Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

*J Mark FitzGerald, Eugene R Bleecker, Parameswaran Nair, Stephanie Korn, Ken Ohta, Marek Lommatzsch, Gary T Ferguson, William W Busse, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Viktoria Werkström, Magnus Aurivillius, Mitchell Goldman, on behalf of the CALIMA study investigators**

Lancet 2016; 388: 2128–41

Published Online September 5, 2016 http://dx.doi.org/10.1016/S0140-6736(16)31322-8

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*For the full list of investigators see the appendix pp 2–5

The Lung Centre, Vancouver General Hospital, UBC Institute for Heart and Lung Health, Vancouver, BC, Canada (J M FitzGerald MD); **Wake Forest School of Medicine, Winston-Salem, NC, USA** (Prof E R Bleecker MD); **McMaster University & St Joseph's Healthcare, Hamilton, ON, Canada** (Prof P Nair MD); **Universitätsmedizin Mainz, Mainz, Germany** (S Korn MD); **National Hospital Organization, Tokyo National Hospital, Tokyo, Japan** (K Ohta MD); **Universitätsklinikum Rostock, Rostock, Germany** (Prof M Lommatzsch MD); **Pulmonary Research Institute of Southeast Michigan, Farmington Hills, MI, USA** (G T Ferguson MD); **University of Wisconsin School of Medicine and Public Health, Madison, WI, USA** (Prof W W Busse MD); **AstraZeneca, Gaithersburg, MD, USA** (P Barker PhD, S Sproule MMath, M Goldman MD); **AstraZeneca, Cambridge, MA, USA** (G Gilmartin MD); **and AstraZeneca, Mölndal, Sweden** (V Werkström MD, M Aurivillius MD)

Correspondence to: Dr J Mark FitzGerald, The Lung Centre, Vancouver General Hospital, Gordon and Leslie Diamond Health Care Centre, Vancouver, BC V5Z 1M9, Canada **mark.fitzgerald@vch.ca**

See Online for appendix

Summary

Background Benralizumab is a humanised, afucosylated, anti-interleukin-5 receptor α monoclonal antibody that induces direct, rapid, and nearly complete depletion of eosinophils. We aimed to assess the efficacy and safety of benralizumab as add-on therapy for patients with severe, uncontrolled asthma and elevated blood eosinophil counts.

Methods In this randomised, double-blind, parallel-group, placebo-controlled, phase 3 study (CALIMA) undertaken at 303 sites in 11 countries, we enrolled patients aged 12–75 years with severe asthma uncontrolled by medium-dosage to high-dosage inhaled corticosteroids plus long-acting β_2-agonists (ICS plus LABA) and a history of two or more exacerbations in the previous year. Patients were randomly assigned (1:1:1) to receive 56 weeks of benralizumab 30 mg every 4 weeks (Q4W), benralizumab 30 mg every 8 weeks (Q8W; first three doses 4 weeks apart), or placebo (all subcutaneous injection). Patients were stratified (2:1) by baseline blood eosinophil counts 300 cells per μL or greater and less than 300 cells per μL, respectively. Patients and study centre staff were masked to treatment allocation. The primary endpoint was annual exacerbation rate ratio versus placebo for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils 300 cells per μL or greater (intention-to-treat analysis). Key secondary endpoints were pre-bronchodilator forced expiratory volume in 1 s (FEV_1) and total asthma symptom score. This study is registered with ClinicalTrials.gov, number NCT01914757.

Findings Between Aug 21, 2013, and March 16, 2015, 2505 patients were enrolled, of whom 1306 patients were randomised; 425 patients were randomly assigned to and received benralizumab 30 mg Q4W, 441 to benralizumab 30 mg Q8W, and 440 to placebo. 728 patients were included in the primary analysis population. Benralizumab resulted in significantly lower annual exacerbation rates with the Q4W regimen (rate 0·60 [95% CI 0·48–0·74], rate ratio 0·64 [95% CI 0·49–0·85], p=0·0018, n=241) and Q8W regimen (rate 0·66 [95% CI 0·54–0·82], rate ratio 0·72 [95% CI 0·54–0·95], p=0·0188, n=239) compared with placebo (rate 0·93 [95% CI 0·77–1·12], n=248). Benralizumab also significantly improved pre-bronchodilator FEV_1 (Q4W and Q8W) and total asthma symptom score (Q8W only) in these patients. The most common adverse events were nasopharyngitis (90 [21%] in the Q4W group, 79 [18%] in the Q8W group, and 92 [21%] in the placebo group) and worsening asthma (61 [14%] in the Q4W group, 47 [11%] in the Q8W group, and 68 [15%] in the group).

Interpretation Benralizumab significantly reduced annual exacerbation rates and was generally well tolerated for patients with severe, uncontrolled asthma with blood eosinophils 300 cells per μL or greater. Our data further refine the patient population likely to receive the greatest benefit from benralizumab treatment.

Funding AstraZeneca and Kyowa Hakko Kirin.

