Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies

J Mark FitzGerald, Eugene R Bleecker, Andrew Menzies-Gow, James G Zangrilli, Ian Hirsch, Paul Metcalfe, Paul Newbold, Mitchell Goldman

Summary

Background **Benralizumab is an anti-eosinophilic, anti-interleukin-5 receptor α monoclonal antibody that has been shown to significantly reduce asthma exacerbations and improve lung function for patients with severe, uncontrolled asthma. We further explored the efficacy of benralizumab for patients with different baseline blood eosinophil thresholds and exacerbation histories.**

Methods **This study is a pooled analysis of the results from the randomised, double-blind, placebo-controlled SIROCCO (NCT01928771) and CALIMA (NCT01914757) phase 3 studies. In these studies, patients with severe, uncontrolled asthma were randomly assigned (1:1:1) to receive subcutaneous benralizumab 30 mg, either every 4 weeks or every 8 weeks (with first three doses given every 4 weeks), or placebo every 4 weeks. The primary endpoint was annual exacerbation rate (AER) ratio versus placebo, analysed by baseline eosinophil counts (≥0, ≥150, ≥300, or ≥450 cells per μL) and by number of exacerbations (two *vs* three or more) during the year before enrolment. The analyses were done in accordance with the intention-to-treat principle.**

Findings **Of 2295 patients, 756 received benralizumab every 4 weeks, 762 received benralizumab every 8 weeks, and 777 patients received placebo. AER among patients with baseline blood eosinophil counts of at least 0 cells per μL was 1·16 (95% CI 1·05–1·28) in patients who received placebo versus 0·75 (0·66–0·84) in patients who received benralizumab every 8 weeks (rate ratio 0·64, 0·55–0·75; p<0·0001). In patients who received benralizumab every 4 weeks who had eosinophil counts of 0 or more cells per μL, AER was 0·73 (0·65–0·82); rate ratio versus placebo was 0·63 (0·54–0·74; p<0·0001). The extent to which exacerbation rates were reduced increased with increasing blood eosinophil thresholds and with greater exacerbation history in patients in the 4-weekly and 8-weekly benralizumab groups. Greater improvements in AER were seen with benralizumab compared with placebo for patients with a combination of high blood eosinophil thresholds and a history of more frequent exacerbations.**

Interpretation **These results will help to guide clinicians when they are deciding whether to use benralizumab to treat patients with severe, uncontrolled, eosinophilic asthma.**

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Introduction

Despite the prescription of high-dosage inhaled corticosteroids in combination with a second controller drug (including oral corticosteroids), severe asthma often remains uncontrolled.[1] Historical estimates suggest that up to 10% of the more than 315 million people worldwide with asthma have severe or uncontrolled disease.[2,3] Patients with severe, uncontrolled asthma have a high disease burden, reduced health-related quality of life, and increased health-care resource use and costs, and are at risk of severe asthma exacerbations.[4–6] Thus, there is an unmet need for additional therapeutic options.[4]

Eosinophilic inflammation is present in about half of patients with asthma and is associated with increased disease severity, exacerbation frequency, and symptom burden, as well as decreased lung function.[7–9] Consequently, therapeutic approaches that target and reduce eosinophilic inflammation selectively with anti-eosinophilic and anti-interleukin-5 monoclonal antibodies have been shown to be efficacious in reducing exacerbations for patients with evidence of eosinophilic inflammation, as measured by baseline blood eosinophil count.[10–15] An understanding of the relationship between blood eosinophil counts (and other baseline disease state characteristics) and response to treatment is necessary to help to identify which patients are most likely to benefit from these novel therapies.

Benralizumab is a humanised, afucosylated, anti-interleukin-5 receptor α monoclonal antibody that induces direct, rapid, and nearly complete depletion of eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity, an apoptotic process of eosinophil elimination involving natural killer cells.[16,17] In combination with high-dosage inhaled corticosteroids plus long-acting β_2 agonists (LABAs), this anti-eosinophilic monoclonal antibody significantly reduced asthma exacerbations and improved disease control for

Research in context

Evidence before this study

We searched PubMed for English-language clinical trial reports on the use of biologicals that target interleukin 5 or the interleukin-5 receptor to treat people with asthma published from Jan 1, 2007, to May 31, 2017. We used the search terms "asthma" AND "interleukin 5" AND "antibody;" as well as the independent terms "benralizumab;" "mepolizumab;" and "reslizumab". The search yielded 26 results, including four multicentre, randomised, double-blind, placebo-controlled phase 3 trials of benralizumab for patients with asthma published in 2016–17, three of which were for patients with severe, uncontrolled asthma with eosinophilic inflammation. In these three phase 3 studies, benralizumab significantly reduced the annual exacerbation rate, increased lung function, improved asthma symptoms, and reduced the need for oral corticosteroid therapy relative to placebo, while completely depleting blood eosinophil counts. In a pooled analysis of data from two of these studies, benralizumab demonstrated efficacy for patients with severe asthma and blood eosinophil counts greater than or equal to 150 cells per µL.

Added value of this study

Our results expand the potential population of patients with severe, uncontrolled asthma with eosinophilic inflammation who might be responsive to benralizumab treatment. Patients with blood eosinophil counts greater than or equal to 0 cells per µL who were treated with benralizumab every 4 or 8 weeks for 48–56 weeks had reduced annual exacerbation rate, increased forced expiratory volume in 1 s, and improved asthma symptoms compared with placebo recipients. Furthermore, patients with a history of more frequent exacerbations had greater efficacy with benralizumab treatment than did patients with fewer exacerbations.

Implications of all the available evidence

Our findings illustrate the limitations of clinicians' and regulatory agencies' use of only blood eosinophil counts greater than or equal to 300 cells per µL to identify patients with eosinophilic inflammation and, hence, probable responders to benralizumab treatment for severe, uncontrolled asthma. If available, other biomarkers of eosinophilic inflammation, along with additional clinical characteristics, such as exacerbation history, should be taken into account alongside blood eosinophil counts in decisions about whether a patient might respond to benralizumab treatment.

patients with severe, uncontrolled asthma and blood eosinophil counts of at least 300 cells per µL in two phase 3 trials, SIROCCO (NCT01928771)[10] and CALIMA (NCT01914757).[11] In these studies, benralizumab was well tolerated and significantly reduced exacerbations by up to 51%, increased lung function, and improved symptom control.[10,11] More recently, add-on benralizumab was reported to allow significant reduction of oral corticosteroid dosage while maintaining asthma control for patients with asthma dependent on oral corticosteroids.[18]

In this study, we analysed the pooled efficacy results from the SIROCCO and CALIMA studies to better understand the relationship between the clinical efficacy of benralizumab and baseline blood eosinophil counts and exacerbation history. The purpose of this analysis was to help clinicians to develop management strategies for the use of benralizumab to treat patients with severe, uncontrolled, eosinophilic asthma.

Methods

Study design and participants

SIROCCO and CALIMA were randomised, double-blind, parallel-group, placebo-controlled, phase 3 studies that enrolled patients at 677 (303 in SIROCCO and 374 in CALIMA) clinical research centres in Africa, Asia, Europe, North America, and South America.[10,11] The designs of the two studies were similar, consisting of an enrolment visit (week –4), a 4-week screening and run-in phase, randomisation (week 0), a treatment period from weeks 0 to 48 (SIROCCO) or 0 to 56 (CALIMA), and a final follow-up visit 4 weeks after the end of the treatment period.

