



Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Benralizumab is a humanised, anti-interleukin 5 receptor α monoclonal antibody that directly and rapidly depletes eosinophils, reduces asthma exacerbations, and improves lung function for patients with severe eosinophilic asthma. The objective of this trial was to assess the safety and efficacy of benralizumab for patients with mild to moderate, persistent asthma.

Methods In this randomised, double-blind, placebo-controlled, phase 3 trial, we recruited patients aged 18–75 years, weighing at least 40 kg, and with a postbronchodilator reversibility in forced expiratory volume in 1 s (FEV₁) of at least 12% at screening, from 52 clinical research centres in six countries. Patients must have been receiving either low- to medium-dosage inhaled corticosteroids (ICS) or low-dosage ICS plus long-acting β_2 agonist fixed-combination therapy at screening, had a morning prebronchodilator FEV₁ of more than 50% to 90% predicted at screening, and had one or more of the following symptoms within the 7 days before randomisation: a daytime or night-time asthma symptom score of at least 1 for at least 2 days, rescue short-acting β_2 agonist use for at least 2 days, or night-time awakenings due to asthma for at least one night. We converted patients' ICS treatments to 180 μ g or 200 μ g budesonide dry powder inhaler twice daily for the entire duration of the study using the approved dosages in the patients' respective countries and randomly allocated them (1:1; stratified by blood eosinophil count [<300 cells per μ L vs ≥ 300 cells per μ L] and region [USA vs the rest of the world]) with an interactive web-based voice response system to receive subcutaneous placebo or benralizumab 30 mg injections every 4 weeks for 12 weeks. All patients and investigators involved in patient treatment or clinical assessment and those assessing outcomes were masked to treatment allocation. The primary endpoint was change from baseline prebronchodilator FEV₁ at week 12. Efficacy analyses used an intention to treat approach. This trial is registered with ClinicalTrials.gov, number NCT02322775.

Findings Between Feb 2, 2015, and April 24, 2015, we enrolled 351 patients, with 211 (60%) randomly assigned (105 [50%] to placebo and 106 [50%] to benralizumab). Benralizumab resulted in an 80 mL (95% CI 0–150; $p=0.04$) greater improvement (least-squares mean difference) in prebronchodilator FEV₁ after 12 weeks than did placebo (placebo group: 2246 mL [SD 768] at baseline vs 2261 mL [796] at week 12, change from baseline of 0 mL; benralizumab group: 2248 mL [606] vs 2310 mL [670], 70 mL). 44 (42%) patients in the benralizumab group had adverse events compared with 49 (47%) in the placebo group. The most common adverse events for both groups were nasopharyngitis (eight [8%] patients in each group) and upper respiratory tract infections (five [5%] patients in each group). Serious adverse events occurred in two (2%) patients each in the benralizumab (pancytopenia and a suicide attempt, both considered unrelated to treatment) and placebo (cervix carcinoma and colon adenoma) groups.

Interpretation This study suggests that active and modifiable disease processes might be ongoing in patients with mild to moderate, persistent asthma receiving ICS. Although the lung function improvement observed does not warrant use of benralizumab in this population because it did not reach the minimum clinically important difference of 10%, further studies to assess this finding should be considered.

Funding AstraZeneca.

Introduction

An estimated 315 million people worldwide had asthma in 2012, and this figure is projected to be greater than 400 million by 2020.^{1,2} Most patients have mild to moderate asthma, which can be well controlled with therapies such as inhaled corticosteroids (ICS), either alone or in combination with a long-acting β_2 agonist (LABA).^{3–5} However, patients with mild to moderate asthma display considerable heterogeneity in symptom

control and health-related quality of life and remain at risk of asthma exacerbations.^{3–6} Exacerbations, which can be severe, occur in as many as 32% of patients with mild to moderate asthma.^{3,7}

Biological therapies against components of the interleukin 5 pathway represent an effective add-on treatment for severe asthma.^{8–13} Serum interleukin 5 concentrations are approximately two-times greater for patients with mild to moderate asthma than for individuals

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Research in context

Evidence before this study

We searched PubMed for clinical trial reports of use of anti-interleukin 5 biological drugs for the treatment of asthma in human beings published between Jan 1, 2006, and Sept 27, 2016, in English. We used the search terms “asthma” AND “interleukin-5” AND “antibody.” This search yielded 21 results, including two multicentre, randomised, double-blind, placebo-controlled phase 3 trials of benralizumab for patients with uncontrolled eosinophilic asthma published in 2016. On the basis of this systematic review of the literature, benralizumab is the only anti-interleukin 5 receptor α monoclonal antibody treatment for asthma. In these two phase 3 studies, benralizumab significantly reduced the annual rate of exacerbations, increased the forced expiratory volume in 1 s, and improved asthma symptoms relative to placebo at the end of treatment, with complete depletion of blood eosinophil counts.

Added value of this study

This report is, to our knowledge, the first on the safety and efficacy of benralizumab for patients with mild to moderate,

persistent asthma in a phase 3 trial setting. Benralizumab administered every 4 weeks for three doses over the course of 12 weeks improved lung function compared with placebo and had a similar safety profile to placebo. However, the lung function improvement does not warrant use of benralizumab in this population because it did not reach the minimum clinically important difference of 10%.

