Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial

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Summary

Background Eosinophilia is associated with worsening asthma severity and decreased lung function, with increased exacerbation frequency. We assessed the safety and efficacy of benralizumab, a monoclonal antibody against interleukin-5 receptor α that depletes eosinophils by antibody-dependent cell-mediated cytotoxicity, for patients with severe, uncontrolled asthma with eosinophilia.

Methods We did a randomised, double-blind, parallel-group, placebo-controlled phase 3 study at 374 sites in 17 countries. We recruited patients (aged 12–75 years) with a physician-based diagnosis of asthma for at least 1 year and at least two exacerbations while on high-dosage inhaled corticosteroids and long-acting β_2-agonists (ICS plus LABA) in the previous year. Patients were randomly assigned (1:1:1) by an interactive web-based voice response system to benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses every 4 weeks) or placebo Q4W for 48 weeks as add on to their standard treatment. Patients were stratified 2:1 according to blood eosinophil counts of at least 300 cells per μL and less than 300 cells per μL. All patients and investigators involved in patient treatment or clinical assessment were masked to treatment allocation. The primary endpoint was annual exacerbation rate ratio versus placebo, and key secondary endpoints were prebronchodilator forced expiratory volume in 1 s (FEV_1) and total asthma symptom score at week 48, for patients with blood eosinophil counts of at least 300 cells per μL. Efficacy analyses were by intention to treat (based on the full analysis set); safety analyses included patients according to study drug received. This study is registered with ClinicalTrials.gov, number NCT01928771.

Findings Between Sept 19, 2013, and March 16, 2015, 2681 patients were enrolled, 1205 of whom met the study criteria and were randomly assigned: 407 to placebo, 400 to benralizumab 30 mg Q4W, and 398 to benralizumab 30 mg Q8W. 267 patients in the placebo group, 275 in the benralizumab 30 mg Q4W group, and 267 in the benralizumab 30 mg Q8W group had blood eosinophil counts at least 300 cells per μL and were included in the primary analysis population. Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when given Q4W (rate ratio 0·55, 95% CI 0·42–0·71; p<0·0001) or Q8W (0·49, 0·37–0·64; p<0·0001). Both benralizumab dosing regimens significantly improved prebronchodilator FEV_1 in patients at week 48 compared with placebo (least-squares mean change from baseline: Q4W group 0·106 L, 95% CI 0·016–0·196; Q8W group 0·159 L, 0·068–0·249). Compared with placebo, asthma symptoms were improved by the Q8W regimen (least-squares mean difference –0·25, 95% CI –0·45 to –0·06), but not the Q4W regimen (–0·08, –0·27 to 0·12). The most common adverse events were worsening asthma (105 [13%] of 797 benralizumab-treated patients *vs* 78 [19%] of 407 placebo-treated patients) and nasopharyngitis (93 [12%] *vs* 47 [12%]).

Interpretation These results confirm the efficacy and safety of benralizumab for patients with severe asthma and elevated eosinophils, which are uncontrolled by high-dosage ICS plus LABA, and provide support for benralizumab to be an additional option to treat this disease in this patient population.

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Introduction

Asthma has been estimated to affect more than 315 million people worldwide, with approximately 10% having severe or uncontrolled asthma.[1,2] The worldwide prevalence of asthma continues to increase, and is projected to reach more than 400 million by 2020,[3] representing a growing unmet need for the treatment of patients with uncontrolled disease.

Patients with severe asthma need high-dosage inhaled corticosteroids in combination with long-acting β_2-agonists to control their disease.[4] Despite the proven effectiveness of this approach for most asthmatics, many patients continue to have uncontrolled disease and are at risk for severe asthma exacerbations. Patients with severe, uncontrolled asthma experience a high disease burden, including recurrent exacerbations and hospital

Research in context

Evidence before this study

Benralizumab is a humanised, anti-eosinophil monoclonal antibody against interleukin-5 receptor α that is intended for patients with severe, uncontrolled asthma with eosinophilic inflammation. We searched PubMed on June 7, 2016, for articles with the terms "asthma", "anti-interleukin-5", and "eosinophil" in the title or abstract. This search yielded 29 results, including one study describing a randomised, controlled, double-blind, dose-ranging phase 2b trial of benralizumab for patients with uncontrolled eosinophilic asthma. Based on this systematic review, benralizumab is the only monoclonal antibody against interleukin-5 receptor α used to treat asthma. Benralizumab induces direct, rapid, and nearly complete depletion of eosinophils in the bone marrow, blood, and target tissue via enhanced antibody-dependent cell-mediated cytotoxicity. Given the promising results obtained in the phase 2b trial, we undertook the phase 3 SIROCCO study to confirm the efficacy and safety of benralizumab 30-mg dosage for patients with severe, uncontrolled, eosinophilic asthma, and to seek regulatory approval in the USA, Europe, and Japan.

Added value of this study

This study is, to our knowledge, the first phase 3 trial of benralizumab in patients with severe, uncontrolled asthma with eosinophilic inflammation. Benralizumab given once every 4 or 8 weeks decreased exacerbations and improved lung function, with improvement in asthma symptoms noted with the once every 8 weeks dosage.

Implications of all the available evidence

Severe asthma affects the health and wellbeing of millions of people worldwide. Exacerbations are life threatening for these patients, and their health-related quality of life is substantially diminished. These findings show the potential for benralizumab to improve outcomes for patients with severe asthma.

admissions (defined as admission to an inpatient facility and/or assessment and treatment in a health-care facility for ≥24 h).[5,6] As a result, most health-care resources used for asthma care are attributable to those patients with severe disease.[5,6] Furthermore, the cost of asthma increases proportionally with disease severity.[7]

Eosinophilic inflammation is present in approximately 50% of patients with asthma[8] and is associated with asthma severity, greater frequency of exacerbations, and decreased lung function.[9,10] Additionally, poor asthma control is associated with progressive increases in sputum and blood eosinophil counts.[11]

Interleukin 5 is one of several cytokine mediators involved in eosinophil development, activation, proliferation, and survival, and concentrations of this cytokine in the lungs are increased in patients with asthma.[12,13] Findings from clinical trials have shown efficacy and safety of treatment with monoclonal antibodies against interleukin 5 in patients with asthma and have led to the approval of mepolizumab and reslizumab in the USA and mepolizumab in Europe as add-on maintenance treatment for patients with severe asthma aged 18 years (reslizumab) or 12 years (mepolizumab) and older with an eosinophilic phenotype.[14–17]

Benralizumab is a humanised, afucosylated, monoclonal antibody against interleukin-5 receptor α 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.[18,19] This mechanism is in contrast to current treatments, which target interleukin 5 directly and act through a passive (ie, indirect) mechanism that ultimately results in eosinophil reduction but not depletion.[12] Benralizumab has a broad efficacy profile for patients with severe, uncontrolled asthma with eosinophilic inflammation.[20–22] In a phase 2b study,[22] benralizumab 100 mg Q8W for 1 year seemed to reduce exacerbation rates compared with placebo (0·34 *vs* 0·57; 41% reduction, 80% CI 11–60; p=0·096) for patients with uncontrolled asthma treated with medium-dosage or high-dosage inhaled corticosteroids and long-acting β_2-agonists (ICS plus LABA). A lower 20 mg dosage was efficacious in reducing exacerbation rates (0·30 *vs* 0·68 in placebo, 57% reduction, 80% CI 33–72; p=0·015) in patients with blood eosinophil counts at least 300 cells per μL.[22] Results from this study prompted the decision to investigate a 30 mg dosage in phase 3 trials.[22,23]

We report the results from SIROCCO, one of two phase 3 trials that investigated the efficacy and safety of benralizumab in patients with severe asthma with eosinophilia inadequately controlled with high-dosage ICS plus LABA.