The enrolment criteria for the studies have been published previously.[10,11] Briefly, male and female patients aged 12–75 years who weighed at least 40 kg and had physician-diagnosed asthma that required treatment with high-dosage inhaled corticosteroids plus LABAs (as well as medium-dosage inhaled corticosteroids in CALIMA) for at least 12 months prior to enrolment were included in the study. Patients had to have had at least two asthma exacerbations within 12 months before the date of enrolment that required systemic corticosteroid therapy or a temporary increase in their usual maintenance dosages of oral corticosteroids. Patients needed to have had documented treatment with inhaled corticosteroids and LABAs, with or without oral corticosteroids and additional asthma controllers for at least 3 months before enrolment. The studies were done in accordance with the Declaration of Helsinki, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, and the Good Clinical Practice guidelines, and the ethics committee at each participating site.

Treatments

In both studies, adult patients from all regions and adolescent patients from outside the European Union

	SIROCCO (n=1204)	CALIMA (high-dosage inhaled corticosteroids; n=1091)
Age (years)	48·8 (14·3)	50·2 (13·5)
Age group (years)		
≥12 to <18	53 (4%)	26 (2%)
≥18 to 50	498 (41%)	448 (41%)
≥50 to <65	510 (42%)	466 (43%)
≥65 to 75	143 (12%)	151 (14%)
Sex		
Female	796 (66%)	676 (62%)
Male	408 (34%)	415 (38%)
Race		
White	874 (73%)	939 (86%)
Black or African American	46 (4%)	33 (3%)
Asian	154 (13%)	118 (11%)
Other*	130 (11%)	1 (<1%)
Ethnic group		
Hispanic or Latino	230 (19%)	235 (22%)
Not Hispanic or Latino	974 (81%)	856 (78%)
Body-mass index (kg/m²)	28·8 (6·8)	29·1 (6·7)
Missing data	2	1
Baseline blood eosinophil count (cells per µL)	379 (0–3440)	380 (0–4494)
Missing data	14	12
Prebronchodilator FEV_1 (L)	1·665 (0·573)	1·741 (0·617)
Missing data	14	11
Prebronchodilator FEV_1 (percentage predicted normal)	56·7 (15%)	57·6 (15%)
Missing data	14	11
Prebronchodilator FEV_1/FVC ratio	61 (13)	60 (13)
Missing data	14	11
Reversibility	19·3% (−26·4 to 156·8)	19·8% (−24·3 to 813·8)
Missing data	73	31
ACQ-6 score	2·81 (0·93)	2·76 (0·93)
Time since asthma diagnosis (years)	14·76 (1·1 to 72·4)	16·13 (1·1 to 69·9)
(Table 1 continues in next column)		
(Continued from previous column)		
Number of exacerbations in the past 12 months	2·9 (1·69)	2·7 (1·62)
Two	749 (62%)	695 (64%)
Three	219 (18%)	238 (22%)
Four or more	236 (20%)	156 (14%)
Number of exacerbations resulting in emergency department visit in the past 12 months	0·3 (0·86)	0·3 (0·93)
Patients with one or more exacerbations resulting in an emergency department visit in the past 12 months	184 (15%)	148 (14%)
Number of exacerbations resulting in hospital admission in the past 12 months	0·4 (0·78)	0·3 (0·66)
Patients with one or more exacerbations resulting in hospital admission in the past 12 months	305 (25%)	188 (17%)
AQLQ(S)+12 score	3·9 (1·0)	3·9 (1·0)
Missing data	49	30
Diagnosis of allergic rhinitis	646 (54%)	593 (54%)
Nasal polyposis	237 (20%)	180 (16%)
Atopic (based on Phadiatop test)	705 (59%)	670 (61%)
Missing data	22	15
History of omalizumab treatment	88 (7%)	35 (3%)
Missing data	5	5
Maintenance oral corticosteroid use	196 (16%)	113 (10%)
Smoker†	236 (20%)	249 (23%)
Nicotine pack-years	5·0 (2·8)	4·7 (3·8)

Data are n (%), mean (SD), or median (minimum to maximum) unless noted otherwise. FVC=forced vital capacity. ACQ-6=Asthma Control Questionnaire 6. AQLQ(S)+12=Standardized Asthma Quality of Life Questionnaire for 12 years and older. *Included electronic case report form race categories "Native Hawaiian or other Pacific Islander", "American Indian or Alaska Native", and "Other". †Current or former smoker.

***Table 1*: Patient baseline characteristics (full analysis set)**

(EU) were randomised 1:1:1 to receive subcutaneous benralizumab 30 mg once every 4 weeks, subcutaneous benralizumab 30 mg once every 4 weeks for the first three doses then once every 8 weeks for the remainder of the treatment period, or placebo every 4 weeks. Treatment was double-blind and lasted for 48 weeks in SIROCCO and 56 weeks in CALIMA. Adolescent patients in the EU were randomised 1:1 to receive subcutaneous benralizumab 30 mg every 8 weeks or placebo to accommodate a request by the Paediatric Committee at the European Medicines Agency to limit the drug burden for adolescents. In both studies, patients were stratified by baseline blood eosinophil counts as having counts of 300 or more cells per µL or counts of less than 300 cells per µL, and were recruited at a ratio of approximately 2:1, respectively.

Outcomes

The original primary efficacy variable for both studies was the annual exacerbation rate (AER) at week 48 (SIROCCO) or week 56 (CALIMA). For both studies, the primary analysis set included patients receiving high-dosage inhaled corticosteroids plus LABA who had baseline blood eosinophil counts of at least 300 cells per µL. An exacerbation was defined as a worsening of asthma that