Implications of all the available evidence

Asthma is a heterogeneous disease, which progresses more rapidly in some patients than in others. Although standard treatment modifications and patient monitoring would be the initial step for most patients with mild to moderate, persistent asthma and disease progression and benralizumab is not being developed for these patients, these findings show the theoretical role of eosinophilia in the disease for these patients, with additional future studies needed to understand benralizumab's potential to modify disease progression.

without asthma.¹⁴ Interleukin 5 is a cytokine that promotes eosinophil development, activation, proliferation, and survival.^{15,16} Two monoclonal antibodies against interleukin 5, mepolizumab and reslizumab, have been approved in the USA and Europe as add-on maintenance treatment for patients with severe asthma and an eosinophilic phenotype.^{8–11} These antibodies reduce eosinophils through a passive mechanism, but do not entirely deplete these cells.^{8,10,11} By contrast, benralizumab, a humanised, afucosylated, monoclonal antibody against interleukin 5 receptor α , induces the direct, rapid, and nearly complete depletion of eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), an apoptotic process of eosinophil elimination involving natural killer cells.^{17,18} Two phase 3 trials, the SIROCCO¹² and CALIMA¹³ trials, have shown that benralizumab in combination with high-dosage ICS plus LABA is well-tolerated and significantly effective at reducing asthma exacerbations and improving symptom control for patients with severe, uncontrolled asthma and eosinophilia (with blood eosinophil counts of ≥ 300 cells per μL). In these studies, benralizumab significantly reduced exacerbations by as much as 51% in the SIROCCO trial and 36% in the CALIMA trial, increased lung function, and improved symptom control.^{12,13} In both studies, benralizumab treatment nearly completely depleted blood eosinophils.^{12,13}

Although a substantial number of patients with mild to moderate asthma have elevated interleukin 5 concentrations and eosinophilia,^{19,20} the efficacy of these anti-interleukin 5-targeted therapies, including benralizumab, has not been explored in mild to moderate disease. If and how these biological pathways might influence mild to moderate disease have not been explored. It is important to investigate

whether such novel therapies can influence or modify mild to moderate disease in patients with asthma to improve understanding of asthma pathophysiology. In this phase 3 trial, the BISE trial, we aimed to assess the effect of antieosinophilic therapy in patients with mild to moderate, persistent asthma receiving maintenance ICS therapy.

Methods

Study design and participants

In this randomised, double-blind, parallel-group, placebo-controlled, phase 3 trial, we recruited patients from 52 clinical research centres in six countries (Canada, Germany, Hungary, Poland, Slovakia, and the USA; appendix p 22). We included in the study male and female patients aged 18–75 years weighing at least 40 kg and with evidence of asthma on the basis of a postbronchodilator reversibility forced expiratory volume in 1 s (FEV_1) of at least 12% at screening. At screening, patients must also have been receiving either low- to medium-dosage ICS (ie, 100–500 μg fluticasone dry powder formulation or equivalent total daily dosage) or low-dosage ICS plus LABA fixed-combination therapy, with or without controller medication. Additionally, patients must have had a morning prebronchodilator FEV_1 of more than 50% to 90% predicted at screening. For inclusion at randomisation, we also required patients to have one or more of the following symptoms within the 7 days before randomisation: a daytime or night-time asthma symptom score of at least 1 for at least 2 days, rescue short-acting β_2 agonist use for at least 2 days, or night-time awakenings due to asthma for at least one night. We excluded patients from the study if they had a clinically important pulmonary disease other than asthma, a history of anaphylaxis with any biological agent, or a helminth

infection diagnosed within 24 weeks before the date of informed consent that had either not been treated with or failed to respond to standard-of-care therapy. Full eligibility criteria are listed in the appendix (pp 4–6).

Approval of the final clinical study protocol was provided by an independent ethics committee or institutional review board of each participating study centre. Before patient enrolment, the final clinical study report was approved by the appropriate national regulatory authority or the national regulatory authority was notified, as per local regulations. All patients provided written informed consent before participation. The study was done in accordance with the ethical principles of the Declaration of Helsinki and is consistent with the International Council for Harmonisation Good Clinical Practice guidelines, applicable regulatory requirements, and the AstraZeneca policy on bioethics.

Randomisation and masking

We randomly allocated patients in a 1:1 ratio to receive either placebo or benralizumab. The study investigators assigned patients a unique enrolment number and randomisation code from an interactive web-based voice response system. We stratified randomisation by baseline blood eosinophil count (<300 cells per μL vs ≥ 300 cells per μL) and region (USA vs the rest of the world). We did the study in a double-blind fashion. To preserve masking, we did not make treatment allocation and effect-revealing laboratory data available to the staff involved in the study, investigators treating the patients, or the patients. Those assessing outcomes were also masked. We visually matched placebo solution to benralizumab solution and provided it in identical accessorised prefilled syringes.

Procedures

We converted all patients' ICS treatments, regardless of their background medications, to therapy with either 180- μg or 200- μg budesonide dry powder inhaler twice daily on enrolment on the basis of the approved dosage in the country of investigation. Patients received this medication for the duration of the study. We provided budesonide (manufactured by AstraZeneca, Gaithersburg, MD, USA) in a Pulmicort Turbuhaler (Flexhalers) inhaler. We withdrew LABA on enrolment for patients who were receiving this agent. Other non-inhaled background asthma therapies allowed during the study are listed in the appendix (pp 2–3).