Methods

Study design and participants

SIROCCO was a phase 3, randomised, double-blind, parallel-group, placebo-controlled study done at 374 clinical research centres in Australia, Brazil, Bulgaria, Czech Republic, France, Italy, Mexico, Peru, Poland, Russia, South Africa, South Korea, Spain, Turkey, the UK, the USA, and Vietnam (appendix pp 2–6).

Patients aged 12–75 years who weighed at least 40 kg and who were diagnosed by a physician to have had asthma needing treatment with medium-dosage or high-dosage ICS plus LABA for at least 1 year before enrolment (week –4) were included in the study. Patients must have had at least two documented asthma exacerbations needing systemic corticosteroid treatment or a temporary increase in their usual maintenance dosages of oral corticosteroids within 1 year before enrolment. To be eligible for participation, patients must have had documented treatment of ICS plus LABA with or without

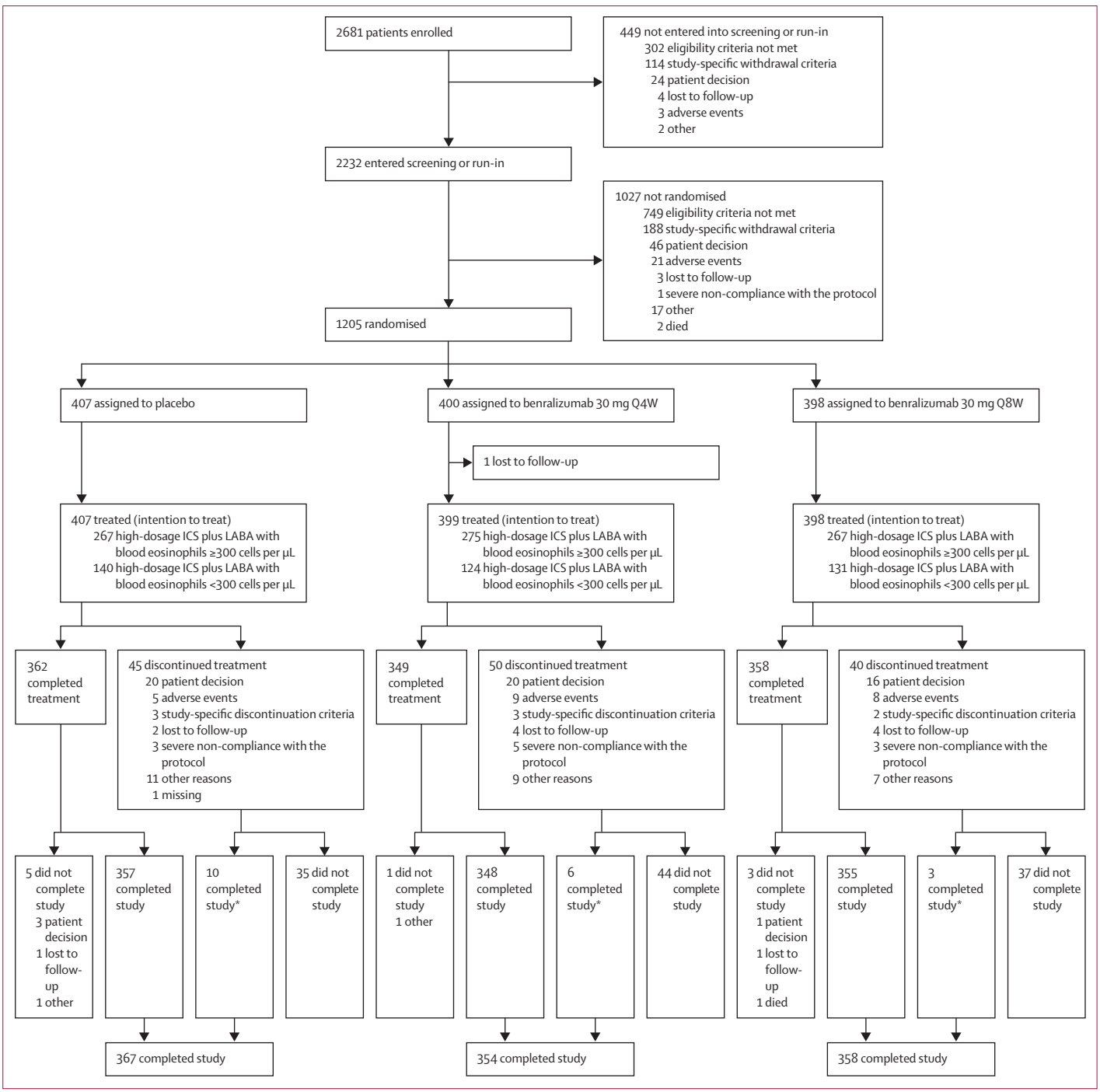

***Figure 1*: Trial profile**

*Discontinued treatment but attended all study visits. ICS=inhaled corticosteroids. LABA=long-acting β_2-agonist. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

oral corticosteroids and additional asthma controllers for at least 3 months before enrolment. Patients aged 18 years or older were permitted only high-dosage inhaled corticosteroid treatment, whereas patients aged 12–17 years could have been receiving medium-dosage or high-dosage inhaled corticosteroids.

Additional inclusion criteria included a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) of less than 80% predicted (<90% predicted for patients aged 12–17 years) at screening (week –3); a documented post-bronchodilator reversibility of at least 12% and at least 200 mL in FEV_1 within 12 months before enrolment