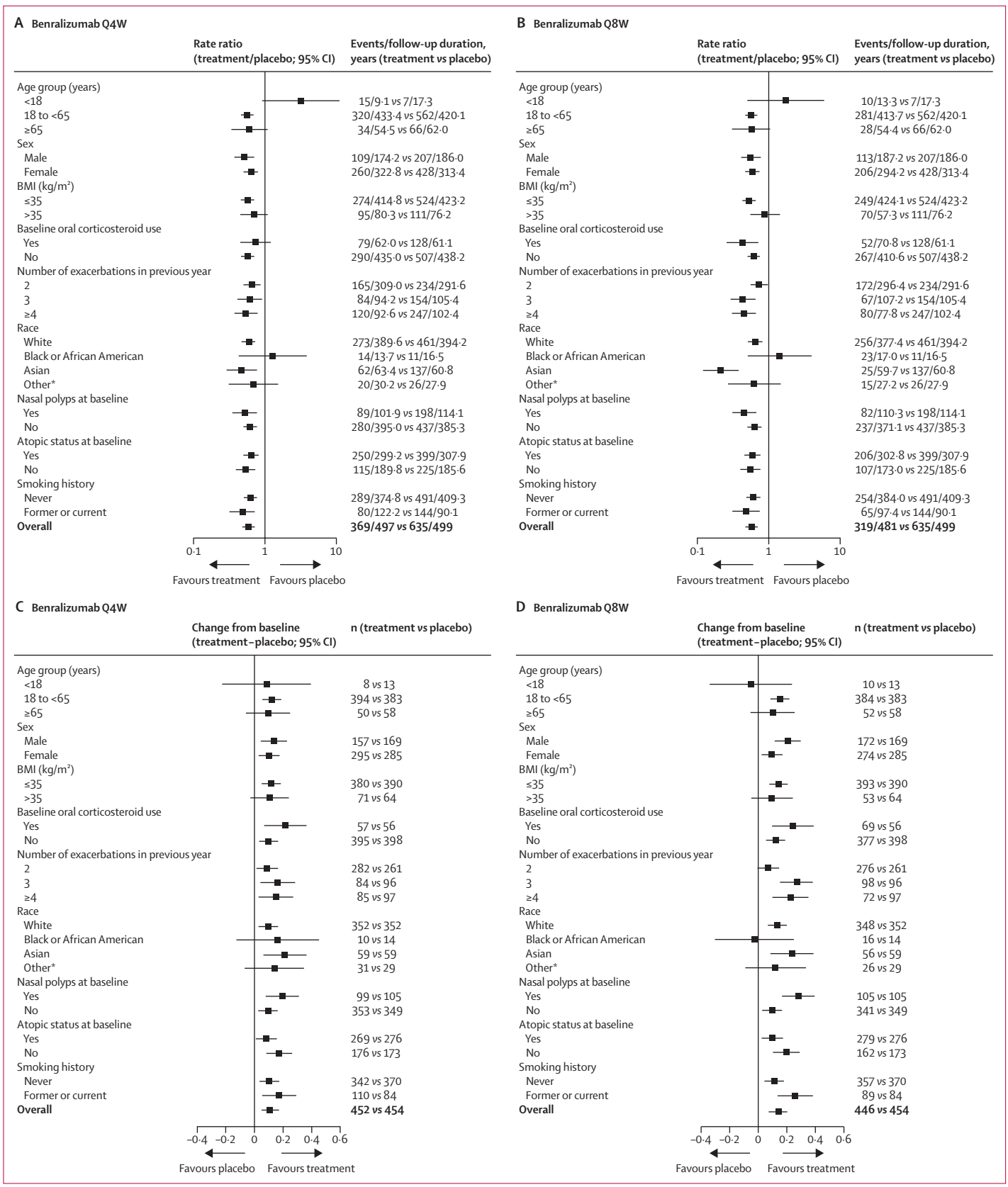

Figure 1: **Subgroup analysis of the effects of benralizumab treatment on AER and FEV_1**
Data are from the intention-to-treat population from the high-dosage inhaled corticosteroid treatment cohorts from the SIROCCO and CALIMA studies (baseline blood eosinophils ≥300 cells per μL; full analysis set, pooled). We analysed AER (A, B) using a negative binomial model. Change in prebronchodilator FEV_1 (L) score (C, D) was from baseline to the end of treatment (48 weeks in SIROCCO and 56 weeks in CALIMA). AER=annual asthma exacerbation rate. BMI=body-mass index. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses every 4 weeks). *Included electronic case report form race categories "Native Hawaiian or other Pacific Islander", "American Indian or Alaska Native", and "Other".

led to one of the following: use of systemic corticosteroids (or temporary increase in a stable oral corticosteroid background dosage) for at least 3 days or a single depot-injectable dose of corticosteroid; an asthma-related emergency department or urgent care visit (duration <24 h) that required use of systemic corticosteroids; or an asthma-related inpatient hospital admission (duration ≥24 h). Worsening of asthma was defined as any new or increased symptoms or signs that were concerning to the patient or related to an asthma daily diary alert.[10,11] The original key secondary endpoints (ie, multiplicity [type I error]-protected endpoints) for the primary analysis population were prebronchodilator FEV_1 and total asthma symptom score by daily diary (a composite of daytime and night-time symptoms scored from 0 to 6 overall) at end of treatment. Additional secondary endpoints measured at baseline and the end of the study included Asthma Control Questionnaire 6 (ACQ-6) score and standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ[S]+12) score. ACQ-6 is a reflective (previous 7 days) six-item questionnaire to assess daytime and night-time symptoms and rescue β-agonist use on a scale from 0 to 6, where small numbers represent better control.[19] AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale.[20] Details on efficacy measurement methods were published previously.[10,11]

Statistical analysis

We based the analyses on the full analysis set according to the intention-to-treat principle for pooled, patient-level data from the SIROCCO and CALIMA studies. This set included all patients who underwent randomisation and received any study treatment, irrespective of their protocol adherence and continued participation in the study. The similar design of the two studies allowed for the results to be pooled. We pooled the results to obtain more accurate estimates of the relationships between efficacy endpoints and baseline blood eosinophil counts and exacerbation frequency histories. We did the analyses with SAS version 9.2 and with R version 3.2.0.[21]

We analysed the AERs using a negative binomial model, with adjustments for treatment, study, region, oral corticosteroid use at time of randomisation, and prior exacerbations. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients' having different exposure times during which the events occurred. We calculated the estimated treatment effect (ie, the rate ratio [RR] of benralizumab *vs* placebo), corresponding 95% CIs, and two-sided p value for the RR. The AER and corresponding 95% CIs were also calculated. We analysed FEV_1 and asthma symptom scores using a mixed-effects model for repeated measures analysis, with adjustments for treatment, study, baseline value, region, oral corticosteroid use at the time of randomisation, visit, and visit×treatment. We calculated least squares means, treatment differences in least squares means, 95% CI, and p values. Factors used as adjustments in the models were prespecified before the database lock of the studies. To account for the 2:1 stratification for baseline blood eosinophil counts (≥300 cells per μL and <300 cells per μL) in analyses using cutpoints below 300, we reweighted patients with baseline blood eosinophil counts less than 300 cells per μL by using the ratio of the number of patients who had baseline blood eosinophil counts greater than or equal to 300 cells per μL to the number of those who had less than 300 cells per μL. The analysis of treatment outcomes by baseline blood eosinophil counts and exacerbation history was not part of the formal testing strategy; therefore, all p values were nominal. Analyses according to cumulative blood eosinophil categories and patients with two, three, and four or more exacerbations in the previous year for AER were prespecified within the individual study statistical analyses plans. Given the similar efficacy in the patients with three and four or more exacerbations in the previous year, and to increase the precision of the treatment effects, we pooled these groups of patients post hoc.

The results of the subgroup analyses of AER and FEV_1 were represented as forest plots. The subgroups analysed were age (<18 years, 18 to <65 years, and ≥65 years), sex, body-mass index (≤35 kg/m² or >35 kg/m²), baseline oral corticosteroid use, number of exacerbations in the previous year (two, three, or four), race (white, black or African-American, Asian, or other), nasal polyposis, atopic status, and smoking history. For both the exacerbation rate and prebronchodilator FEV_1 change endpoints, we used gradient-boosted regression tree modelling[22] to explore, in a hypothesis-free manner, the relative importance of factors that might be associated with response. This type of modelling is a tree-based method that does not produce parameter estimates or p values; instead, plots are generated to show the relative contribution of each variable to the overall model. We used locally weighted smoothing regression (LOESS) plots with corresponding 95% CIs to model AER and prebronchodilator FEV_1 changes from baseline versus baseline blood eosinophil counts.