We administered benralizumab 30 mg/mL (manufactured by AstraZeneca, Gaithersburg, MD, USA) or placebo as a subcutaneous injection solution in a deliverable volume of 1 mL every 4 weeks for 12 weeks. We chose the dosing regimen on the basis of available data from previous phase 2 benralizumab trials.^{21,22} Patients received benralizumab or placebo at week 0, week 4, and week 8 during their study centre visits. We rotated the injection site between different anatomic sites for each visit.

After enrolment (visit 1), patients had two visits during a 2–4 week screening or run-in period (visits 1 and 2), had a randomisation visit (week 0), received treatment for 12 weeks (weeks 0–12), and then had two follow-up visits (weeks 16 and 20). We obtained data from all patients at enrolment, screening, treatment, and follow-up visits. We measured lung function with spirometry at each study centre with equipment that was provided by a central vendor (eResearch Technology, Hoechst, Germany) and met American Thoracic Society and European Respiratory Society recommendations.²³ Properly certified personnel did spirometry according to these guidelines. Additional assessments were asthma symptom score, the Asthma Control Questionnaire with six questions (ACQ-6; six-item questionnaire to assess daytime and night-time asthma symptoms and rescue β agonist use on a 0–6 scale [lesser numbers represent better control]), and the Standardised Asthma Quality of Life Questionnaire for patients 12 years and older (AQLQ(S)+12; 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale [greater numbers represent better quality of life]; appendix pp 7–8). We measured lung function and ACQ-6 at the study centres at week 0, week 4, week 8, and week 12, whereas we did AQLQ(S)+12 assessment at week 0 and week 12. We recorded patient-reported outcomes and daily metrics, including asthma symptom scores, in an electronic asthma daily diary. The asthma daily diary, ACQ-6, and AQLQ(S)+12 have been validated for use in clinical trials.²⁴ We monitored safety over the course of the study and at the follow-up visits on week 16 and week 20 according to the Medical Dictionary for Regulatory Activities version 18.1.

Outcomes

The primary efficacy endpoint was change from baseline in prebronchodilator FEV₁ at week 12, which was centrally assessed. Secondary efficacy endpoints were change from baseline at week 12 in total asthma symptom score, ACQ-6 score, and AQLQ(S)+12 score. Additional secondary endpoints were peripheral blood eosinophil counts, immunogenicity, pharmacokinetics, asthma exacerbations, and change from baseline at week 12 in morning and evening peak expiratory flow at home, total asthma rescue medication use, and night-time awakening due to asthma requiring rescue medication. Safety endpoints were adverse events, serious adverse events, laboratory variables, and physical examination. A complete list of secondary and safety endpoints is available in the appendix (p 9).

Statistical analysis

We deemed approximately 200 patients to be required for the study to be powered for the primary efficacy endpoint analysis. We stratified patients to remove potential confounding effects of geographic region and eosinophil counts on treatment effect. The study had 80% power to

detect a true treatment difference between the benralizumab and placebo groups of 140 mL, assuming an SD of 350 mL and a two-sided 5% level *t* test, and 90% power to detect a true treatment difference of 162 mL. On the basis of the above assumptions, the minimum difference that would be significant at the 5% level was expected to be 98 mL.

We analysed primary and continuous secondary efficacy endpoints (except for AQLQ(S)+12 score) with a mixed-effects model for repeated-measures analysis, with covariates of treatment, baseline value, baseline blood eosinophil count (<300 cells per μL or ≥ 300 cells per μL), protocol-specified visit (week 4, week 8, and week 12), region (Europe or North America), and a treatment-by-visit interaction term. We analysed AQLQ(S)+12 score with analysis of covariance that included covariates of treatment, baseline AQLQ(S)+12 score, baseline blood eosinophil count (<300 cells per μL or ≥ 300 cells per μL), and region (Europe or North America). We used a logistic regression model for responder analysis of ACQ-6 and AQLQ(S)+12 scores, with covariates of treatment, baseline blood eosinophil count (<300 cells per μL or ≥ 300 cells per μL), region (Europe or North America), and baseline value. We did subgroup analyses on the primary efficacy variable for eosinophil counts (<300 cells per μL and ≥ 300 cells per μL), sex, region (Europe or North America), age (<65 years and ≥ 65 years), body-mass index (≤ 35 kg/m² and > 35 kg/m²), and race with a repeated-measures model similar to that of the primary analysis, but with additional subgroup and treatment-by-subgroup interaction terms added. We also did a post-hoc analysis on the primary efficacy variable for patients who did or did not receive LABA before the study. We applied no imputation for the missing data except for ACQ-6 and AQLQ(S)+12 score responder analyses. For the ACQ-6 and AQLQ(S)+12 score responder analyses, we considered a patient to be a non-responder if the data were missing.

We used an intention to treat approach based on the full analysis set for all efficacy analyses. The full analysis set included all patients who were randomly allocated and received treatment, irrespective of their protocol adherence and continued participation in the study. We used the safety analysis set, which included all patients who received at least one dose of study treatment and were classified according to the treatment that they actually received, in the analysis of all safety outcomes. We did all analyses using SAS version 9.2.