	All patients (n=1204)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per μL (n=809)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per μL (n=395)		
	Placebo (n=407)	Benralizumab 30 mg Q4W (n=399)	Benralizumab 30 mg Q8W (n=398)	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=124)	Benralizumab 30 mg Q8W (n=131)
Age (years)	48·7 (14·9)	50·1 (13·4)	47·6 (14·5)	48·6 (14·7)	49·2 (13·1)	47·6 (14·6)	49·0 (15·3)	52·0 (13·9)	47·8 (14·3)
Age group (years)									
≥12 to <18	23 (6%)	11 (3%)	19 (5%)	12 (4%)	8 (3%)	10 (4%)	11 (8%)	3 (2%)	9 (7%)
≥18 to 75	384 (94%)	388 (97%)	379 (95%)	255 (96%)	267 (97%)	257 (96%)	129 (92%)	121 (98%)	122 (93%)
Sex									
Male	138 (34%)	124 (31%)	146 (37%)	87 (33%)	102 (37%)	93 (35%)	51 (36%)	22 (18%)	53 (40%)
Female	269 (66%)	275 (69%)	252 (63%)	180 (67%)	173 (63%)	174 (65%)	89 (64%)	102 (82%)	78 (60%)
Race									
White	302 (74%)	285 (71%)	287 (72%)	191 (72%)	191 (69%)	192 (72%)	111 (79%)	94 (76%)	95 (73%)
Black or African American	16 (4%)	15 (4%)	15 (4%)	10 (4%)	11 (4%)	10 (4%)	6 (4%)	4 (3%)	5 (4%)
Asian	50 (12%)	54 (14%)	50 (13%)	36 (13%)	39 (14%)	35 (13%)	14 (10%)	15 (12%)	15 (11%)
Other*	39 (10%)	45 (11%)	46 (12%)	30 (11%)	34 (12%)	30 (11%)	9 (6%)	11 (9%)	16 (12%)
Ethnic group									
Hispanic or Latino	77 (19%)	73 (18%)	80 (20%)	57 (21%)	52 (19%)	52 (19%)	20 (14%)	21 (17%)	28 (21%)
Not Hispanic or Latino	330 (81%)	326 (82%)	318 (80%)	210 (79%)	223 (81%)	215 (81%)	120 (86%)	103 (83%)	103 (79%)
Body-mass index (kg/m^2)	28·9 (7·1)	29·2 (7·1)	28·2 (6·2)	28·7 (7·0)	28·9 (6·9)	27·7 (6·1)	29·3 (7·1)	29·9 (7·3)	29·3 (6·2)
Missing data	0	2	0	0	2	0	0	0	0
Eosinophil count (cells per μL)	370 (0–2690)	390 (0–3440)	360 (0–3100)	500 (300–2690)	500 (300–3440)	500 (300–3100)	130 (0–290)	160 (0–297)	180 (0–290)
Missing data	4	4	6	3	1	4	1	3	2
Central eosinophil count (cells per μL)	350 (0–3580)	360 (0–3170)	325 (0–3110)	480 (70–2220)	470 (40–3170)	460 (10–3110)	130 (0–3580)	160 (0–760)	150 (0–460)
Missing data	12	12	16	9	6	10	3	6	6
Prebronchodilator FEV_1 (L)	1·660 (0·584)	1·655 (0·553)	1·680 (0·582)	1·654 (0·580)	1·673 (0·577)	1·660 (0·574)	1·672 (0·594)	1·615 (0·493)	1·721 (0·597)
Predicted normal (%)	56·6% (15·0)	57·4% (14·1)	56·1% (14·6)	56·4% (14·6)	56·5% (14·4)	55·5% (14·6)	57·0% (15·7)	59·4% (13·2)	57·3% (14·7)
Missing data	7	6	1	5	2	1	2	4	0
Prebronchodilator FEV_1/FVC	61 (13)	62 (12)	61 (13)	61 (13)	62 (12)	60 (13)	62 (13)	63 (12)	62 (14)
Missing data	7	6	1	5	2	1	2	4	0
Reversibility (%)	20% (–26 to 154)	18% (–7 to 136)	22% (–12 to 157)	20% (–26 to 154)	18% (–7 to 136)	21% (–10 to 157)	20% (–7 to 138)	17% (–2 to 96)	22% (–12 to 134)
Missing data	26	24	23	16	13	14	10	11	9
ACQ-6 score†	2·87 (0·94)	2·77 (0·96)	2·80 (0·88)	2·90 (0·95)	2·77 (0·95)	2·81 (0·89)	2·82 (0·93)	2·78 (1·00)	2·78 (0·85)

(Table 1 coninues on next page)

or identified at screening; and an Asthma Control Questionnaire, six-question version (ACQ-6) score of at least 1·5 at enrolment.[24] The ACQ-6 is a six-item questionnaire to assess daytime and night-time symptoms and rescue β-agonist use on a 0–6 scale. Patients were excluded from the study if they had a history of anaphylaxis with any biologic drug, a clinically important pulmonary disease other than asthma, or a helminthic parasitic infection diagnosed within 24 weeks before enrolment that had either not been treated or did not respond to standard-of-care treatment. Full inclusion and exclusion criteria are included in the appendix (pp 7–10).

Because the aim of the SIROCCO trial was to establish the effect of benralizumab as an add-on treatment, patients continued receiving their background asthma controller treatments at a stable dosage during the study. Short-acting β_2-agonists were permitted as rescue drugs to control worsening asthma symptoms; the appendix (pp 11–13) lists restricted asthma drugs.

Before any patient was enrolled, an independent ethics committee or institutional review board at each study centre approved the clinical study protocol, and the national regulatory authority either approved the clinical study protocol or received a notification according to local regulations. All patients provided written informed consent at enrolment. The study was done in accordance with the principles of the Declaration of Helsinki and was consistent with the International Council for Harmonisation/Good Clinical Practice and applicable regulatory requirements and AstraZeneca company policy on bioethics.

	All patients (n=1204)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=809)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL (n=395)		
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(Continued from previous page)									
Time since asthma diagnosis (years)	14·2 (1·1–72·4)	15·3 (1·1–70·4)	14·4 (1·1–66·9)	13·4 (1·1–65·2)	14·9 (1·1–62·6)	14·6 (1·1–66·9)	16·8 (1·1–72·4)	17·4 (1·2–70·4)	14·0 (1·2–58·8)
Number of exacerbations in the past 12 months	3·0 (1·8)	2·9 (1·8)	2·8 (1·5)	3·1 (2·0)	3·0 (2·0)	2·8 (1·5)	2·7 (1·5)	2·7 (1·2)	2·6 (1·3)
Number resulting in ED visit	0·3 (0·8)	0·3 (1·0)	0·2 (0·8)	0·3 (0·8)	0·4 (1·0)	0·3 (0·9)	0·2 (0·8)	0·2 (0·9)	0·2 (0·6)
Patients with ≥1 exacerbations resulting in ED visit	67 (16%)	64 (16%)	53 (13%)	48 (18%)	51 (19%)	40 (15%)	19 (14%)	13 (10%)	13 (10%)
Number resulting in hospital admission	0·4 (0·8)	0·4 (0·7)	0·4 (0·8)	0·4 (0·8)	0·3 (0·7)	0·4 (0·9)	0·4 (0·8)	0·4 (0·9)	0·3 (0·8)
Patients with ≥1 exacerbations resulting in hospital admission	107 (26%)	98 (25%)	100 (25%)	67 (25%)	66 (24%)	71 (27%)	40 (29%)	32 (26%)	29 (22%)
Total asthma symptom score	2·68 (1·07)	2·72 (1·02)	2·70 (1·11)	2·74 (1·08)	2·67 (1·01)	2·68 (1·09)	2·57 (1·07)	2·84 (1·02)	2·73 (1·14)
Missing data	0	1	3	0	1	2	0	0	1
Diagnosis of allergic rhinitis	220 (54%)	207 (52%)	219 (55%)	156 (58%)	148 (54%)	150 (56%)	64 (46%)	59 (48%)	69 (53%)
Nasal polyps	79 (19%)	84 (21%)	74 (19%)	62 (23%)	66 (24%)	62 (23%)	17 (12%)	18 (15%)	12 (9%)
Atopic (based on Phadiatop test)	230 (57%)	231 (58%)	244 (61%)	152 (57%)	156 (57%)	169 (63%)	78 (56%)	75 (60%)	75 (57%)
History of omalizumab treatment	31 (8%)	29 (7%)	28 (7%)	22 (8%)	16 (6%)	18 (7%)	9 (6%)	13 (10%)	10 (8%)
Missing data	3	1	1	2	1	1	1	0	0
AQLQ(S)+12 score‡	3·90 (1·02)	3·93 (0·98)	3·94 (1·00)	3·87 (0·99)	3·93 (1·00)	3·93 (0·97)	3·97 (1·07)	3·92 (0·95)	3·97 (1·04)
Missing data	15	17	17	12	12	12	3	5	5
Smoker	5 (1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)	4 (3%)	0	0
Nicotine pack-years	5·0 (0–9)	5·0 (0–9)	5·0 (0–9)	5·0 (0–9)	6·0 (0–9)	5·0 (0–9)	5·0 (0–9)	5·0 (1–9)	5·0 (0–9)

Data are mean (SD), number (%), or median (range). Some percentages do not add up to 100 because of rounding. ICS=inhaled corticosteroids. LABA=long-acting β_2-agonsists. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). ACQ-6=Asthma Control Questionnaire, six-question version. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. ED=emergency department. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. *Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or other. †Low numbers represent better symptom control. ‡High numbers suggest better quality of life. §Current smoker or former smoker with a smoking history of ≥10 packs per year.