Role of the funding source

Authors employed by or who have received compensation from the funder were involved in the study de-

sign, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

We used pooled results from 1204 patients in SIROCCO and 1091 patients in CALIMA for the analyses. Of these 2295 patients, 756 received 4-weekly benralizumab,

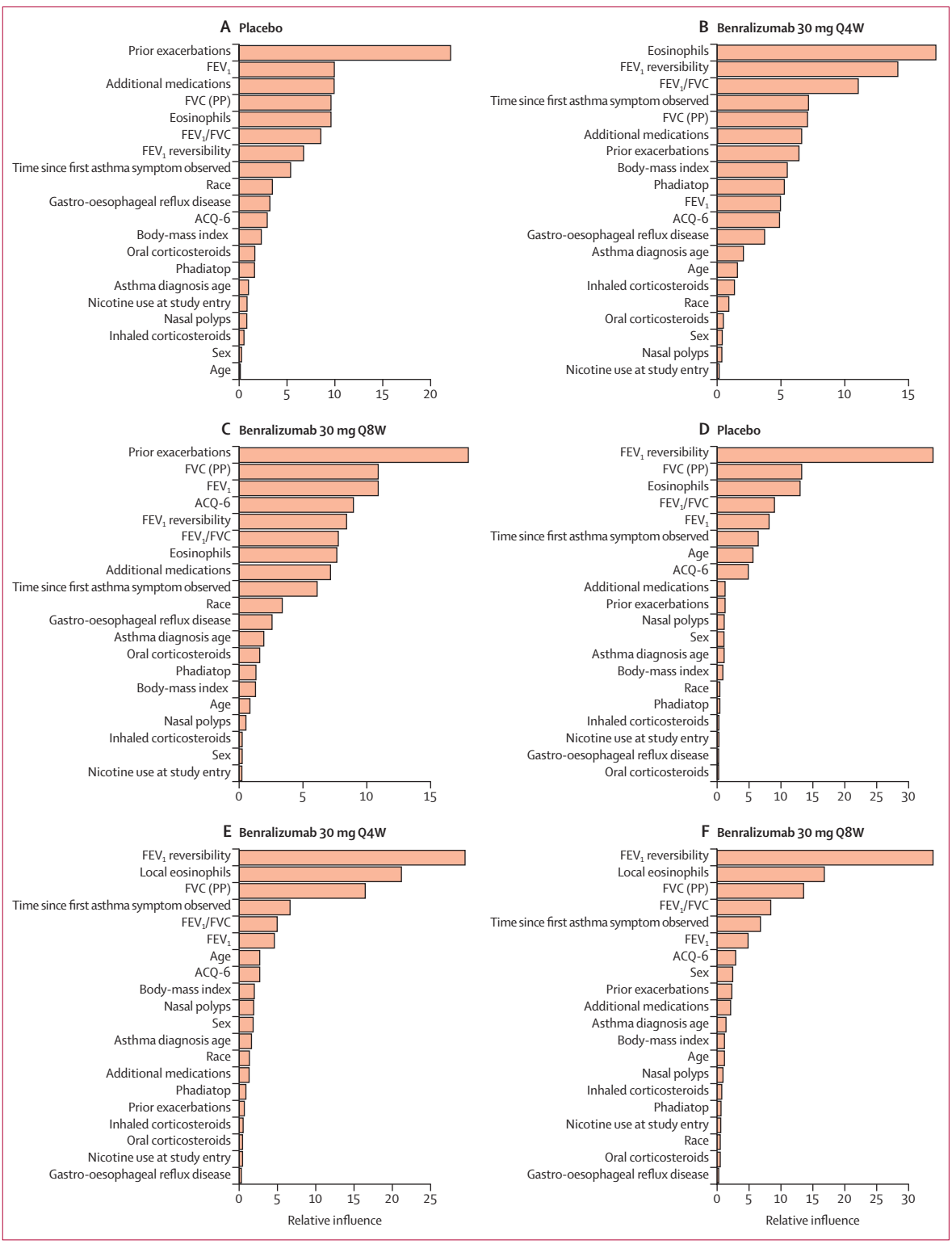

***Figure 2*: Baseline factors relevant for prediction of treatment response with respect to exacerbations and FEV_1**

We assessed relative importance in the pooled full analysis set for predicting annual asthma exacerbation rate (A–C) and prebronchodilator FEV_1 changes (D–F) for the pooled placebo (A, D) benralizumab Q4W (B, E), and benralizumab Q8W (C, F) treatment groups. Models were generated with gradient-boosted regression modelling with ten-fold cross-validation, an interaction depth of 3, and per-iteration shrinkage of 0·001, with a count endpoint for exacerbations and a Gaussian endpoint for FEV_1. Change in prebronchodilator FEV_1 score was from baseline to the end of treatment (48 weeks in SIROCCO and 56 weeks in CALIMA). ACQ-6=Asthma Control Questionnaire-6. FVC=forced vital capacity. PP=percent predicted. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses every 4 weeks).

	Placebo (n=777)	Benralizumab Q4W (n=756)	Benralizumab Q8W (n=762)
≥0 cells per μL			
Number of patients analysed	770	748	751
Rate estimate (95% CI)	1·16 (1·05 to 1·28)	0·73 (0·65 to 0·82)	0·75 (0·66 to 0·84)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·43 (−0·57 to −0·28)	−0·41 (−0·56 to −0·27)
Rate ratio *vs* placebo (95% CI)	..	0·63 (0·54 to 0·74)	0·64 (0·55 to 0·75)
p value *vs* placebo	..	<0·0001	<0·0001
≥150 cells per μL			
Number of patients analysed	648	647	646
Rate estimate (95% CI)	1·14 (1·02 to 1·28)	0·69 (0·61 to 0·79)	0·72 (0·63 to 0·82)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·45 (−0·60 to −0·29)	−0·42 (−0·58 to −0·27)
Rate ratio *vs* placebo (95% CI)	..	0·61 (0·51 to 0·72)	0·63 (0·53 to 0·74)
p value *vs* placebo	..	<0·0001	<0·0001
≥300 cells per μL			
Number of patients analysed	511	511	499
Rate estimate (95% CI)	1·14 (1·00 to 1·29)	0·68 (0·59 to 0·78)	0·65 (0·56 to 0·75)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·46 (−0·64 to −0·29)	−0·49 (−0·67 to −0·32)
Rate ratio *vs* placebo (95% CI)	..	0·59 (0·49 to 0·72)	0·57 (0·47 to 0·69)
p value *vs* placebo	..	<0·0001	<0·0001
≥450 cells per μL			
Number of patients analysed	306	295	298
Rate estimate (95% CI)	1·25 (1·06 to 1·47)	0·73 (0·61 to 0·89)	0·62 (0·51 to 0·76)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·51 (−0·76 to −0·27)	−0·63 (−0·87 to −0·39)
Rate ratio *vs* placebo (95% CI)	..	0·59 (0·46 to 0·75)	0·50 (0·38 to 0·64)
p value *vs* placebo	..	<0·0001	<0·0001

Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses every 4 weeks).