AstraZeneca representatives monitored the study at the respective study centres. A global quality assurance group, independent of the study monitors, audited the clinical study process and its associated documentation. This trial is registered with ClinicalTrials.gov, number NCT02322775.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing

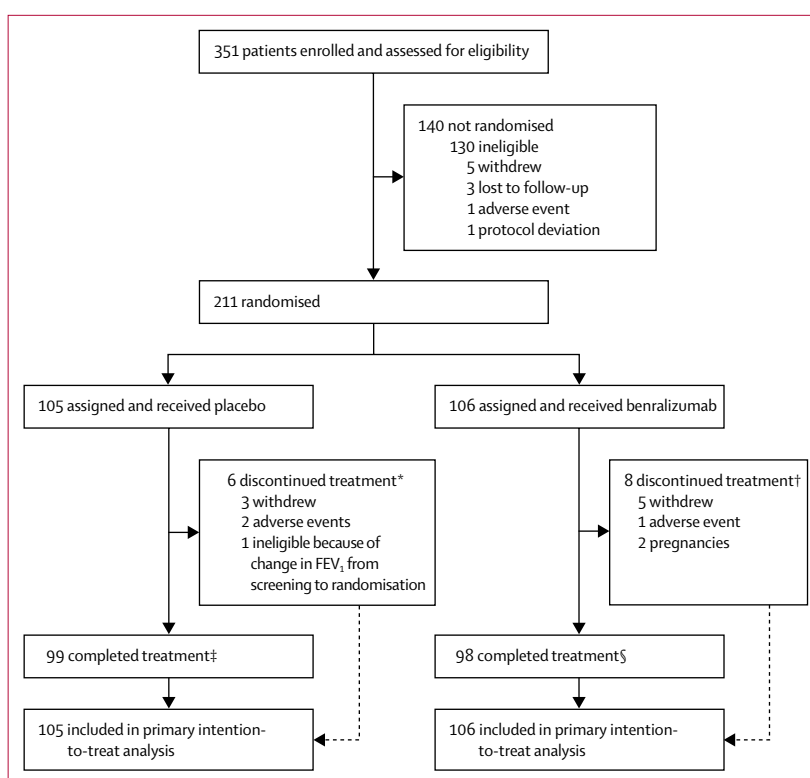


Figure 1: Trial profile

FEV₁=forced expiratory volume in 1 s. *Two patients discontinued treatment but completed the study—ie, attended all study visits. †Five patients discontinued treatment but completed the study. ‡Two patients completed treatment but did not complete the study (one was lost to follow-up and one withdrew). §Two patients completed treatment but did not complete the study (one had a protocol deviation and one had an adverse event).

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

Between Feb 2, 2015, and April 24, 2015, of 351 patients enrolled and assessed for eligibility, we randomly assigned 211 eligible patients to treatment: 105 (50%) to placebo and 106 (50%) to benralizumab (figure 1). The last patient completed the study on Oct 7, 2015. All randomly allocated patients received their intended treatment. 197 (93%) of 211 patients completed treatment (99 [94%] in the placebo group vs 98 [92%] in the benralizumab group) and 14 (7%) discontinued treatment (six [6%] vs eight [8%]). The most common reason for discontinuation for both groups was patients deciding to withdraw: three patients (3%) in the placebo group and five (5%) in the benralizumab group.

Patients had a lower baseline prebronchodilator FEV₁ than what would be expected for this population and were symptomatic, with elevated ACQ-6 scores (table 1). Baseline characteristics were generally similar between the placebo and benralizumab groups. A greater percentage of patients randomly allocated to the placebo

