the placebo group and 8·0 (1·24) in the reslizumab group: LSM difference 0·9, 95% CI –1·52 to 3·27.

Change in pre-bronchodilator FVC

The LSM changes from baseline for pre-bronchodilator FVC for reslizumab were numerically higher than placebo at all timepoints (supplementary figure S7).

Supplementary Figure S7: Pre-bronchodilator FVC: LS mean (SE) change from baseline to each visit by treatment group (ITT population)

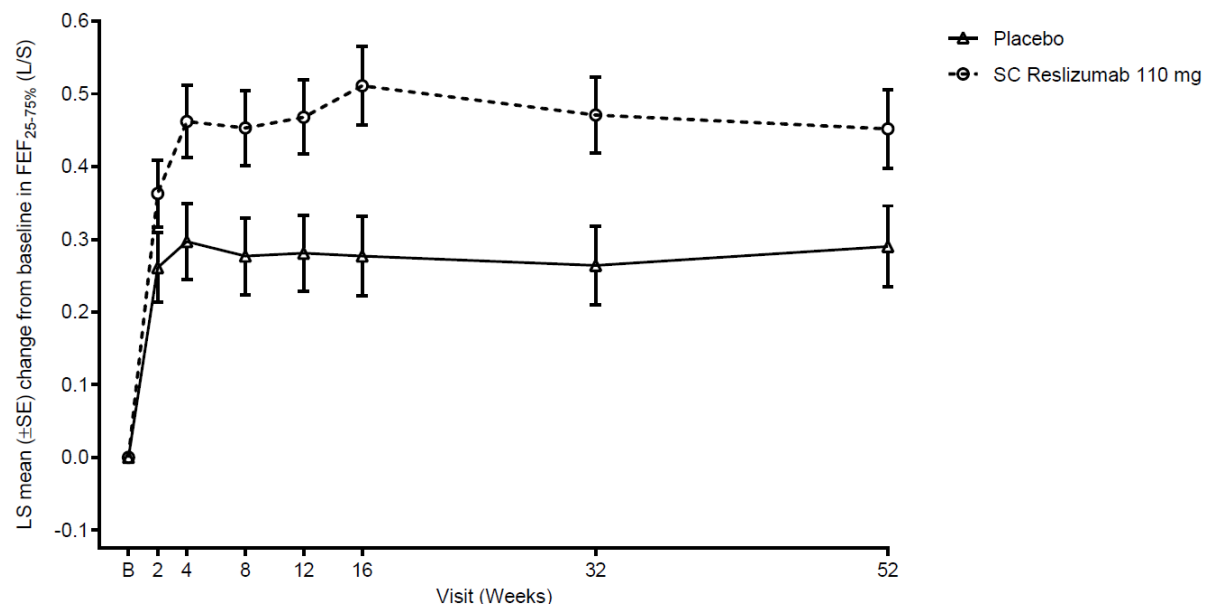


B=baseline. FVC=forced vital capacity. ITT=intention-to-treat. LS=least squares. SC=subcutaneous. SE=standard error.

Change in pre-bronchodilator $FEF_{25-75\%}$

The LSM changes from baseline for pre-bronchodilator $FEF_{25-75\%}$ for reslizumab were numerically higher than placebo at all timepoints (supplementary figure S8).

Supplementary Figure S8: Pre-bronchodilator $FEF_{25-75\%}$: LS mean (SE) change from baseline to each visit by treatment group (ITT population)



B=baseline. $FEF_{25-75\%}$ =forced expiratory flow at 25-75% of forced vital capacity. ITT=intention-to-treat. LS=least squares. SC=subcutaneous. SE=standard error.

OCS-Sparing Study (Study II) efficacy outcomes

Categorised percent OCS dose reduction (five-level response) at weeks 20–24

Supplementary Table S3: Analyses of categorised percent OCS dose reduction (five-level response) at weeks 20–24 (PP population)

	Placebo	SC reslizumab 110 mg
Categorised percent OCS dose reduction (five-level response) at weeks 20–24, n (%)*		
Weeks 20–24, N	77	78
90–100%	19 (25)	14 (18)
75–<90%	4 (5)	8 (10)
50–<75%	6 (8)	10 (13)
>0–<50%	5 (6)	6 (8)
No decrease [†]	43 (56)	40 (51)
OR reslizumab vs placebo (95% CI)	1·07 (0·585–1·975)	
P value	0·82	

*All data were included; missing data were included as non-responders.