Table 2: **Annual asthma exacerbation rates by baseline eosinophil count and treatment (full analysis set, pooled)**

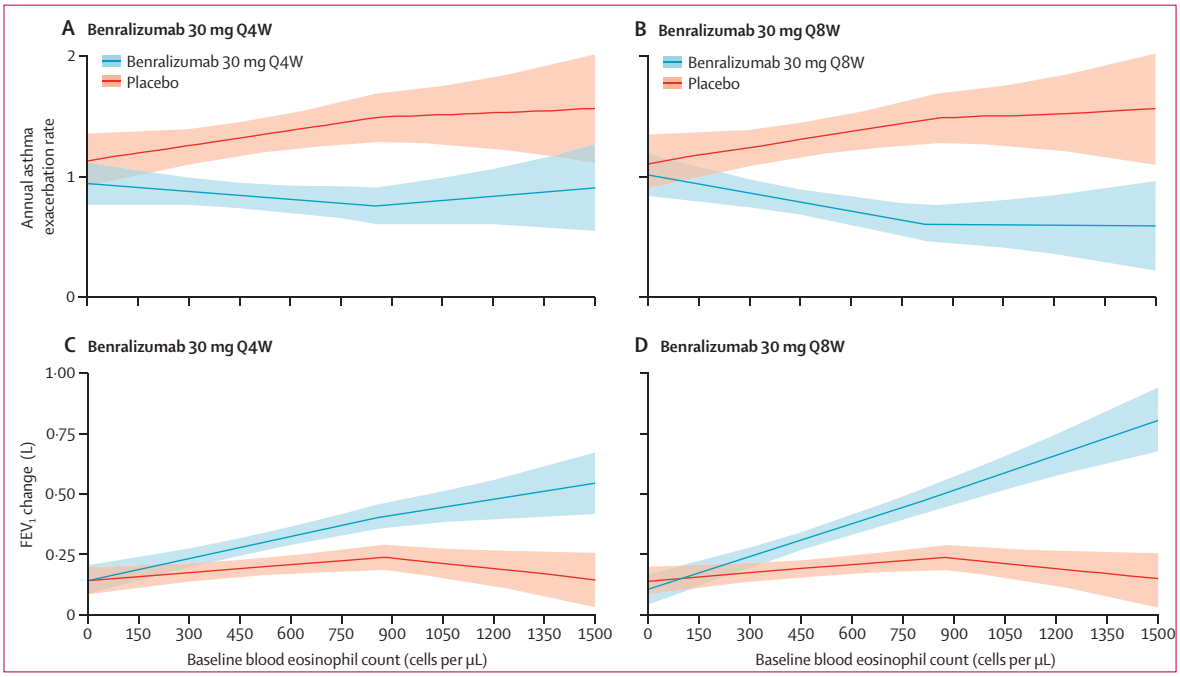

Figure 3: **Modelling of asthma exacerbation rate and FEV_1 outcomes by baseline blood eosinophil counts**
Asthma exacerbation rate (A, B) and prebronchodilator FEV_1 change from baseline (C, D) for benralizumab Q4W (A, C) and benralizumab Q8W (B, D) treatments in the pooled full analysis set. Lines show locally weighted smoothing local regression plot and shading shows 95% CI. Change in prebronchodilator FEV_1 score was from baseline to the end of treatment (48 weeks in SIROCCO and 56 weeks in CALIMA). Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses every 4 weeks).

	Placebo	Benralizumab Q4W	Benralizumab Q8W
Annual exacerbation rate			
<150 cells per μL			
Number of patients analysed	122	101	105
Rate estimate (95% CI)	1·26 (0·98 to 1·61)	0·97 (0·72 to 1·30)	0·91 (0·67 to 1·22)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·29 (−0·71 to 0·13)	−0·35 (−0·76 to 0·06)
Rate ratio *vs* placebo (95% CI)	..	0·77 (0·52 to 1·13)	0·72 (0·49 to 1·06)
p value *vs* placebo	..	0·18	0·10
150–299 cells per μL			
Number of patients analysed	137	136	147
Rate estimate (95% CI)	1·22 (0·96 to 1·54)	0·78 (0·60 to 1·02)	0·94 (0·73 to 1·21)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·43 (−0·79 to −0·08)	−0·27 (−0·65 to 0·10)
Rate ratio *vs* placebo (95% CI)	..	0·64 (0·45 to 0·92)	0·77 (0·55 to 1·09)
p value *vs* placebo	..	0·0152	0·15
300–449 cells per μL			
Number of patients analysed	205	216	201
Rate estimate (95% CI)	1·03 (0·85 to 1·26)	0·62 (0·50 to 0·78)	0·72 (0·57 to 0·90)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·41 (−0·66 to −0·17)	−0·32 (−0·58 to −0·05)
Rate ratio *vs* placebo (95% CI)	..	0·60 (0·44 to 0·81)	0·69 (0·51 to 0·94)
p value *vs* placebo	..	0·0008	0·0178
≥450 cells per μL			
Number of patients analysed	306	295	298
Rate estimate (95% CI)	1·16 (1·00 to 1·36)	0·69 (0·58 to 0·83)	0·58 (0·48 to 0·70)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·47 (−0·69 to −0·25)	−0·59 (−0·80 to −0·37)
Rate ratio *vs* placebo (95% CI)	..	0·59 (0·47 to 0·75)	0·50 (0·39 to 0·64)
p value *vs* placebo	..	<0·0001	<0·0001
Prebronchodilator FEV_1 (L)			
<150 cells per μL			
Number of patients in analysis	117	97	101
Number of patients with end of treatment data	103	84	90
Least squares mean change	0·170	0·148	0·214
Least squares mean difference *vs* placebo (95% CI)	..	−0·022 (−0·132 to 0·089)	0·044 (−0·065 to 0·153)
p value *vs* placebo	..	0·70	0·43
150–299 cells per μL			
Number of patients in analysis	134	136	145
Number of patients with end of treatment data	120	121	124
Least squares mean change	0·151	0·256	0·211
Least squares mean difference *vs* placebo (95% CI)	..	0·105 (0·006 to 0·204)	0·060 (−0·037 to 0·157)
p value *vs* placebo	..	0·0367	0·23
300–449 cells per μL			
Number of patients in analysis	201	212	200
Number of patients with end of treatment data	180	186	174
Least squares mean change	0·252	0·281	0·286
Least squares mean difference *vs* placebo (95% CI)	..	0·029 (−0·052 to 0·110)	0·034 (−0·049 to 0·116)
p value *vs* placebo	..	0·48	0·42
≥450 cells per μL			
Number of patients in analysis	300	292	295
Number of patients with end of treatment data	270	262	265
Least squares mean change	0·194	0·348	0·417
Least squares mean difference *vs* placebo (95% CI)	..	0·154 (0·085 to 0·224)	0·224 (0·154 to 0·293)
p value *vs* placebo	..	<0·0001	<0·0001

The p value for the interaction test of treatment by baseline blood eosinophil count category was 0·31 and the p value for the interaction test of treatment by baseline blood eosinophil count category was 0·0008 for prebronchodilator FEV_1. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses every 4 weeks).

Table 3: **Annual exacerbation rates and lung function outcomes and changes at end of treatment by baseline eosinophil blood count (full analysis set, pooled)**