	All patients		Baseline blood eosinophil count ≥300 cells per µL		Baseline blood eosinophil count <300 cells per µL	
	Placebo (n=105)	Benralizumab (n=106)	Placebo (n=33)	Benralizumab (n=28)	Placebo (n=72)	Benralizumab (n=78)
Age (years)	51.1 (12.6)	48.3 (14.4)	49.6 (13.3)	46.4 (16.0)	51.8 (12.3)	49.0 (13.8)
Age group (years)						
≥18 to <50	44 (42%)	49 (46%)	13 (39%)	11 (39%)	31 (43%)	38 (49%)
≥50 to <65	46 (44%)	43 (41%)	15 (45%)	16 (57%)	31 (43%)	27 (35%)
≥65 to ≤75	15 (14%)	14 (13%)	5 (15%)	1 (4%)	10 (14%)	13 (17%)
Sex						
Male	38 (36%)	44 (42%)	12 (36%)	14 (50%)	26 (36%)	30 (38%)
Female	67 (64%)	62 (58%)	21 (64%)	14 (50%)	46 (64%)	48 (62%)
Race						
White	99 (94%)	98 (92%)	31 (94%)	28 (100%)	68 (94%)	70 (90%)
Black or African American	4 (4%)	7 (7%)	2 (6%)	0 (0%)	2 (3%)	7 (9%)
Asian	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Other*	2 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)	0 (0%)
Ethnic group						
Hispanic or Latino	3 (3%)	6 (6%)	1 (3%)	1 (4%)	2 (3%)	5 (6%)
Not Hispanic or Latino	102 (97%)	100 (94%)	32 (97%)	27 (96%)	70 (97%)	73 (94%)
BMI (kg/m ²)	29.4 (6.9)	29.8 (7.0)	29.1 (7.1)	28.6 (7.3)	29.5 (6.9)	30.2 (7.0)
Eosinophil count (cells per µL)	210 (0–1150)	205 (0–940)	440 (300–1150)	455 (300–940)	165 (0–290)	145 (0–290)
FEV ₁ prebronchodilator (mL)	2246 (768)	2248 (606)	2246 (690)	2403 (710)	2247 (805)	2193 (559)
FEV ₁ prebronchodilator (% predicted normal)	71.6% (12.8)	69.7% (10.9)	71.2% (12.9)	70.0% (11.2)	71.7% (12.8)	69.5% (10.8)
FEV ₁ to FVC prebronchodilator	65 (10)	68 (9)	63 (11)	67 (9)	67 (10)	69 (9)
Reversibility (%)	18% (12–42)	19% (12–54)	21% (12–33)	19% (13–53)	18% (12–42)	19% (12–54)
Time since asthma diagnosis (years)	13.0 (0.0–69.0)	15.0 (0.0–66.0)	NA	NA	NA	NA
Number of exacerbations in the last 12 months	0.3 (0.6)	0.3 (0.8)	NA	NA	NA	NA
Total asthma symptom score	1.95 (1.04)	1.93 (0.93)	NA	NA	NA	NA
ACQ-6 score	2.09 (0.90)	2.12 (0.84)	NA	NA	NA	NA
AQLQ(S)+12 score	4.90 (1.03)	4.82 (0.98)	NA	NA	NA	NA
Diagnosis of allergic rhinitis	69 (66%)	66 (62%)	NA	NA	NA	NA
Nasal polyps	7 (7%)	9 (8%)	NA	NA	NA	NA
Smoker†	36 (34%)	19 (18%)	NA	NA	NA	NA
Nicotine pack-years	4.0 (0–9)	5.0 (1–37)	NA	NA	NA	NA

Data are mean (SD), n (%), or median (range). BMI=body mass index. FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. NA=not available. ACQ-6=Asthma Control Questionnaire with six questions. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for patients 12 years and older. *Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other. †Current or former smoker.

Table 1: Baseline characteristics

group than to the benralizumab group were former or current smokers. The most commonly reported asthma trigger was allergen exposure (64 [60%] patients in the benralizumab group vs 63 [60%] in the placebo group). Baseline characteristics were similar between patients with eosinophil blood counts of 300 cells per µL or more and fewer than 300 cells per µL (table 1).

Benralizumab treatment resulted in an 80 mL (95% CI 0–150; p=0.04) greater improvement (least-squares mean difference) from baseline in prebronchodilator FEV₁ after 12 weeks than did placebo treatment (placebo group: 2246 mL [SD 768] at baseline vs 2261 mL [796] at week 12,

change from baseline of 0 mL; benralizumab group: 2248 mL [606] vs 2310 mL [670], 70 mL; table 2, figure 2). In a post-hoc analysis, the difference of change (least-squares mean difference) from baseline in prebronchodilator FEV₁ between the benralizumab and placebo groups was similar for patients who did (least-squares change from baseline of 15 mL in the placebo group vs 83 mL in the benralizumab group; difference between groups 68 mL [95% CI –19 to 154]; p=0.12) or did not (–34 mL vs 50 mL; 84 mL [95% CI –22 to 191]; p=0.12) receive LABA before the study began (appendix p 10). Prebronchodilator FEV₁ changes from baseline between the benralizumab and

placebo groups were similar between patients with baseline blood eosinophil counts of 300 cells per μL or more and fewer than 300 cells per μL (table 2). Other subgroup analyses are presented in the appendix (p 11).

For the secondary endpoints, we noted no significant differences between the benralizumab and placebo groups in total asthma symptom score, ACQ-6 score, or AQLQ(S)+12 score (overall [table 3, figure 3] and domain [appendix p 12] scores). We observed no clear relationship between baseline blood eosinophil counts and total asthma symptom score with benralizumab treatment at week 12 (appendix p 13). We also noted no significant least-squares mean differences between treatment groups for the secondary endpoints of morning peak expiratory flow (least-squares change from baseline of -7.38 mL in the placebo group vs 1.46 mL in the benralizumab group; difference between groups 8.84 mL [95% CI -5.74 to 23.42]; $p=0.23$; appendix p 14), evening peak expiratory flow (-3.65 mL vs 1.64 mL; 5.29 mL [-8.67 to 19.25]; $p=0.46$; appendix p 14), asthma rescue medication use (-0.76 mL vs -1.12 mL; -0.36 mL [-0.91 to 0.19]; $p=0.20$; appendix p 15), or night-time awakenings (-0.14 mL vs -0.16 mL; -0.03 mL [-0.08 to 0.03]; $p=0.38$; appendix p 16).

Benralizumab treatment reduced median blood eosinophil counts to 0 cells per μL (range 0–110) at week 12 compared with 230 cells per μL (30–1000) in the placebo group; depletion of blood eosinophils was maintained through to week 20 in the benralizumab group (table 4). During the study, one (1%) patient had two exacerbations in the benralizumab group and two (2%) in the placebo group had one exacerbation each (appendix p 17). None of the exacerbations required admission to hospital or emergency room visits. At week 12, serum concentrations of benralizumab were an arithmetic mean of 1242 ng/mL (appendix p 18).