[†]No decrease in OCS, loss of asthma control during weeks 20–24, or discontinuation from study drug.

OR, 95% CIs, and p value were based on proportional odds model adjusted for treatment, stratification factors (age group and OCS dose group), duration of OCS use, and baseline value.

CI=confidence interval. OR=odds ratio. OCS=oral corticosteroid. PP=per protocol. SC=subcutaneous.

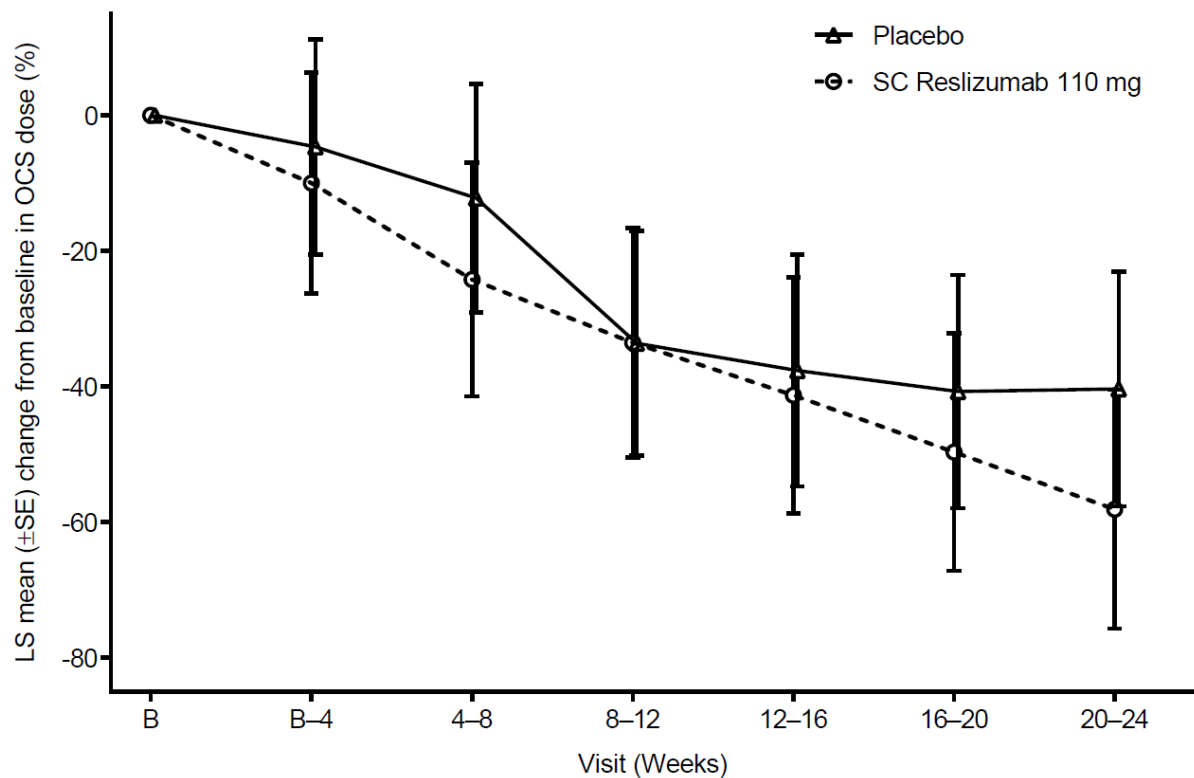
A summary of the analysis of percent reduction in daily OCS dose during weeks 20–24 by prespecified subgroup is provided below. Model results are reported only if there were at least 15 patients contributing to the analysis in each treatment group; otherwise, only the descriptive statistics are displayed.