Table 1: **Baseline demographics and clinical characteristics (full analysis set)**

Randomisation and masking

All adult patients, and adolescent patients enrolled at non-European Union (EU) sites, were randomly assigned (1:1:1) to one of three 48-week treatment groups: subcutaneous benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses given 4 weeks apart), or matching placebo. This dosing regimen was chosen based on an exposure–response analysis of data from the phase 2b study with benralizumab involving patients with uncontrolled asthma.[22,23] Adolescent patients enrolled at sites in the EU were randomly assigned to one of two treatment groups: subcutaneous benralizumab 30 mg Q8W (first three doses given Q4W) or matching placebo to accommodate a request by the Paediatric Committee at the European Medicines Agency to limit drug burden in adolescents.

Each patient was assigned a unique enrolment number and randomisation code by an interactive web-based voice response system. Randomisation was stratified by age group (adult or adolescent), country (in adults) or region (within the EU and outside the EU for adolescents), and blood eosinophil counts. The randomisation stratified patients (2:1) for blood eosinophil counts of at least 300 cells per µL and less than 300 cells per µL, which were measured at a local laboratory. The randomisation was stratified to enrich the study population with patients most likely to benefit from benralizumab treatment and to provide insight into efficacy in patients with low baseline blood eosinophil counts. Randomisation codes were assigned by the study investigator sequentially in each stratum as patients became eligible for randomisation, until each stratum was full.

The study was planned with a double-blind, double-dummy design to ensure masking throughout. The identity of the treatment allocation was not made available to the patients, investigators involved in patient treatment or clinical assessment, or study funder. Placebo solution was visually matched with benralizumab solution.

	High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per μL			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per μL		
	Placebo	Benralizumab 30 mg Q4W	Benralizumab 30 mg Q8W	Placebo	Benralizumab 30 mg Q4W	Benralizumab 30 mg Q8W
Primary endpoint						
Annual asthma exacerbation rate over 48 weeks*						
Number of patients analysed	267	275	267	140	124	131
Rate estimate (95% CI)	1·33 (1·12–1·58)	0·73 (0·60–0·89)	0·65 (0·53–0·80)	1·21 (0·96–1·52)	0·85 (0·65–1·11)	1·00 (0·78–1·28)
Absolute difference estimate (95% CI)	..	−0·60 (−0·87 to −0·33)	−0·68 (−0·95 to −0·42)	..	−0·36 (−0·71 to −0·00)	−0·21 (−0·58 to 0·16)
Rate ratio *vs* placebo (95% CI; p value)	..	0·55 (0·42–0·71; <0·0001)	0·49 (0·37–0·64; <0·0001)	..	0·70 (0·50–1·00; 0·0471)	0·83 (0·59–1·16; 0·2685)
Key secondary endpoints (48 weeks)						
Prebronchodilator FEV_1 (L)†						
Number of patients analysed‡	261	271	264	138	120	129
LS mean change (number of patients§)	0·239 (233)	0·345 (236)	0·398 (235)	0·145 (125)	0·120 (105)	0·248 (119)
LS mean difference *vs* placebo (95% CI; p value)	..	0·106 (0·016 to 0·196; 0·0215)	0·159 (0·068 to 0·249; 0·0006)	..	−0·025 (−0·134 to 0·083; 0·6438)	0·102 (0·003 to 0·208; 0·568)
Total asthma symptom score†¶						
Number of patients analysed‡	267	273	263	139	123	127
LS mean change (number of patients§)	−1·04 (180)	−1·12 (197)	−1·30 (178)	−0·77 (99)	−0·97 (93)	−1·06 (91)
LS mean difference *vs* placebo (95% CI; p value)	..	−0·08 (−0·27 to 0·12; 0·4420)	−0·25 (−0·45 to −0·06; 0·0118)	..	−0·20 (−0·48 to 0·08; 0·1688)	−0·29 (−0·57 to −0·01; 0·0431)

ICS=inhaled corticosteroids. LABA=long-acting β_2-agonsists. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). FEV_1=forced expiratory volume in 1 s. LS=least squares. *Estimates calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations. †Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment. ‡Patients with a baseline and at least one post-baseline assessment. §Numbers of patients at 48 weeks. ¶A decrease in score suggests an improvement.

***Table 2*: Primary and key secondary endpoints**

Procedures

Benralizumab and placebo were provided in pre-filled syringes (accessorised with needle guards and finger phalanges) containing a deliverable volume of 1 mL containing 30 mg/mL solution or matching placebo solution for injection (manufactured by AstraZeneca, Gaithersburg, MD, USA). Patients assigned to the benralizumab Q4W dosing schedule or placebo were given their randomly assigned treatments at study centre visits at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44, whereas patients assigned to the benralizumab Q8W dosing schedule were given benralizumab at study centre visits on weeks 0, 4, 8, 16, 24, 32, and 40 and placebo at the intervening visits. The site of injection was rotated between different anatomical sites at each visit.

Data were collected from all patients at enrolment, screening, randomisation (week 0), every 4-week interval during the treatment period (weeks 4–48), and follow-up (week 56, for patients not continuing in BORA [NCT02258542], an open-label extension study). Study investigators at each site did prebronchodilator spirometry at screening, then weeks 0, 4, 8, 16, 24, 32, 40, and 48. Lung function assessments (FEV_1 and forced vital capacity) were done according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[25] Properly certified personnel did the spirometry testing using equipment that was supplied by a central spirometry vendor (eResearch Technology GmbH, Estenfeld, Germany) and met ATS/ERS recommendations. Additional assessments included asthma symptom score, ACQ-6,[24] Standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12; a 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale), anti-drug antibodies, and overall measurement of response to treatment (appendix pp 14–15). Patient-reported outcomes and daily metrics, including ACQ-6, AQLQ(S)+12, and asthma symptom scores, were recorded using an electronic Asthma Daily Diary. The Asthma Daily Diary, ACQ-6, and AQLQ(S)+12 have been validated for use in clinical trials.[24] Safety was monitored at each study centre visit from enrolment, during the screening or run-in period, during the treatment period, and at a follow-up visit on week 56.

Outcomes

The primary efficacy endpoint was the annual asthma exacerbation rate ratio versus placebo, which is summarised as total number of exacerbations × 365·25/ total duration of follow-up within the treatment group (days). An exacerbation was defined as a worsening of asthma that led to one of the following: (1) use of systemic corticosteroids, or temporary increase in a stable oral corticosteroid background dosage, for at least 3 days or a single injectable dose of corticosteroids; (2) emergency department or visit to an urgent care centre (<24 h) because of asthma that needed systemic corticosteroids; or (3) inpatient hospital stay (≥24 h) because of asthma. 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 (appendix p 16).

Key secondary endpoints (ie, multiplicity [type I error]–protected endpoints) for the primary analysis population were prebronchodilator FEV_1 and total asthma symptom score (a composite of daytime and night-time symptoms scored 0–6 overall) at week 48. The primary and key secondary analyses of efficacy included patients with blood eosinophil counts at least 300 cells per µL. Additional secondary endpoints were time to first asthma exacerbation, annual rate of asthma exacerbations that were associated with a visit to an emergency department or urgent care centre or admission to hospital, post-bronchodilator FEV_1, ACQ-6 score,[24] and AQLQ(S)+12 score. All efficacy endpoints were also assessed in patients with blood eosinophil counts less than 300 cells per µL, with statistical comparisons not done for patients with less than 300 eosinophils per µL for non-key secondary outcomes (except ACQ-6) and summarised descriptively. Safety outcomes were adverse events, serious adverse events, laboratory variables, electrocardiograms, vital signs, and immunogenicity.