Similar incidences of adverse events were reported for patients in the benralizumab and placebo groups during the study period (table 5). The most common adverse events ($\geq 3\%$ of patients in either group) for patients in both the benralizumab and placebo groups were nasopharyngitis, upper respiratory tract infection, worsening asthma, and headaches. Two (2%) patients in the benralizumab group and two (2%) in the placebo group had serious adverse events. For the benralizumab group, serious adverse events were pancytopenia and a suicide attempt, both of which were considered by the investigators to be unrelated to treatment. For the placebo group, serious adverse events were cervix carcinoma and adenoma of the colon. The one (1%) patient in the benralizumab group who developed pancytopenia (occurring 27 days after receiving the third treatment dose) died after exiting the study (157 days after the last dose); the death was not considered to be related to treatment by the investigator (appendix p 19). The patient had normal blood cell counts before the first treatment dose (appendix p 20). We noted no clinically relevant changes in vital signs,

	All patients		Baseline blood eosinophil count of ≥ 300 cells per μL *		Baseline blood eosinophil count < 300 cells per μL *	
	Placebo (n=104) [†]	Benralizumab (n=102) [‡]	Placebo (n=33) [§]	Benralizumab (n=27) [¶]	Placebo (n=71)	Benralizumab (n=75) ^{**}
Baseline (SD [mL])	2246 (768)	2248 (606)	2246 (691)	2403 (710)	2247 (805)	2193 (559)
Week 12 (SD [mL])	2261 (796)	2310 (670)	2341 (694)	2557 (718)	2259 (845)	2230 (624)
LS mean change from baseline to week 12 (mL)	0	70	10	110	-30	40
LS mean difference versus placebo (95% CI [mL])	..	80 (0 to 150)	..	100 (-20 to 220)	..	60 (-20 to 150)
p value	..	0.04	..	0.09	..	0.12

LS=least-squares. *Interaction p value for treatment $\times$ baseline blood eosinophil count=0.57. [†]100 (96%) patients had week 12 data. [‡]98 (96%) patients had week 12 data. [§]31 (94%) patients had week 12 data. [¶]26 (96%) patients had week 12 data. ^{||}69 (97%) patients had week 12 data. ^{**}72 (96%) patients had week 12 data.

Table 2: Prebronchodilator forced expiratory volume in 1 s by baseline eosinophil count

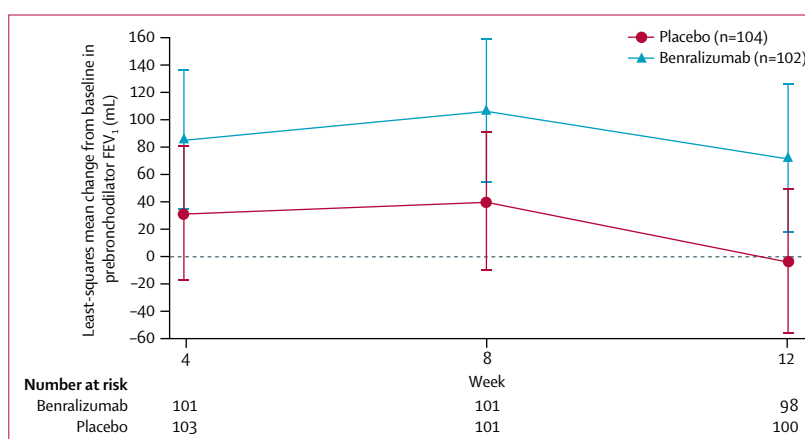


Figure 2: Change in prebronchodilator FEV₁ from baseline with benralizumab treatment for patients with mild to moderate, persistent asthma

Error bars are 95% CIs. FEV₁=forced expiratory volume in 1 s.

electrocardiograms, physical examinations, or laboratory variables between groups (data not shown).

14 (13%) of 106 patients in the benralizumab group had a positive antidrug antibody response compared with two (2%) of 105 in the placebo group (appendix p 21). For these patients with a positive antidrug antibody response in the benralizumab group, median blood eosinophil count at week 12 was 0 cells per μL (IQR 0–10) and it was also 0 cells per μL (0–10) for the negative antidrug antibody group; at week 20, it was 10 cells per μL (0–30) for those with a positive antibody response and 0 cells per μL (0–10) for the negative antidrug antibody group.

Discussion

In the 12 week BISE study, benralizumab administered in combination with ICS yielded a small improvement in lung function. We did this study to provide insight