- There was one patient in the placebo group who was in the 12–<18 years of age subgroup (15 years of age). This patient reduced OCS use by 90–100%. The reslizumab versus placebo OR was not calculated for patients 12–<18 years of age. The reslizumab versus placebo OR for patients ≥18 years of age was 1·23 (95% CI 0·702 to 2·157)
- The reslizumab versus placebo OR was 0·80 (95% CI 0·298 to 2·142) for male patients and 1·58 (95% CI 0·786 to 3·179) for female patients
- The reslizumab versus placebo OR was 1·24 (95% CI 0·680 to 2·277) for white patients. The reslizumab versus placebo OR was not calculated for black, Asian, and other patients
- The reslizumab versus placebo OR was not calculated for patients in the USA/Canada. The reslizumab versus placebo OR was 0·87 (95% CI 0·421 to 1·810) for patients in Europe and 2·09 (95% CI 0·659 to 6·654) in other geographical regions
- The reslizumab versus placebo OR was 1·10 (95% CI 0·577 to 2·095) for patients receiving OCS doses ≤10 mg at baseline and 2·60 (95% CI 0·740 to 9·115) in patients receiving OCS doses >10 mg at baseline
- The reslizumab versus placebo OR was 1·14 (95% CI 0·617 to 2·100) for patients entering the study with a duration of OCS use <5 years and 2·92 (95% CI 0·576 to 14·772) for patients entering the study with a duration of OCS use ≥5 years
- The reslizumab versus placebo OR was 2·70 (95% CI 1·069 to 6·845) for patients with a negative Phadiatop test result at baseline and 0·79 (95% CI 0·370 to 1·698) in patients with a positive Phadiatop test at baseline

Percent change in OCS dose at weeks 20–24

A decrease in OCS dose was observed in both treatment groups over the treatment period (supplementary figure S9). The percent change (LSM) from DoR/baseline in OCS dose at weeks 20–24 was -40.34% for the placebo group and -58.08% for the reslizumab group: LSM difference -17.75% , 95% CI -38.986 to 3.494 .

Supplementary Figure S9: OCS dose: LS mean (SE) percent change from baseline to each visit by treatment group (ITT population)



B=baseline. ITT=intention-to-treat. LS=least squares. OCS=oral corticosteroid. SC=subcutaneous. SE=standard error.

CAE rates

When exacerbation duration was excluded from the offset variable, the adjusted CAE rate was 1.86 (95% CI 1.283 to 2.682) with placebo and 1.51 (95% CI 1.052 to 2.177) with reslizumab; CAE RR 0.82, 95% CI 0.504 to 1.321.