	Prebronchodilator FEV_1 (L)			Total asthma symptom score		
	Placebo	Benralizumab Q4W	Benralizumab Q8W	Placebo	Benralizumab Q4W	Benralizumab Q8W
≥0 cells per μL						
Number of patients in analysis	752	737	741	768	744	740
Number of patients with end of treatment data	673	653	653	552	556	533
Least squares mean change	0·185	0·257	0·284	−0·98	−1·11	−1·16
Least squares mean difference *vs* placebo (95% CI)	..	0·072 (0·023 to 0·121)	0·099 (0·051 to 0·148)	..	−0·14 (−0·25 to −0·02)	−0·19 (−0·30 to −0·07)
p value *vs* placebo	..	0·0038	<0·0001	..	0·0198	0·0015
≥150 cells per μL						
Number of patients in analysis	635	640	640	647	645	637
Number of patients with end of treatment data	570	569	563	468	483	457
Least squares mean change	0·191	0·296	0·311	−1·03	−1·19	−1·22
Least squares mean difference *vs* placebo (95% CI)	..	0·105 (0·052 to 0·159)	0·120 (0·066 to 0·173)	..	−0·16 (−0·28 to − 0·04)	−0·19 (−0·31 to −0·07)
p value *vs* placebo	..	0·0001	<0·0001	..	0·0115	0·0027
≥300 cells per μL						
Number of patients in analysis	501	504	495	510	509	493
Number of patients with end of treatment data	450	448	439	365	377	359
Least squares mean change	0·224	0·339	0·370	−1·10	−1·21	−1·36
Least squares mean difference *vs* placebo (95% CI)	..	0·114 (0·051 to 0·177)	0·146 (0·082 to 0·209)	..	−0·11 (−0·25 to 0·03)	−0·26 (−0·40 to −0·12)
p value *vs* placebo	..	0·0004	<0·0001	..	0·12	0·0003
≥450 cells per μL						
Number of patients in analysis	300	292	295	306	294	294
Number of patients with end of treatment data	270	262	265	208	218	212
Least squares mean change	0·209	0·364	0·448	−1·19	−1·39	−1·54
Least squares mean difference *vs* placebo (95% CI)	..	0·155 (0·071 to 0·239)	0·239 (0·155 to 0·322)	..	−0·20 (−0·38 to −0·02)	−0·35 (−0·53 to −0·17)
p value *vs* placebo	..	<0·0003	<0·0001	..	0·0307	0·0002

Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses every 4 weeks).

Table 4: **Lung function outcomes and asthma symptoms changes at end of treatment by baseline eosinophil counts (full analysis set, pooled)**

762 received 8-weekly benralizumab, and 777 received placebo. Patients from both studies had similar baseline demographic and clinical characteristics (table 1). In an analysis of demographic and clinical characteristics of patients with baseline eosinophil counts greater than or equal to 300 cells per μL, larger AER reductions and FEV_1 improvements were associated with a history of more frequent exacerbations (figure 1, appendix). In addition, larger FEV_1 improvements were consistently associated with oral corticosteroid use and history of nasal polyposis in both benralizumab dosing groups. Our unbiased structured analysis with a data-driven approach suggested that previous exacerbations, baseline blood eosinophil counts, and baseline lung function indices were consistent and influential predictors of exacerbation reduction (figure 2A–C). Baseline lung function indices (especially reversibility) and eosinophil counts were also important predictors of FEV_1 change (figure 2D–F). Exacerbation history had a reduced effect on change in the FEV_1 outcome compared with its effect on AER reduction between treatment cohorts (figure 2). In the context of the structured analysis, lower than normal lung function values at baseline (FEV_1, forced vital capacity [FVC] percentage predicted, or FEV_1/FVC) were the factors with the greatest relative importance associated with response.

Of patients with blood eosinophil counts greater than 0 cells per μL, the RR versus placebo was 0·63 (95% CI 0·54–0·74; p<0·0001) with 4-weekly benralizumab and 0·64 (95% CI 0·55–0·75; p<0·0001) with 8-weekly benralizumab (table 2). The degree of improvement in AER with benralizumab treatment increased with increasing baseline blood eosinophil counts (figure 3; table 2). A similar improvement in AER with increasing blood eosinophil counts was observed when blood eosinophil counts were categorised as less than 150, 150–299, 300–449, and greater than or equal to 450 cells per μL (table 3).

Both benralizumab regimens improved prebronchodilator FEV_1 at end of treatment for the total study population. The difference in least squares mean change from baseline compared with the placebo group was 0·099 L (95% CI 0·051–0·148; p<0·0001; table 4) for the 8-weekly benralizumab groups and 0·072 (0·023–0·121; p=0·0038) for the 4-weekly benralizumab group for patients with blood eosinophil counts greater than or equal to 0 cells per μL. The magnitude of the difference in prebronchodilator FEV_1 between benralizumab and placebo increased with

See Online for appendix

	ACQ-6			AQLQ(S)+12		
	Placebo	Benralizumab Q4W	Benralizumab Q8W	Placebo	Benralizumab Q4W	Benralizumab Q8W
≥0 cells per µL						
Number of patients in analysis	767	747	746	741	718	720
Number of patients with end of treatment data	567	562	546	554	546	532
Least squares mean change	−1·02	−1·19	−1·25	1·11	1·25	1·33
Least squares mean difference *vs* placebo (95% CI)	..	−0·17 (−0·28 to −0·06)	−0·23 (−0·34 to −0·12)	..	0·14 (0·03 to 0·26)	0·22 (0·10 to 0·34)
p value *vs* placebo	..	0·0025	<0·0001	..	0·0172	0·0002
≥150 cells per µL						
Number of patients in analysis	646	646	642	624	620	619
Number of patients with end of treatment data	478	481	470	465	467	458
Least squares mean change	−1·10	−1·28	−1·29	1·19	1·36	1·38
Least squares mean difference *vs* placebo (95% CI)	..	−0·18 (−0·29 to −0·06)	−0·18 (−0·30 to −0·07)	..	0·17 (0·05 to 0·29)	0·19 (0·07 to 0·31)
p value *vs* placebo	..	0·0036	0·0022	..	0·0071	0·0025
≥300 cells per µL						
Number of patients in analysis	510	510	495	490	490	475
Number of patients with end of treatment data	379	387	371	367	375	362
Least squares mean change	−1·16	−1·35	−1·45	1·27	1·45	1·57
Least squares mean difference *vs* placebo (95% CI)	..	−0·19 (−0·32 to −0·05)	−0·29 (−0·43 to −0·16)	..	0·18 (0·04 to 0·32)	0·30 (0·15 to 0·44)
p value *vs* placebo	..	0·0064	<0·0001	..	0·0130	<0·0001
≥450 cells per µL						
Number of patients in analysis	305	295	296	293	285	283
Number of patients with end of treatment data	223	218	227	216	213	219
Least squares mean change	−1·24	−1·56	−1·55	1·35	1·63	1·71
Least squares mean difference *vs* placebo (95% CI)	..	−0·32 (−0·50 to −0·15)	−0·31 (−0·48 to −0·14)	..	0·27 (0·09 to 0·46)	0·35 (0·17 to 0·54)
p value *vs* placebo	..	0·0003	0·0005	..	0·0038	0·0002

ACQ-6=Asthma Control Questionnaire-6. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses every 4 weeks).

Table 5: **ACQ-6 and AQLQ(S)+12 changes at end of treatment by baseline eosinophil counts (full analysis set, pooled)**

increasing baseline blood eosinophil counts (figure 3; table 3; table 4). The decrease in total asthma symptom score at the end of treatment was greater for all patients receiving benralizumab than for those receiving placebo, with a least squares mean change from baseline difference in the 8-weekly benralizumab cohort of −0·19 (95% CI −0·30 to −0·07; p=0·0015; table 4) for patients with blood eosinophil counts greater than or equal to 0 cells per µL. For the 8-weekly benralizumab cohort, the magnitude of difference in total asthma score increased with greater baseline blood eosinophil counts (table 4). We noted a similar pattern of improvement with benralizumab treatment with respect to blood eosinophil counts for asthma control and asthma-related quality of life (table 5).