	Placebo	Benralizumab
Total asthma symptom score		
n	105*	104†
Baseline (SD)	1.95 (1.04)	1.93 (0.93)
Week 12 (SD)	1.54 (1.12)	1.33 (1.04)
LS mean change from baseline to week 12	-0.45	-0.57
LS mean difference versus placebo (95% CI)	..	-0.13 (-0.35 to 0.10)
p value	..	0.27
ACQ-6 score‡		
n	104§	104¶
Baseline (SD)	2.09 (0.90)	2.12 (0.84)
Week 12 (SD)	1.57 (1.01)	1.43 (0.86)
LS mean change from baseline to week 12	-0.55	-0.72
LS mean difference versus placebo (95% CI)	..	-0.17 (-0.39 to 0.04)
p value	..	0.11
Number of responders/total (%)	52/105 (50%)	58/106 (55%)
Odds ratio (95% CI)	..	1.25 (0.72 to 2.19)
p value	..	0.43
AQLQ(S)+12 score 		
n	102**	102**
Baseline (SD)	4.90 (1.03)	4.83 (0.98)
Week 12 (SD)	5.28 (1.09)	5.42 (0.95)
LS mean change from baseline to week 12	0.41	0.62
LS mean difference versus placebo (95% CI)	..	0.21 (0.00 to 0.42)
p value	..	0.06
Number of responders/total (%)	34/105 (32%)	46/106 (43%)
Odds ratio (95% CI)	..	1.65 (0.92 to 2.96)
p value	..	0.10

LS=least-squares. ACQ-6=Asthma Control Questionnaire with six questions. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for patients 12 years and older. *94 (90%) patients had week 12 data. †90 (87%) patients had week 12 data. ‡We defined responders as patients who achieved the minimum important difference between baseline and week 12 in ACQ-6 score of at least -0.5. §100 (96%) patients had week 12 data. ¶99 (95%) patients had week 12 data. ||We defined responders as patients who achieved the minimum important difference between baseline at week 12 in AQLQ(S)+12 score of at least 0.5. **All 102 (100%) patients had week 12 data.

Table 3: Total asthma symptom score, asthma control, and health-related quality of life

into whether or not eosinophilic inflammatory processes play a role in the pathophysiology of mild to moderate forms of asthma. To our knowledge, this study is the first that is powered to assess the effects of an antieosinophilic biological for patients with mild to moderate asthma. Although antieosinophilic treatment is not recommended for this patient population on the basis of these data, our findings suggest that active and modifiable disease processes might be ongoing in patients with mild to moderate asthma receiving ICS.

Patients with mild to moderate asthma are a heterogeneous population with varying symptom severity, exacerbation frequency, responses to standard of care medication, immune system involvement, and biomarker concentrations.^{6,7,14} Mild to moderate disease does not equate to well controlled asthma because patients with mild to moderate asthma do have exacerbations.⁴ Progression of asthma severity from mild to severe is poorly understood, although structural and functional changes in the airways related to exacerbations and airway inflammation are believed to be involved in this process.²⁵ Patients with mild to moderate disease might have active and modifiable disease processes that might benefit from biologicals targeted to inflammatory mechanisms, such as benralizumab.

Persistent sputum eosinophilia is present in 32% of patients with mild to moderate asthma.^{19,20} For these patients, persistent sputum eosinophilia is associated with lower FEV₁ and more severe bronchial hyper-responsiveness than for patients without sputum eosinophilia.⁷ Our finding that benralizumab was associated with a small increase in FEV₁ raises the possibility that some patients enrolled in this study had persistent airway eosinophilia. Small sample sizes of eosinophil subgroups or a poor association between blood eosinophil concentrations and concentrations in other biological fluids and tissue compartments (eg, sputum, airways, and lung parenchyma) could be responsible for the absence of a clear relationship between blood eosinophil counts and FEV₁ in this study. Studies involving larger patient cohorts, longer durations of observation, and more precise assessments of blood, sputum, and tissue eosinophil counts than in this study are needed to further characterise these responders to benralizumab and establish if the response was associated with the degree of eosinophilia.

We chose FEV₁ as the primary endpoint because it is a highly responsive, established indicator for asthma. A significant difference in FEV₁ was achieved with benralizumab treatment. As this difference could potentially have been a result of the requirement to withdraw from LABA at randomisation, we did a post-hoc analysis, indicating that patients whose ICS treatment was converted to budesonide who did or did not receive LABA before the study began had similar FEV₁ improvements. Nevertheless, the improvement in FEV₁, although significant, did not reach the minimum clinically important difference for improvement. The minimum clinically important difference for improvement or worsening of FEV₁ is approximately 10%, although this benchmark is not well established.²⁶ Thus, FEV₁ alone might not be the best assessment of asthma improvement for patients with mild to moderate asthma. The annual exacerbation rate ratio, the primary endpoint for the SIROCCO¹² and CALIMA¹³ trials, was not feasible to assess in this population because the trial was too short to measure this long-term outcome. Future studies

of this patient population need to be of sufficient length and include powered endpoints of annual exacerbation rate ratio and asthma symptoms in addition to those of lung function.

Because an ICS plus LABA regimen is more efficacious than is ICS alone in treatment of asthma,²⁷ this requirement to discontinue LABA use could explain why patients in this study had a lesser baseline pre-bronchodilator FEV₁ and greater ACQ-6 scores than the normally expected values for patients with mild to moderate asthma. An additional potential limitation of this study was source of bias related to reversibility. We limited variability related to reversibility with the inclusion criteria at randomisation, potentially also limiting the ability to see greater improvements in FEV₁.