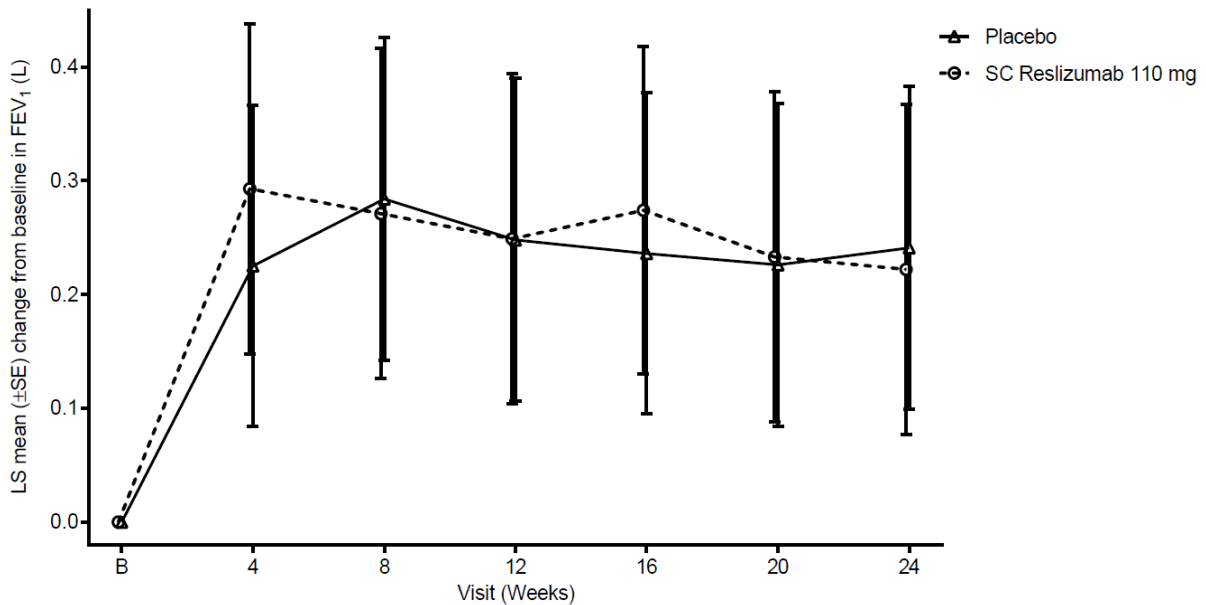
Probability of having a CAE by week 24

The Kaplan-Meier estimate of the probability of not experiencing a CAE by week 24 was 0.52 (95% CI 0.41 to 0.62) for the placebo group and 0.57 (95% CI 0.46 to 0.67) for the reslizumab group; HR 0.80, 95% CI 0.519 to 1.247.

Pre-bronchodilator FEV₁

Increases in pre-bronchodilator FEV₁ from DoR/baseline to week 24 or early withdrawal were similar for both treatment groups (supplementary figure S10). LSM (SE) change from baseline was 0·241 (0·142) L with placebo and 0·222 (0·145) L with reslizumab; LSM difference –0·019 L, 95% CI –0·122 to 0·085.

Supplementary Figure S10: Pre-bronchodilator FEV₁: LS mean (SE) change from baseline to each visit by treatment group (ITT population)

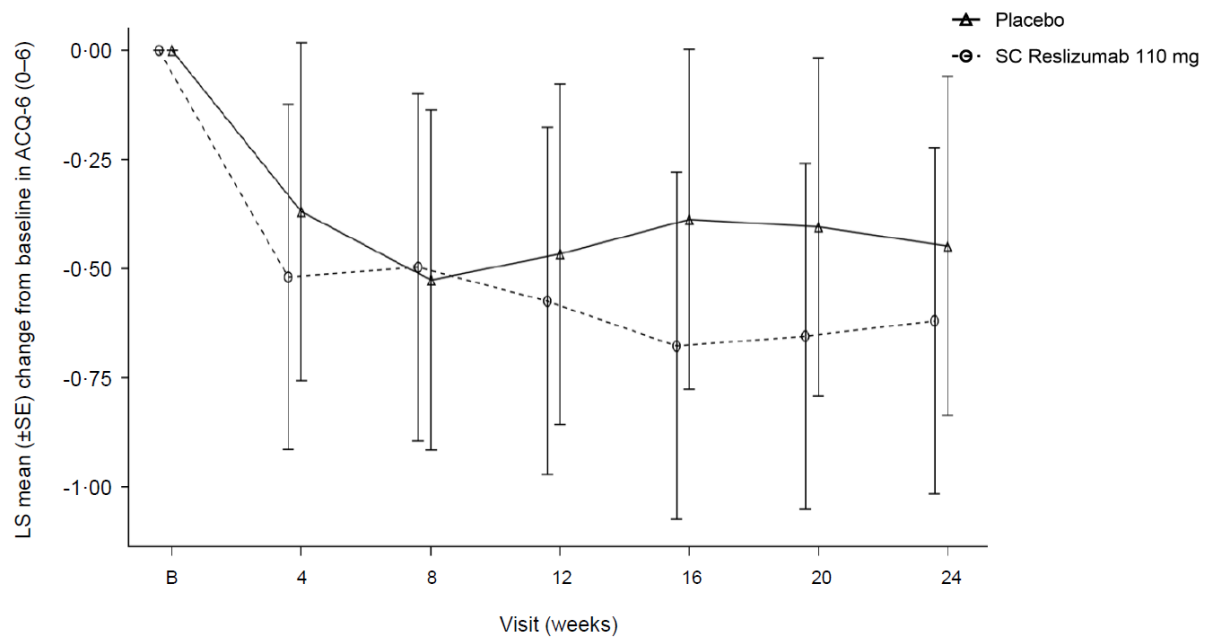


B=baseline. FEV₁=forced expiratory volume in 1 second. ITT=intention-to-treat. LS=least squares. SC=subcutaneous. SE=standard error.