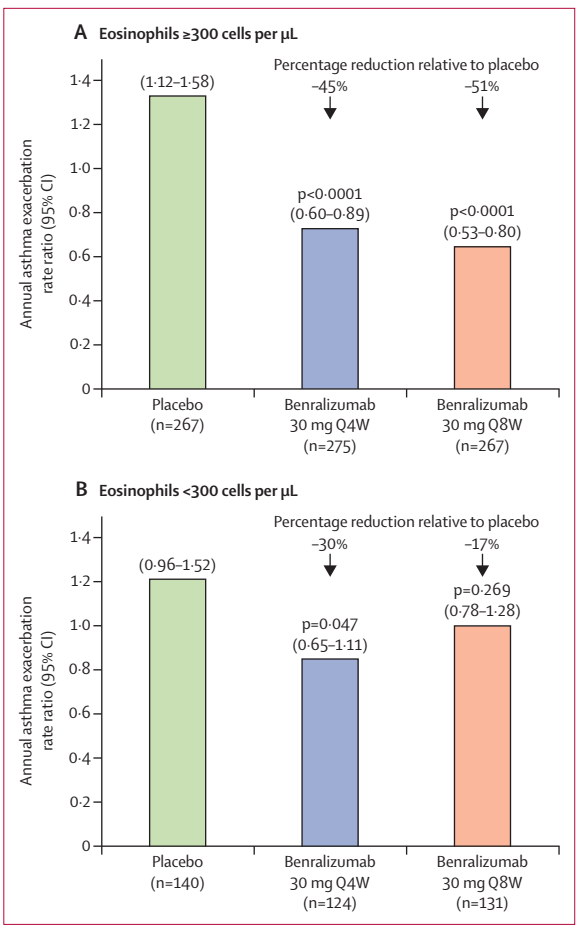

***Figure 2*: Annual asthma exacerbation rate estimates at 48 weeks according to baseline blood eosinophil concentrations**

Data for patients with baseline blood eosinophils (A) ≥300 cells per µL and (B) <300 cells per µL in the full analysis set are shown. Estimates were calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

Statistical analysis

We calculated that for the primary analysis of efficacy, approximately 252 patients with blood eosinophil counts at least 300 cells per µL per treatment group (756 total) were needed for 90% power to detect a 40% reduction in annual exacerbation rate in both benralizumab dosage regimens compared with placebo, assuming a two-sided 4% α (appendix p 18) and an annual placebo exacerbation rate of 0·88 events per patient, based on published phase 2b data.[22,23] The sample size calculation was based on simulations and a negative binomial shape parameter of 0·9, on the basis of corresponding data from phase 2b trial results.[22] A total enrolment of 1134 adults and adolescents for randomisation was needed, including the enrolment of 126 patients per group (378 total) for the less than 300 cells per µL blood eosinophil cohort.

We analysed the primary efficacy endpoint using a negative binomial model, with adjustment for treatment, region, exacerbations in the previous year (two, three, or four or more), and oral corticosteroid use at time of randomisation. The estimated treatment effect (ie, rate ratio of benralizumab *vs* placebo), corresponding 95% CI, and two-sided p value for the rate ratio were calculated. The annual exacerbation rate and corresponding 95% CIs within each treatment group were also calculated. We also did prespecified subgroup analyses to assess the exacerbation rate in subgroups of clinical relevance (appendix p 17). We did a post-hoc analysis in the primary analysis population to assess the treatment effect of a history of at least three exacerbations experienced by patients in the previous year using a separate negative binomial model with adjustment for treatment, region, oral corticosteroid use, and number of previous exacerbations.

We analysed the key secondary endpoints using a mixed-effects model for repeated measures analysis, with

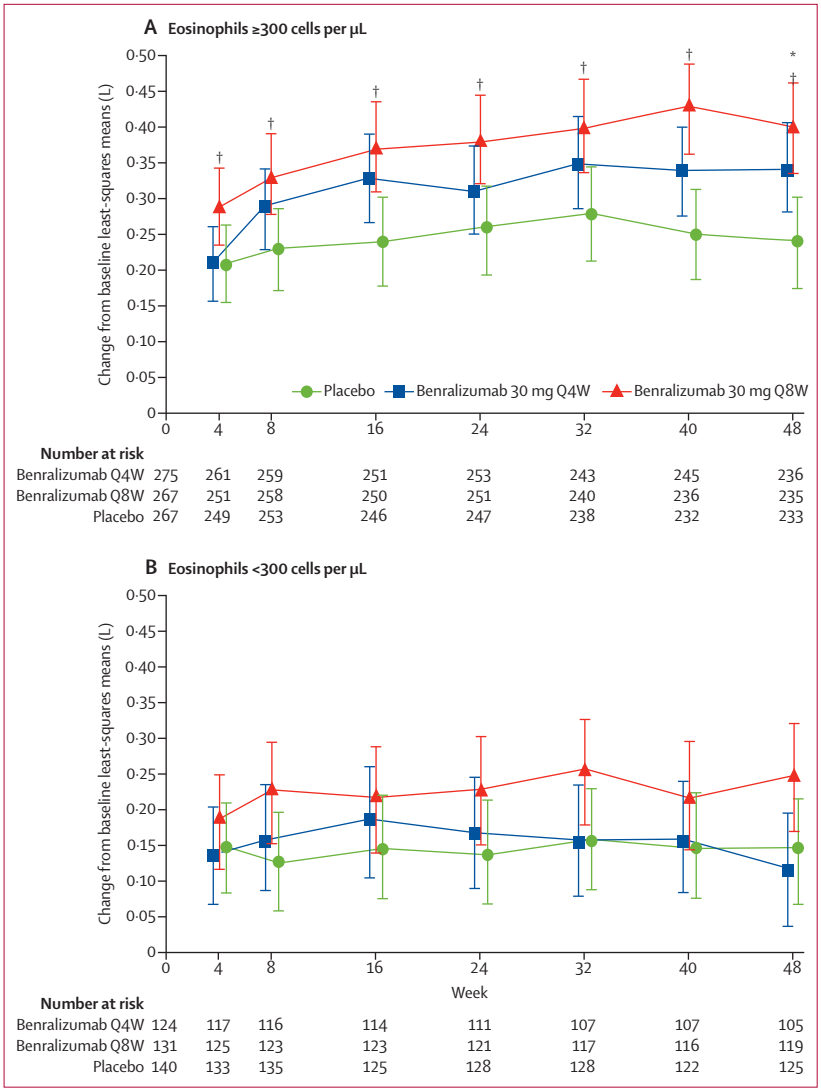

***Figure 3*: Change from baseline in prebronchodilator forced expiratory volume in 1 s according to baseline blood eosinophil concentrations**

Data for patients with baseline blood eosinophils (A) ≥300 cells per μL and (B) <300 cells per μL in the full analysis set are shown. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *p<0·05 for benralizumab 30 mg Q4W *vs* placebo. †p<0·05 for benralizumab 30 mg Q8W *vs* placebo.

adjustment for treatment, region, baseline value, oral corticosteroid use at time of randomisation, visit, and visit×treatment. Least-squares means, treatment differences in least-squares means, 95% CIs, and p values were calculated. We analysed the other continuous secondary efficacy endpoints using a mixed-effects model for repeated measures analysis. Time to first asthma exacerbation was analysed using a Cox proportional hazard model, with adjustment for treatment, region, exacerbations in the previous year, and oral corticosteroid use at time of randomisation.

To account for multiplicity to test the primary endpoint and two key secondary endpoints (ie, change from baseline in FEV_1 and asthma symptom score) for each of the two benralizumab dosing regimens, we followed a multiple testing procedure to control the overall type I error rate (appendix p 18). The testing procedure permitted two tests of annual asthma exacerbation rate (one test for each dosing regimen *vs* placebo) at the family-wise error rate of 0·04 using a Hochberg procedure. If both p values were less than 0·04, then the two key secondary endpoints could be tested for both dosing regimens at a family-wise error rate of 0·05 using a Holm procedure.