Of patients with eosinophil counts greater than or equal to 300 cells per µL, compared with patients with two exacerbations, patients with a history of three or more exacerbations in the 12 months before study entry had a greater degree of improvement in AER, prebronchodilator FEV_1, and total asthma symptom score at end of treatment with benralizumab treatment relative to placebo (table 6). For the patients in the 8-weekly benralizumab cohort who had three or more exacerbations in the year before study entry, the RR relative to placebo was 0·45 (95% CI 0·34–0·60; p<0·0001) compared with 0·73 (0·55–0·95; p=0·0194) for those with two exacerbations. For patients with three or more exacerbations in the year before study entry, improvements in AER and prebronchodilator FEV_1 at end of treatment with benralizumab were greater with increasing baseline blood eosinophil counts (figure 4).

Discussion

The results of the SIROCCO and CALIMA studies previously demonstrated that benralizumab, in combination with high-dosage inhaled corticosteroids plus LABAs, significantly improved AER, prebronchodilator FEV_1, and total asthma symptom scores compared with placebo for patients with severe, uncontrolled asthma with baseline blood eosinophil counts greater than or equal to 300 cells per µL.[10,11] A subsequent pooled analysis of data from the SIROCCO and CALIMA studies supported the efficacy and safety of benralizumab for patients with severe asthma and blood eosinophil counts greater than or equal to 150 cells per µL.[12]

In this study, we extend these findings to patients with baseline blood eosinophil counts greater than or equal to 0

	Two exacerbations in previous year			Three or more exacerbations in previous year		
	Placebo	Benralizumab Q4W	Benralizumab Q8W	Placebo	Benralizumab Q4W	Benralizumab Q8W
Annual exacerbation rate						
Number of patients analysed	300	322	308	215	194	198
Rate estimate (95% CI)	0·80 (0·67 to 0·96)	0·52 (0·42 to 0·63)	0·58 (0·48 to 0·71)	1·79 (1·51 to 2·14)	0·98 (0·80 to 1·21)	0·82 (0·65 to 1·02)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·28 (−0·46 to −0·10)	−0·22 (−0·40 to −0·03)	..	−0·81 (−1·18 to −0·44)	−0·98 (−1·34 to −0·62)
Rate ratio *vs* placebo (95% CI)	..	0·65 (0·49 to 0·85)	0·73 (0·55 to 0·95)	..	0·55 (0·42 to 0·72)	0·45 (0·34 to 0·60)
p value *vs* placebo	..	0·0016	0·0194	..	<0·0001	<0·0001
Prebronchodilator FEV_1 (L)						
Number of patients in analysis	295	318	305	210	191	197
Number of patients with end of treatment data	261	283	276	193	169	170
Least squares mean change	0·236	0·341	0·306	0·215	0·336	0·467
Least squares mean difference *vs* placebo (95% CI)	..	0·105 (0·027 to 0·183)	0·070 (−0·008 to 0·149)	..	0·121 (0·017 to 0·226)	0·252 (0·148 to 0·357)
p value *vs* placebo	..	0·0087	0·08	..	0·0232	<0·0001
Total asthma symptom score						
Number of patients in analysis	299	320	304	215	194	196
Number of patients with end of treatment data	208	241	219	159	140	144
Least squares mean change	−1·08	−1·22	−1·27	−1·14	−1·17	−1·49
Least squares mean difference *vs* placebo (95% CI)	..	−0·14 (−0·32 to 0·04)	−0·18 (−0·36 to −0·00)	..	−0·04 (−0·25 to 0·18)	−0·36 (−0·57 to −0·14)
p value *vs* placebo	..	0·12	0·0490	..	0·74	0·0014

Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses every 4 weeks).

Table 6: **Association of exacerbation history with effect of benralizumab treatment on efficacy variables for patients with baseline eosinophil counts ≥300 cells per µL (full analysis set, pooled)**

cells per µL. We demonstrated that benralizumab reduced exacerbation frequency, increased lung function, and improved asthma symptoms and health-related quality of life in this population, especially when particular baseline characteristics were present. Efficacy with respect to these outcome measures increased with increasing baseline blood eosinophil counts. Furthermore, exacerbation history could be used to identify patients who would potentially be responsive to benralizumab, with patients with a history of more frequent exacerbations achieving greater benefit. Patients with a combination of greater baseline blood eosinophil counts and a history of more frequent exacerbations achieved the greatest benefit. Subgroup analyses of baseline oral corticosteroid use and history of nasal polyposis suggested that these factors were associated with enhanced AER reduction and FEV_1 improvement. This association was corroborated by the unbiased structured analysis. These observations support the idea that, in the setting of severe asthma, oral corticosteroid use and nasal polyposis are indicative of the presence of corticosteroid-resistant eosinophilic airway inflammation.

Identification of eosinophilic inflammation in the airways through bronchial biopsies or induced sputum is the gold standard for the diagnosis of eosinophilic asthma.[23] However, such methods are not feasible for clinical settings because of their invasive nature and the expertise needed to use them. As a consequence, blood eosinophil counts have emerged as a useful surrogate biomarker for sputum eosinophilia because of their superior predictive accuracy relative to other biomarkers.[24,25] High blood eosinophil counts have good specificity for airway eosinophilia.[25,26] However, because of some other factors, including variability related to the circadian rhythm and corticosteroid usage, low blood eosinophil counts might not be an accurate indicator of the absence of eosinophilic airway inflammation.[27,28] In a study of children with severe, therapy-resistant asthma, although 86% of patients had normal blood eosinophil counts, 84% had airway eosinophilia.[29] In a separate study, sputum eosinophil counts increased 17-fold from baseline values at exacerbation compared with a 50% increase for blood eosinophil counts.[30] Our results underscore the potential limitations of identifying probable responders to eosinophil depletion therapy mainly on the basis of a blood eosinophil counts greater than or equal to 300 cells per µL. In the consideration of treatment options, other factors, including clinical characteristics such as exacerbation history, should be factored in alongside blood eosinophil counts.