ACQ-6 score

Overall ACQ-6 scores decreased in both treatment groups from DoR/baseline to week 24 or early withdrawal (supplementary figure S11). LSM (SE) change in ACQ-6 score at week 24 was –0·45 (0·389) in the placebo group and –0·62 (0·397) in the reslizumab group; LSM difference –0·17, 95% CI –0·458 to 0·114.

Supplementary Figure S11: ACQ-6 score: LS mean (SE) change from baseline to each visit by treatment group (ITT population)

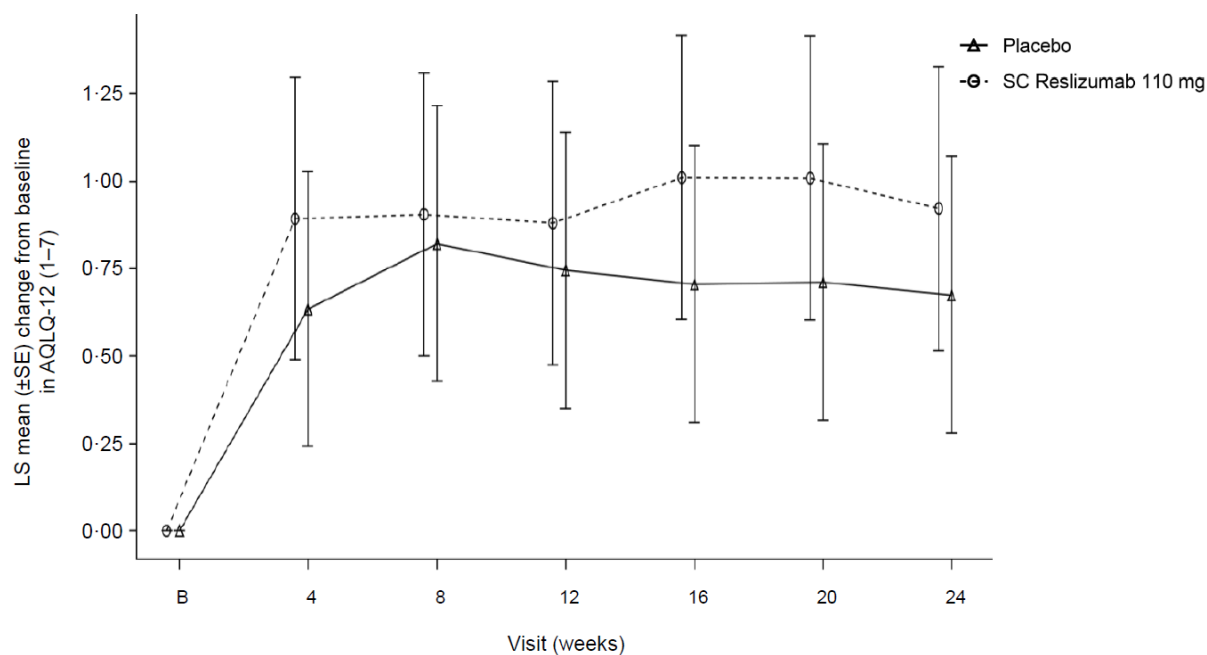


ACQ-6=Asthma Control Questionnaire-6. B=baseline. ITT=intention-to-treat. LS=least squares. SC=subcutaneous. SE=standard error.

AQLQ+12 score

An increase in overall AQLQ+12 score was observed in both treatment groups during the study (supplementary figure S12). LSM (SE) change in AQLQ+12 score from DoR/baseline to week 24 was 0·67 (0·396) in the placebo group and 0·92 (0·407) in the reslizumab group: LSM difference 0·25, 95% CI –0·056 to 0·551.