All efficacy analyses were done in the intention-to-treat population; that is, all randomly assigned patients who received any study treatment, regardless of their protocol adherence and continued participation in the study. Safety analyses were based on the actual treatment regimen received and included all patients who received at least one dose of study drug. All analyses were done using SAS version 9.2.

A data safety monitoring board and two independent adjudication committees (one for asthma-associated emergency department visits and/or hospital admissions; the other for major adverse cardiovascular events or malignancies) oversaw the study (appendix p 19). This study is registered with ClinicalTrials.gov, number NCT01928771.

Role of the funding source

The funders of the study participated in the study design. All authors, including those employed by the funders of the study, participated in the 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

Between Sept 19, 2013, and March 16, 2015, we enrolled 2681 patients, 2232 of whom were screened for eligibility (figure 1). 1205 patients who met study entry criteria were randomly assigned to treatment: 407 to placebo, 400 to benralizumab 30 mg Q4W, and 398 to benralizumab Q8W. One patient in the benralizumab 30 mg Q4W group was lost to follow-up before treatment; all other patients received their assigned treatments. 267 patients in the placebo group, 275 in the benralizumab 30 mg Q4W group, and 267 in the benralizumab 30 mg Q8W group had blood eosinophil counts at least 300 cells per μL (figure 1). 1069 (89%) of 1204 patients completed treatment with the study drug and 135 (11%) discontinued treatment. The proportions of patients who discontinued treatment were similar across groups. The most common reason for discontinuation of treatment was patient decision (56 patients [5%]; figure 1). Baseline characteristics were similar across randomised treatment groups and between patients with blood eosinophil counts at least 300 cells per μL and less than 300 cells per μL (table 1). Use of

	High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per μL			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per μL		
	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=124)	Benralizumab 30 mg Q8W (n=131)
ACQ-6 score (week 48)*†						
Number of patients analysed‡	267	274	263	138	124	130
LS mean change	–1·17 (186)	–1·32 (198)	–1·46 (191)	–0·89 (97)	–0·89 (89)	–1·11 (94)
LS mean difference *vs* placebo (95% CI; p value)	..	–0·15 (–0·34 to 0·04; 0·1107)	–0·29 (–0·48 to –0·10; 0·0028)	..	0·00 (–0·27 to 0·27; 0·9903)	–0·22 (–0·48 to 0·05; 0·1066)
AQLQ(S)+12 score*§						
Number of patients analysed‡	254	261	252	..	..	..
LS mean change	1·26 (180)	1·44 (192)	1·56 (187)	..	..	..
LS mean difference *vs* placebo (95% CI; p value)	..	0·18 (–0·02 to 0·37; 0·0811)	0·30 (0·10–0·50; 0·0036)	..	..	..

We did not do a formal statistical analysis of the data from the <300 cells per μL group for AQLQ(S)+12 score. ICS=inhaled corticosteroids. LABA=long-acting β_2-agonsists. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). ACQ-6=Asthma Control Questionnaire, six-question version. LS=least squares. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. *Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit × treatment. †Low numbers represent better control. ‡Patients with a baseline and at least one post-baseline assessment. §High numbers suggest better quality of life.

***Table 3*: Changes in health-related quality of life, and productivity at week 48 (secondary endpoints)**

maintenance asthma treatment use was similar across groups, with a mean fluticasone propionate or equivalent total daily dosage of 899 μg (range 125–3000; appendix p 20). 196 (16%) patients were receiving oral corticosteroids, with similar dosing between cohorts.

Unless otherwise specified, all results are presented for patients with baseline blood eosinophil counts at least 300 cells per μL. For the primary endpoint, both dosing regimens of benralizumab significantly decreased the annual asthma exacerbation rate compared with placebo at week 48 (table 2; figure 2). For the Q4W cohort, the rate ratio versus placebo was 0·55 (95% CI 0·42–0·71; p<0·0001), and for the Q8W cohort, it was 0·49 (0·37–0·64; p<0·0001).

Both benralizumab dosing regimens significantly improved prebronchodilator FEV_1 in patients at week 48 compared with placebo (table 2). The difference in least-squares mean change from baseline between the benralizumab Q4W and placebo cohorts was 0·106 L (95% CI 0·016–0·196; p=0·0215) and between the benralizumab Q8W and placebo cohorts it was 0·159 L (0·068–0·249; p=0·0006). Benralizumab treatment Q8W also resulted in improved asthma symptoms, as indicated by a greater decrease in total asthma symptom score at week 48 compared with placebo treatment (least-squares mean difference –0·25, 95% CI –0·45 to –0·06; p=0·0118); however, the difference was not significant for the Q4W regimen (–0·08, –0·27 to 0·12; p=0·4420; table 2).

During the 48-week period, the curves for the cumulative number of exacerbations in the benralizumab-treated and placebo cohorts diverged as early as 4 weeks (the first sampling timepoint; appendix p 21). Additionally, the time to first asthma exacerbation was longer for both benralizumab treatment cohorts compared with placebo, with the probability of having an asthma exacerbation reduced by 37% (hazard ratio 0·63, 95% CI 0·49–0·82; p=0·0005) for the Q4W cohort and by 40% (0·60, 0·46–0·78; p=0·0002) for the Q8W cohort (appendix p 22). The prebronchodilator FEV_1 increase relative to baseline for the benralizumab Q8W cohort was greater than for the placebo cohort throughout the treatment period starting at week 4 (p<0·05; figure 3). Post-bronchodilator FEV_1 also increased at week 48 with both treatment regimens (Q4W cohort p=0·0369; Q8W cohort p=0·0357; appendix p 23). The decrease in total asthma score for the Q8W cohort also began early in treatment, with the decrease being consistently greater than placebo treatment (p<0·05 from week 36; appendix p 24); however, differences between placebo and the benralizumab Q4W cohort were not statistically significant.

The benralizumab Q8W cohort had reduced asthma exacerbations leading to emergency department visits or hospital admissions compared with placebo treatment (rate ratio 0·37, 95% CI 0·20–0·67; p=0·0010), and for the Q4W cohort, the rate ratio was 0·61 (0·37–1·01; p=0·0529; appendix p 25). Compared with placebo, benralizumab treatment Q8W also improved ACQ-6 (least-squares mean difference –0·29, 95% CI –0·48 to –0·10; p=0·0028) and health-related quality of life (AQLQ(S)+12 score; 0·30, 0·10–0·50; p=0·0036), but findings for the benralizumab Q4W group were not significant (ACQ-6 p=0·1107; AQLQ(S)+12 p=0·0811; table 3).

Patients who had blood eosinophil counts less than 300 cells per μL and received benralizumab Q4W achieved improvements in exacerbation rate (p=0·0471), and those who received the Q8W dosage had improvements in asthma symptoms (p=0·0431); no