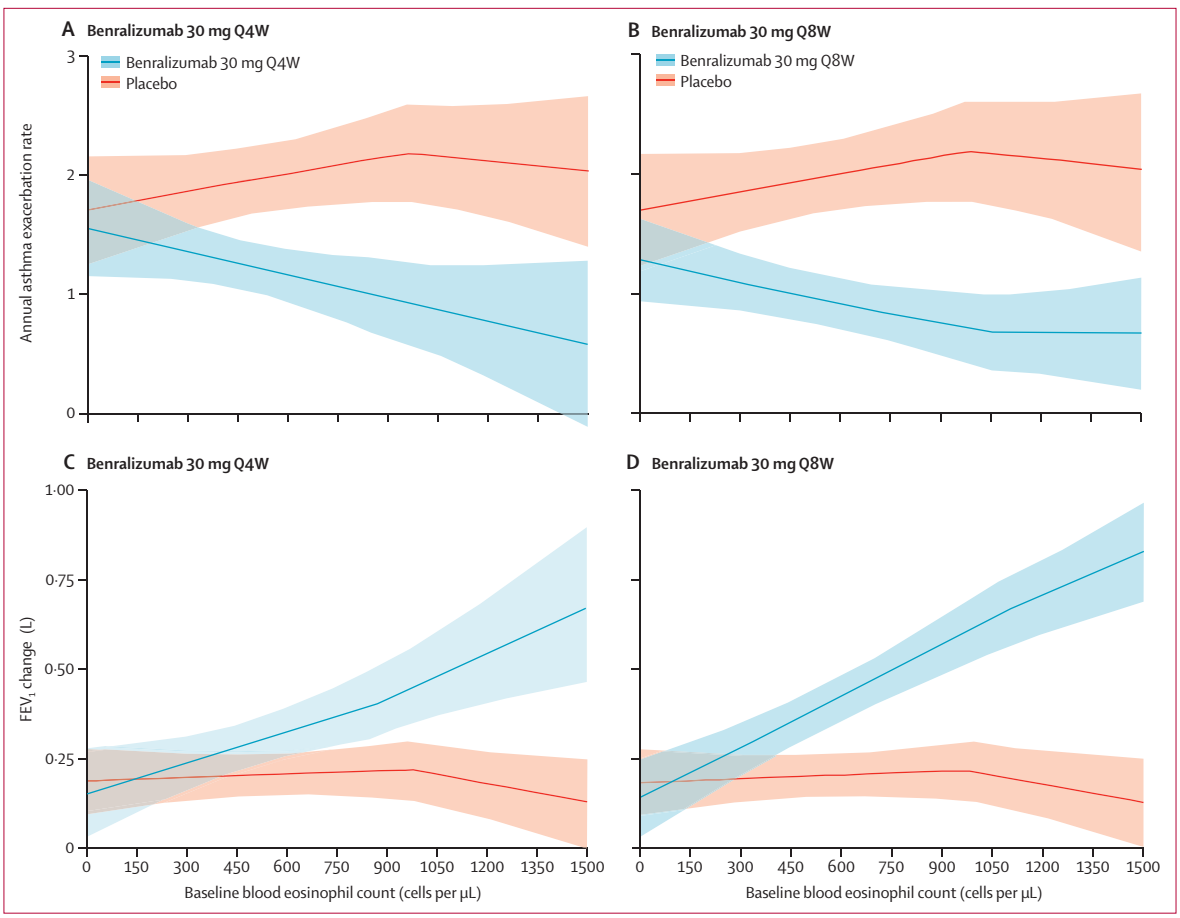

Figure 4: **Modelling of asthma exacerbation rate and FEV_1 outcomes by baseline blood eosinophil counts for patients with baseline history of three or more exacerbations in the year before treatment**

Asthma exacerbation rate (A, B) and prebronchodilator FEV_1 (L) change from baseline (C, D) for benralizumab Q4W (A, C) and benralizumab Q8W (B, D) in the pooled full analysis set. Lines show locally weighted smoothing local regression plot and shading shows 95% CI. Prebronchodilator FEV_1 score change was from baseline to the end of treatment (48 weeks in SIROCCO and 56 weeks in CALIMA). Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses every 4 weeks).

Consistent with results from the SIROCCO and CALIMA studies for patients with blood eosinophil counts greater than or equal to 300 cells per µL, benralizumab administered every 8 weeks was generally better than the 4-weekly dosage for reducing exacerbation frequency and improving lung function and asthma symptoms for patients across a range of blood eosinophil counts. Since both dosing regimens depleted blood eosinophils to the same degree in the pivotal studies, the reason for this occasional numerical difference is unclear, and might be a result of chance. These results further support the use of the 8-weekly dosing regimen for patients with severe, uncontrolled asthma with eosinophilic inflammation.

Mepolizumab and reslizumab, the two currently marketed anti-interleukin-5 antibodies indicated for severe, eosinophilic asthma, have been studied in patients with minimum blood eosinophil counts of 150 cells per µL at screening,[13] 300 cells per µL in the previous year,[14] and 400 cells per µL at baseline,[15] respectively. Unlike benralizumab, these agents act through a passive (indirect) mechanism that ultimately results in eosinophil reduction. For the combined phase 3 DREAM[14] and MENSA[13] studies, mepolizumab treatment, given every 4 weeks, had an AER ratio versus placebo of 0·48 (95% CI 0·39–0·58) for patients with blood eosinophil counts greater than or equal to 150 cells per µL. For pre-bronchodilator FEV_1, improvement with mepolizumab for the combined studies versus placebo was 0·064 L (0·001–0·127) for patients with blood eosinophil counts of at least 150 cells per µL. Because of differences in baseline characteristics, our ability to compare the results from the mepolizumab studies with those of the current analysis directly is limited. In this analysis, benralizumab had demonstrable effects across an expanded range of blood eosinophil counts, including patients with greater than or equal to 150 cells per µL.

Our study had some limitations. Although improvements in ACQ-6 and AQLQ(S)+12 scores relative to placebo had nominal p values less than or equal to

0·05, the changes might not indicate a minimum clinically important difference. This could partly be because improvements in ACQ-6 and AQLQ(S)+12 were also quite high in the placebo groups of SIROCCO and CALIMA. In addition, these patient-reported outcome tools might be less responsive to complex interventions, such as biological therapy added to inhaled corticosteroids and LABA. Thus, the overall response should be considered in evaluations of efficacy. We have attributed the relatively large lung function responses seen in patients with increased blood eosinophil counts plus particular baseline clinical characteristics (eg, oral corticosteroid dependency or nasal polyposis) as indicative of benralizumab-sensitive active eosinophilic airway inflammation. Reversibility to short-acting bronchodilator seemed to affect lung function improvements in the unbiased analysis. Because reversibility was required for all patients per protocol, we cannot comment on the effects of benralizumab in severe asthma that is resistant to bronchodilators.[31] Another limitation is that the study was not powered to detect differences within groups and for some evaluations, such as the effect of exacerbation history, we combined groups post hoc to obtain a meaningful number of patients.

Overall, when added to high-dosage inhaled corticosteroids plus LABA therapy, benralizumab provided additional benefit for patients with severe, uncontrolled asthma and at least two exacerbations in the previous year across the spectrum of baseline blood eosinophil counts. Enhanced efficacy was observed for patients with increased blood eosinophils and a history of three or more exacerbations per year. Identification of clinical characteristics and predictive biomarkers that are associated with increased benralizumab responsiveness will help to improve the therapeutic management of severe asthma by more precisely identifying which patents will benefit the most from this agent.

Contributors

JMF, ERB, and MG conceived and designed the study. AM-G, JGZ, IH, PM, PN, and MG acquired the data. All authors had access to and analysed and interpreted the data. All authors participated in the development and critical review of the manuscript. All authors provided final approval for publication submission and are accountable for the accuracy and integrity of the work.

Declaration of interests

JMF reports being a member of advisory boards for AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi-Regeneron, Cicassia, and Teva; has been paid honoraria for lecturing at symposia organised by these companies; and has also has undertaken clinical trials through his employer, the University of British Columbia, for these companies and GlaxoSmithKline (GSK). ERB has undertaken clinical trials through his employer, the Wake Forest School of Medicine, for AstraZeneca, Boehringer Ingelheim, Cephalon/Teva, Forest, Genentech, GSK, Johnson & Johnson (Janssen), MedImmune, Novartis, Pfizer, and Sanofi; and has also served as a paid consultant for AstraZeneca, Boehringer Ingelheim, Forest, GSK, MedImmune, Novartis, Pfizer, Regeneron, and Sanofi. AM-G has attended advisory boards for GSK, Novartis, AstraZeneca, Boehringer Ingelheim, and Teva; has received speaker fees from Novartis, AstraZeneca, Vectura, Boehringer Ingelheim, and Teva; has received clinical trial funding from AstraZeneca and has participated in research with Hoffmann La Roche, GSK, and Boehringer Ingelheim, for which his institution has been remunerated; and has attended international conferences with Napp and AstraZeneca and has consultancy agreements with AstraZeneca and Vectura. JGZ, IH, PM, and MG are employees of AstraZeneca. PN is an employee of MedImmune.

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