Supplementary Figure S12: AQLQ+12 overall score: LS mean (SE) change from baseline to each visit by treatment group (ITT population [patients 12–70 years of age])



The analysis of AQLQ+12 is restricted to the subset of the ITT population within the specified age range (12–70 years) at baseline. AQLQ+12=Asthma Quality of Life Questionnaire for patients aged ≥12 years. B=baseline. ITT=intention-to-treat. LS=least squares. SC=subcutaneous. SE=standard error.

Drug exposure

Supplementary Table S4: Asthma Exacerbation Study (Study I): mean serum reslizumab concentration data at each visit by age group (pre-dose trough concentrations) (safety population)

Timepoint	12–<18 years of age	≥18 years of age	Total
Week 4			
n	28	203	231
Mean (SD), µg/mL	5.26 (2.25)	3.32 (1.32)	3.56 (1.59)
Week 8			
n	26	200	226
Mean (SD), µg/mL	8.54 (3.67)	5.09 (2.08)	5.48 (2.56)
Week 12			
n	27	198	225
Mean (SD), µg/mL	9.31 (4.26)	5.54 (2.45)	6.00 (2.98)
Week 16			
n	28	196	224
Mean (SD), µg/mL	10.49 (3.58)	6.01 (2.88)	6.57 (3.32)
Week 20			
n	27	191	218
Mean (SD), µg/mL	10.32 (4.83)	6.11 (2.85)	6.63 (3.44)
Week 32			
n	28	190	218
Mean (SD), µg/mL	10.16 (5.17)	6.353 (2.92)	6.842 (3.52)
Week 48			
n	26	181	207
Mean (SD), µg/mL	9.24 (5.79)	6.15 (3.45)	6.54 (3.94)
Week 52			
n	25	184	209
Mean (SD), µg/mL	11.07 (4.68)	6.37 (3.38)	6.93 (3.87)
Week 64 follow-up			
n	17	80	97
Mean (SD), µg/mL	1.48 (1.09)	1.13 (1.04)	1.19 (1.05)

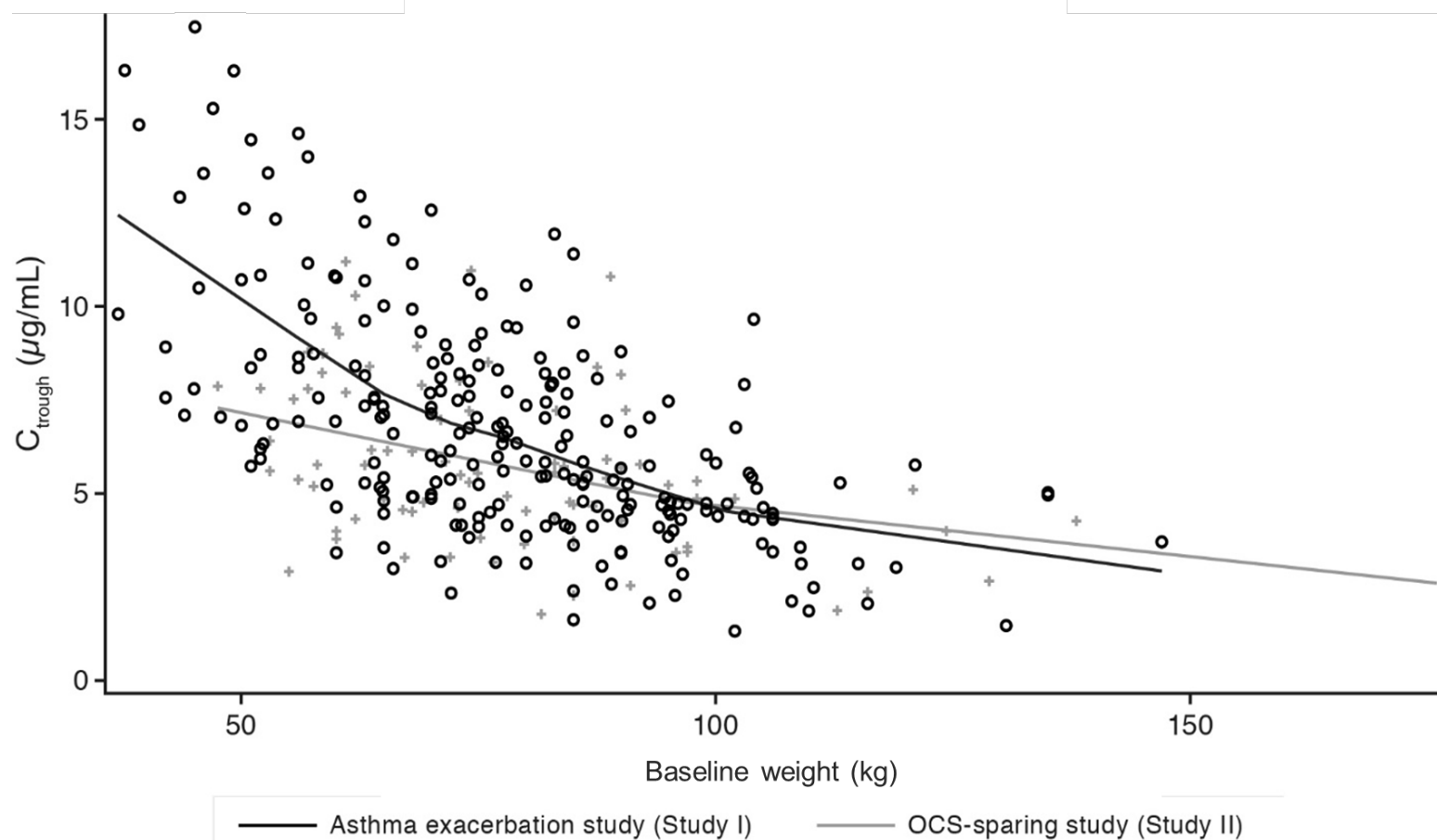
SD=standard deviation.