	Placebo (n=407)	Benralizumab 30 mg Q4W (n=403)*	Benralizumab 30 mg Q8W (n=394)
Any adverse event	311 (76%)	293 (73%)	281 (71%)
Any adverse event leading to treatment discontinuation	3 (<1%)	9 (2%)	8 (2%)†
Any serious adverse event	55 (14%)	47 (12%)	52 (13%)
Deaths	2 (1%)	2 (<1%)	1 (<1%)
Adverse events in >3% of patients‡			
Asthma	78 (19%)	60 (15%)	45 (11%)
Nasopharyngitis	47 (12%)	47 (12%)	46 (12%)
Upper respiratory tract infection	36 (9%)	44 (11%)	32 (8%)
Headache	21 (5%)	30 (7%)	37 (9%)
Bronchitis	30 (7%)	24 (6%)	19 (5%)
Sinusitis	28 (7%)	17 (4%)	22 (6%)
Influenza	23 (6%)	17 (4%)	19 (5%)
Pharyngitis	14 (3%)	17 (4%)	23 (6%)
Rhinitis	15 (4%)	16 (4%)	10 (3%)
Arthralgia	10 (2%)	11 (3%)	18 (5%)
Cough	10 (2%)	15 (4%)	13 (3%)
Pyrexia	8 (2%)	16 (4%)	12 (3%)
Back pain	15 (4%)	11 (3%)	8 (2%)
Acute sinusitis	10 (2%)	10 (2%)	13 (3%)
Rhinitis allergic	8 (2%)	11 (3%)	12 (3%)
Nausea	8 (2%)	8 (2%)	12 (3%)
Gastroenteritis	6 (1%)	9 (2%)	12 (3%)
Pain in extremity	5 (1%)	3 (1%)	13 (3%)
Injection-site reactions	8 (2%)	16 (4%)	9 (2%)
Hypersensitivity adverse events§	11 (3%)	13 (3%)	11 (3%)
Causally related¶	2 (<1%)	2 (<1%)	2 (<1%)
Urticaria	2 (<1%)	1 (<1%)	2 (<1%)
Allergic granulomatous angiitis	0	1 (<1%)	0

Data are number of patients (%). The on-treatment period was defined as the day of first dose of study treatment to the scheduled end-of-treatment visit. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).*Includes four patients in the Q8W cohort who received extra doses of benralizumab. †One additional patient discontinued the study after receiving their last dose but before attending the end-of-treatment visit. ‡Medical Dictionary for Regulatory Activities version 18.1. §High-level term. ¶In the opinion of the investigator.

***Table 4*: Adverse events, injection-site reactions, and hypersensitivity during the on-treatment period in the safety population**

other secondary endpoints were significant in patients who had blood eosinophil counts less than 300 cells per µL (tables 2 and 3). However, this study was not powered to detect differences within this group.

Findings from prespecified subgroup analyses suggested that geographical region might affect treatment response (appendix p 27). Patients from each region displayed substantial heterogeneity of baseline characteristics between regions, particularly with regard to exacerbation history (appendix p 28).

In the at least 300 cells per µL population, blood eosinophil counts were reduced in both benralizumab groups by week 4 to a median of 0 cells per µL (IQR 0–10) from similar baseline values (450 cells per µL [300–720] for Q4W and 440 cells per µL [280–691] for Q8W), whereas blood eosinophil counts in the placebo cohort remained similar between baseline and week 4 (appendix p 29). This reduction was maintained at week 48. Findings were similar for patients with blood eosinophil counts less than 300 cells per µL (appendix p 29).

In a post-hoc analysis of patients who had at least three exacerbations in the previous year, patients in the benralizumab Q8W cohort who had at least 300 blood eosinophils per µL had greater improvements relative to placebo in annual exacerbation rate ($p<0·0001$), FEV_1 ($p=0·0018$), total asthma symptom score ($p=0·0420$), and ACQ-6 ($p=0·0458$) than the overall population with at least 300 cells per µL (appendix). Patients in the benralizumab Q4W cohort also had greater improvements relative to placebo in annual exacerbation rate ($p=0·0010$); whereas FEV_1, total asthma symptom score, ACQ-6, and AQLQ(S)+12 were similar to placebo (see appendix for results for patients with a history of two exacerbations in the previous year).

Adverse events during the treatment period were reported by similar percentages of patients who received benralizumab (574 [72%] of 797) or placebo (311 [76%] of 407; table 4). Percentages of patients experiencing adverse events were also similar between treatment groups, irrespective of baseline eosinophil counts (appendix p 30). The most common adverse events in patients treated with benralizumab were worsening asthma (105 [13%]), nasopharyngitis (93 [12%]), and upper respiratory tract infection (76 [10%]); adverse events related to asthma were reported by proportionally less patients in the benralizumab-treated groups than in the placebo group (table 4). Serious adverse events were also reported by similar percentages of patients who received benralizumab (99 [12%]) or placebo (55 [14%]). The most common serious adverse event in all patients was worsening asthma (31 [8%] in the placebo group *vs* 22 [5%] in the benralizumab Q4W group *vs* 24 [6%] in the benralizumab Q8W group); no other serious adverse event was experienced by more than 1% of patients. Four serious adverse events were judged by the investigator to be related to treatment: three in the benralizumab Q4W cohort (allergic granulomatous angiitis, panic attack, and paraesthesia) and one in the placebo cohort (injection-site erythema). 18 patients (2%) receiving benralizumab and three (1%) receiving placebo discontinued treatment because of adverse events. Five patients died during treatment: two in the benralizumab Q4W cohort (cerebral haemorrhage and asthma), one in the benralizumab Q8W cohort (accidental opioid overdose), and two in the placebo cohort (pulmonary embolism and cause unknown). Additionally, one patient with a post-treatment adverse event died in the Q8W

cohort (sudden death of unknown cause). None of the deaths was considered related to treatment.

33 patients (3%) experienced injection-site reactions: 16 (4%) of 403 patients on benralizumab Q4W, nine (2%) of 394 on benralizumab Q8W, and eight (2%) of 407 on placebo (table 4). Similar percentages of patients experienced hypersensitivity adverse events: 13 (3%) on benralizumab Q4W, 11 (3%) on benralizumab Q8W, and 11 (3%) on placebo. Six patients reported hypersensitivity adverse events that the investigator deemed to be causally related to treatment (five with urticaria and one with allergic granulomatous angiitis). Positive anti-drug antibody response was noted in 105 (13%) of 797 patients in the benralizumab groups (appendix p 31). There was no suggestion that positive anti-drug antibody response was associated with hypersensitivity or affected efficacy outcomes (data not shown).

Discussion

In the phase 3 SIROCCO study, the anti-eosinophil monoclonal antibody benralizumab significantly reduced the annual rate of exacerbations by up to 51% after 48 weeks of treatment in patients with severe, uncontrolled asthma with eosinophilia (blood eosinophil counts ≥300 cells per µL). Benralizumab also significantly improved pulmonary function, with a 0·106–0·159 L increase in prebronchodilator FEV_1 relative to placebo, depending on the dosing regimen. Differences from placebo were generally greater for the Q8W cohort than the Q4W cohort, especially for symptom endpoints; for example, patient-reported asthma symptoms were significantly reduced in the Q8W cohort, but not in the Q4W cohort, compared with placebo at week 48. Our findings suggest that the clinical benefit obtained with benralizumab translates into better asthma control and, for the Q8W dosage, improved health-related quality of life. Benralizumab treatment resulted in direct, rapid, and nearly complete eosinophil depletion at 4 weeks, the first sampling timepoint, consistent with phase 1 and 2 study results that showed such depletion to occur as early as day 1.[20–22]

These results are consistent with those presented from the similarly designed 56-week CALIMA phase 3 trial[26] of benralizumab for patients with severe, uncontrolled asthma with eosinophilia (table 5). After assignment to the same treatment groups as the SIROCCO study, both benralizumab regimens significantly decreased the annual exacerbation rate and improved prebronchodilator FEV_1 compared with placebo for patients with blood eosinophil counts at least 300 cells per µL. These improvements in asthma symptoms were also substantial compared with baseline.[26] Furthermore, both studies indicated improvements in patient-reported asthma symptoms with benralizumab Q8W, a prespecified outcome measure. Consistent with findings from previous studies,[19,23] both dosage regimens of benralizumab reduced blood eosinophil counts rapidly and extensively.[19,22]

	SIROCCO		CALIMA[26]	
	Benralizumab Q4W	Benralizumab Q8W	Benralizumab Q4W	Benralizumab Q8W
Annual rate of exacerbations	↓ 45%	↓ 51%	↓ 36%	↓ 28%
Prebronchodilator FEV_1 (L)	↑ 0·106	↑ 0·159	↑ 0·125	↑ 0·116
Total asthma symptom score (score 0–6)*	↓ 0·08†	↓ 0·25	↓ 0·12†	↓ 0·23

All results are differences from placebo; week 48 results for SIROCCO and week 56 results for CALIMA. FEV_1=forced expiratory volume in 1 s. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Reduced score suggests improvement. †Non-significant.