Benralizumab was well-tolerated, with only 1% of patients discontinuing benralizumab treatment because of adverse events. The percentages of patients reporting adverse events were similar between the two groups, which is consistent with previous studies.^{12,13} One death, which the investigator associated with pancytopenia, was reported in the benralizumab group. After careful examination, the study investigator deemed the case not to be associated with study treatment. During the study, the patient was receiving amiodarone, a drug associated with a risk of development of pancytopenia.²⁸ No other patient in this study had pancytopenia. Additionally, both the SIROCCO¹² and CALIMA¹³ studies, which involved more than 1500 patients receiving benralizumab combined with a full year of drug exposure data, did not report any deaths related to pancytopenia, and only one (non-serious) pancytopenia adverse event was reported in the benralizumab groups for the pooled studies (unpublished). In human beings, interleukin 5 receptor α is exclusively expressed on the surface of eosinophils, basophils, and eosinophil progenitor cells, although data suggest that innate lymphoid type 2 cells might also express interleukin 5 receptor α . Absence of fucose in the Fc domain of benralizumab also results in high affinity for Fc γ RIIIa receptors expressed on immune effector cells, such as natural killer cells, which ultimately leads to apoptosis of interleukin 5 receptor α -expressing cells, through enhanced ADCC.¹⁷ As the ADCC activity of benralizumab is specific to cells that express interleukin 5 receptor α , pancytopenia is unlikely to be related to treatment with benralizumab.

Biologicals for treatment of asthma were initially developed and approved for patients with severe, uncontrolled disease.^{8–13,29} As cost-benefit evaluations for biological therapy are done, identification of biomarkers, such as blood eosinophil concentrations, will be important to establish which patients might benefit most from treatment. The idea of expansion of use of biologicals to patients with less severe disease is a very complicated issue that requires additional studies, but it

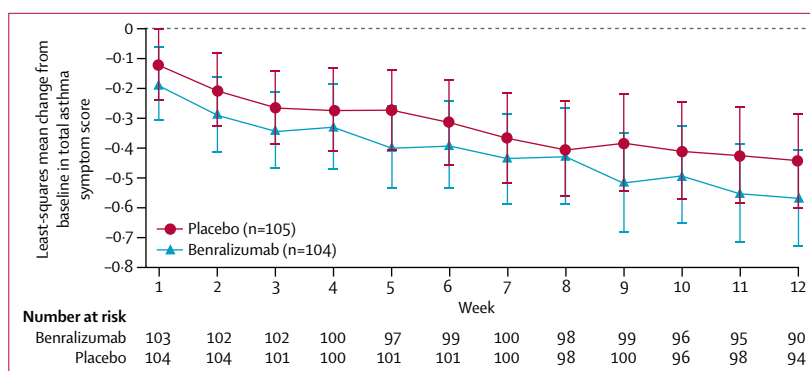


Figure 3: Effect of benralizumab treatment on asthma symptoms of patients with mild to moderate, persistent asthma. Error bars are 95% CIs.

	Placebo (cells per μ L)	Benralizumab (cells per μ L)
Baseline		
n	105	106
Median (range)	220 (40–1140)	170 (30–1060)
Week 12		
n	102	102
Median (range)	230 (30–1000)	0 (0–110)
Week 20		
n	97	100
Median (range)	210 (40–1440)	0 (0–490)

Table 4: Blood eosinophil counts

	Placebo (n=105)	Benralizumab (n=106)
Any adverse event	49 (47%)	44 (42%)
Any treatment-related adverse event	4 (4%)	4 (4%)
Any adverse event leading to treatment discontinuation	2 (2%)	1 (1%)
Any adverse event leading to death	0 (0%)	1 (1%)
Any serious adverse event	2 (2%)	2 (2%)
Adverse events in $\geq 3\%$ of patients		
Nasopharyngitis	8 (8%)	8 (8%)
Upper respiratory tract infection	5 (5%)	5 (5%)
Worsening asthma	3 (3%)	4 (4%)
Headache	1 (1%)	4 (4%)
Injection-site reactions	3 (3%)	0 (0%)
Hypersensitivity*	2 (2%)	1 (1%)

Data are n (%). *None were treatment related.

Table 5: Adverse events, injection-site reactions, and hypersensitivity

is not unlike the approach used for treatment of rheumatoid arthritis.^{30,31} We show in this 12 week study that benralizumab treatment might have an effect on modifiable disease processes in patients with mild to moderate asthma. These results further expand our understanding of disease mechanisms involved in this patient population.

Contributors

GTF, JMF, ERB, and MG conceived and designed the study. PB, YW, MJ, and MG acquired data. All authors analysed and interpreted data and developed, critically reviewed, and approved the manuscript.

Declaration of interests

GTF reports grants and personal fees from AstraZeneca, Novartis, Pearl Therapeutics, and Sunovion, grants from Forest, and personal fees from GlaxoSmithKline (GSK). JMF reports being a member of advisory boards for and has been paid honoraria for lecturing at symposia organised by ALK, AstraZeneca, Boehringer Ingelheim, Novartis, and Teva. ERB has done 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 served as a paid consultant for AstraZeneca, Boehringer Ingelheim, Forest, GSK, MedImmune, Novartis, Pfizer, Regeneron, and Sanofi. ML, DB, and CL received clinical trial funding from AstraZeneca. LM is an advisory board member for Aimmune and has done clinical research for AstraZeneca, Glenmark, GSK, Mylan, Novartis, Pearl, Roche-Genentech, Roxanne, Sanofi, and Teva. PB, YW, MJ, and MG are employees of AstraZeneca.

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