Supplementary Table S5: OCS-Sparing Study (Study II): mean serum reslizumab concentration data at each visit (pre-dose trough concentrations) (safety population)

Timepoint		
Week 4	n	85
	Mean (SD), µg/mL	3.09 (1.25)
Week 8	n	84
	Mean (SD), µg/mL	4.77 (1.91)
Week 12	n	85
	Mean (SD), µg/mL	5.15 (2.07)
Week 16	n	83
	Mean (SD), µg/mL	5.61 (2.31)
Week 20	n	83
	Mean (SD), µg/mL	5.33 (2.62)
Week 24	n	83
	Mean (SD), µg/mL	5.65 (2.66)
Week 32 follow-up	n	64
	Mean (SD), µg/mL	1.03 (0.73)

OCS=oral corticosteroid. SD=standard deviation.

Supplementary Figure S13: Correlation between body weight and trough reslizumab concentrations in the Asthma Exacerbation Study (Study I) and OCS-Sparing Study (Study II)



C_{trough} =trough reslizumab concentration ($\mu\text{g/mL}$). OCS=oral corticosteroid.

Safety

Six potential hypersensitivity cases occurred in both studies. In Study I, there were five events in the placebo group (drug hypersensitivity to concomitant medications, food/supplement allergy, bronchospasm, urticaria, unknown allergic reaction urticaria/hives) and one event in the SC reslizumab group (unknown allergic reaction urticaria/hives) which was not considered related to reslizumab and did not lead to treatment discontinuation. In Study II, there were two hypersensitivity AEs in the placebo group (pruritus generalised and urticaria) and four in the SC reslizumab group (drug hypersensitivity to concomitant medications, food/supplement allergy, allergy to arthropod bite) which were not considered related to reslizumab and which did not lead to treatment discontinuation.

There were no clinically meaningful trends in mean changes from baseline for clinical laboratory variables in either study, except for blood eosinophil levels. Shifts in clinical laboratory values from the normal range at baseline to outside the normal range occurred with similar frequency in the placebo and reslizumab treatment groups. In both studies, there were no clinically meaningful trends in changes from baseline for any vital signs variables, physical examination findings, or ECG results.