Table 5: **Efficacy results for patients who received high-dosage inhaled corticosteroids plus long-acting β_2-agonists with baseline blood eosinophils at least 300 cells per µL in the CALIMA and SIROCCO studies**

Similar to findings from previous studies,[20,22] benralizumab was well tolerated, with approximately 90% of patients assigned to benralizumab still receiving treatment after 48 weeks, and only 2% of patients stopping treatment because of adverse events. The safety profile was consistent with that anticipated from previous studies of similar patient populations.[20,22] Injection-site reactions were low overall, reported by 3% of patients receiving benralizumab.

Two monoclonal antibody treatments against interleukin 5 (mepolizumab and reslizumab) have been approved in the European Union and the USA by the European Medicines Agency and the US Food and Drug Administration, respectively, for the treatment of severe asthma.[16,17] Unlike benralizumab, both these antibodies target the interleukin-5 ligand directly, rather than the receptor. Therefore, benralizumab is likely to circumvent potential issues with cytokine-directed antibodies, such as the induction of increased cytokine production.[27] Furthermore, benralizumab depletes eosinophils directly, whereas mepolizumab and reslizumab work through a passive mechanism, which seems to reduce eosinophils rather than deplete them entirely.[14,15] Studies for mepolizumab and reslizumab generally involved similar patients to those included in this study, although for mepolizumab, patients included in the MENSA[28] and DREAM[29] phase 3 studies had more severe exacerbation phenotypes than those in the SIROCCO study, as noted by a greater mean baseline number of exacerbations in the previous year (2·8–3·0 for the SIROCCO cohorts *vs* 3·4–3·8 for DREAM and MENSA cohorts) and a greater annual exacerbation rate in the placebo group. Similar to benralizumab, clinical efficacy of mepolizumab was related to baseline blood eosinophil counts. In a post-hoc analysis of DREAM and MENSA,[14] in which mepolizumab was given Q4W for at least 32 weeks to patients with severe, uncontrolled asthma with evidence of eosinophilic airway inflammation, the reduction of the annualised exacerbation rate compared with placebo was 52% for patients with baseline eosinophil counts of at least 150 cells per µL and 59% for counts of at least 300 cells per µL. Efficacy of intravenous reslizumab treatment was reported in two duplicate phase 3 studies[15]

only for patients with blood eosinophil counts at least 400 cells per μL, with a reduction of 54% in the annual exacerbation rate relative to placebo when given once Q4W for 52 weeks. Although studies of different biologics are not directly comparable, increases in lung function with benralizumab treatment seemed to be greater than those reported for mepolizumab and reslizumab,[14,15] with improvements noted as early as 4 weeks, the first timepoint assessed.

An additional biologic drug in clinical development for the treatment of uncontrolled asthma is dupilumab, a human monoclonal antibody against the interleukin-4 receptor α that inhibits interleukin-4 and interleukin-13 signalling. The results of a phase 2b study[30] showed that this drug increases lung function and reduces severe exacerbations in patients with uncontrolled, persistent asthma.

The finding that the Q8W dosage was efficacious suggests that benralizumab has the potential to lower disease burden and reduce health-care costs relative to other biologics that are required to be administered more regularly.

Patients with blood eosinophil counts less than 300 cells per μL had a substantial but smaller treatment effect; the size of this cohort was limited because of protocol-mandated enrichment for the at least 300 cells per μL cohort. Therefore, the threshold eosinophil count that results in significant therapeutic improvement with benralizumab treatment should be investigated in larger populations of severe or uncontrolled patients with asthma and different degrees of eosinophilia. An additional study limitation was that long-term safety with benralizumab treatment cannot be ascertained in a 1-year trial; this will be addressed in the BORA extension study (NCT02258542), in which patients from this study and CALIMA[26] will be followed up for up to 2 additional years. Also, because of the small sample size, differences noted in subgroup analyses need to be confirmed in a larger patient population.

The SIROCCO study validates and expands on the results from the phase 2b study[22] of the use of biologic treatments to deplete eosinophils through antibody-dependent cell-mediated cytotoxicity to treat patients with severe, uncontrolled asthma with eosinophilia. In the phase 2b study,[22] benralizumab 100 mg Q8W reduced the annual exacerbation rate by 41% relative to placebo at 52 weeks, while improving lung function and asthma symptoms for patients with uncontrolled eosinophilic asthma. Although not directly comparable, the magnitudes of improvements in exacerbations, lung function, asthma symptoms, and health-related quality of life in SIROCCO were even greater than in the phase 2b study. Moreover, positive findings from these studies support the assessment of benralizumab in the treatment of other diseases with an eosinophilic component, such as chronic obstructive pulmonary disease, chronic rhinosinusitis, and hypereosinophilic syndrome.

Both the SIROCCO and CALIMA studies met their primary endpoints, and confirm their respective results. Benefits were noted not only through asthma exacerbation reductions, but also through improvements in lung function and asthma symptoms. Improvements in these variables occurred early in the study, after 4 weeks, which is earlier than reported for improvements in studies of mepolizumab and reslizumab.[15,28,29] Furthermore, these benefits were obtained with dosages provided once Q8W, unlike other biologic treatments for asthma, which are given once every 2–4 weeks.

Contributors

ERB, JMF, and MG conceived and designed the study. PB, SS, GG, MA, VW, and MG acquired the data. All authors analysed and interpreted the data. All authors participated in the development and review of the manuscript and gave approval to submit for publication.

Declaration of interests

ERB has undertaken clinical trials through his employer, Wake Forest School of Medicine, for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, Cephalon/Teva, Forest, Genentech, GSK, Johnson & Johnson (Janssen), Novartis, and Sanofi. He has also served as a paid consultant for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, GSK, Forest, Novartis, Regeneron, and Sanofi. JMF reports being a member of advisory boards for AstraZeneca, Novartis, Teva, ALK, and Boehringer Ingelheim, and has been paid honoraria for lecturing at symposia organised by these companies. PC has provided consultancy services for Almirall, Boehringer Ingelheim, Johnson & Johnson, GlaxoSmithKline, Merck Sharp & Dohme, AstraZeneca, Novartis, Teva, Chiesi, and SNCF; has served on advisory boards for Almirall, Boehringer Ingelheim, Johnson & Johnson, GlaxoSmithKline, AstraZeneca, Novartis, Teva, Chiesi, Schering Plough, and ALK; has received lecture fees from Almirall, Boehringer Ingelheim, Centocor, GlaxoSmithKline, AstraZeneca, Novartis, Teva, Chiesi, and Merck Sharp & Dohme; and has received industry-sponsored grants from Almirall, Boston Scientific, Boehringer Ingelheim, Centocor, GlaxoSmithKline, AstraZeneca, Novartis, Teva, and Chiesi. AP reports grants, personal fees, and travel expenses reimbursement from Chiesi Farmaceutici, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, Pfizer, Takeda, Munidipharma, Menarini, Zambon, and Teva. SFW reports being a consultant for Teva and has received research grants from AstraZeneca, GSK, Merck, Teva, Mylan, Roxane, and Sanofi. SS is an employee of Optimum Statistics (LaSalle, MB, Canada), and provided statistical analyses and support under contract to AstraZeneca, through inVentiv Health Clinical. PB, GG, MA, VW, and MG are employees of AstraZeneca.

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