Introduction

Asthma affects an estimated 315 million people worldwide, approximately 10% of whom have severe or uncontrolled asthma.[1,2] Patients with severe asthma require treatment with high-dosage inhaled corticosteroids plus long-acting β_2-agonists (LABA) to control their disease.[2] Despite currently available treatments, asthma remains uncontrolled for many patients. Because this difficult-to-treat group is at high risk of exacerbations and admissions to hospital, often has diminished health-related quality of life, and represents a major health-care burden,[3] additional therapeutic options to control severe asthma are needed.

For many patients, eosinophilia is a hallmark of severe, uncontrolled asthma.[4] Increased numbers of airway and circulating eosinophils are associated with an increased frequency of asthma exacerbations, a high symptom burden, and impaired lung function.[5–7] Conversely, maintaining lowered eosinophils has been linked with fewer asthma exacerbations and hospital admissions.[8] The cytokine interleukin 5 is a main driver of eosinophil proliferation, maturation, activation, and survival.[9]

Research in context

Evidence before this study

We searched PubMed for all clinical trial reports published in English before June 12, 2016, on the use of anti-interleukin-5 biologic drugs for the treatment of asthma in humans. Our search terms included "eosinophils", "interleukin-5", "monoclonal antibody", "asthma", "benralizumab", "mepolizumab", and "reslizumab". Our search identified 29 results, including two phase 1 studies of benralizumab that reported reduced blood eosinophil counts in patients with mild atopic and eosinophilic asthma, as well as a phase 2b benralizumab dose-ranging study that reported decreased exacerbation rates for patients with severe eosinophilic asthma. In the phase 2b study, benralizumab efficacy seemed to be enhanced for patients with blood eosinophil counts exceeding 300 cells per µL. In addition, we identified two phase 3 studies and a subsequent secondary analysis of phase 3 trial data for mepolizumab, as well as a report of two duplicate phase 3 studies of reslizumab treatment for patients with severe, uncontrolled asthma. Together, these studies reinforced the clinical benefit of therapies targeting the interleukin-5 pathway for patients with severe asthma and provided evidence that clinical efficacy of anti-interleukin-5 biologic therapy is linked to baseline eosinophil counts and exacerbation history.

Added value of this study

The results of the CALIMA trial validate the approach of targeting the interleukin-5 receptor α to deplete eosinophil counts, reduce asthma exacerbations, improve lung function, and substantially alleviate asthma symptoms of patients with severe, uncontrolled asthma.

Implications of all the available evidence

New and existing data support the current Global Initiative for Asthma management strategy, which recommends the addition of anti-interleukin-5 biologic therapy to inhaled corticosteroids and LABA treatment to reduce exacerbations for patients with severe, uncontrolled asthma and eosinophilia. Our data further refine the patient population likely to receive the greatest benefit from benralizumab treatment.

Thus, the interleukin-5 pathway is an attractive therapeutic target to decrease eosinophils, with the goal of eliminating lung and airway inflammation.

Current treatment guidelines for patients with severe, uncontrolled asthma with eosinophilia recommend add-on anti-interleukin-5 biologic therapy.[10] Mepolizumab and reslizumab are humanised monoclonal antibodies, directed against the interleukin-5 molecule, that disrupt eosinophil maturation.[11,12] Both medications have shown clinical efficacy for patients with severe asthma with an eosinophilic phenotype.[13–16] However, targeting the interleukin-5 molecule could result in suboptimal depletion of eosinophils.[17–20]

Benralizumab is a humanised, afucosylated, anti-interleukin-5 receptor α monoclonal antibody that induces direct, rapid, and nearly complete depletion of eosinophils via enhanced antibody-dependent cell-mediated cytotoxicity, the process by which natural killer cells cause eosinophil apoptosis.[18] In phase 1 studies, benralizumab rapidly depleted eosinophils for patients with mild atopic or eosinophilic asthma.[21,22] In a subsequent phase 2B, dose-ranging study, benralizumab significantly reduced the rate of asthma exacerbations for patients with eosinophilic asthma uncontrolled by inhaled corticosteroids plus LABA therapy.[23] Moreover, patients with baseline blood eosinophils 300 cells per µL or greater achieved the greatest therapeutic benefit.[23]

In the 56-week, phase 3 CALIMA trial, we aimed to investigate the efficacy and safety of benralizumab for patients with severe asthma uncontrolled by high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils 300 cells per µL or greater.

Methods

Study design and participants

This was a randomised, double-blind, parallel-group, placebo-controlled, phase 3 trial (CALIMA). Patients were enrolled at 303 clinical research centres in the USA, Canada, Germany, Sweden, Poland, Romania, Ukraine, Argentina, Chile, Japan, and the Philippines (appendix pp 2–5). The study design comprised an enrolment visit (week –4), a 4-week screening and run-in phase, randomisation (week 0), the treatment period (weeks 0–56), and a final follow-up visit (week 60).

Male and female patients aged 12–75 years with a body weight 40 kg or heavier and a history of physician-diagnosed asthma requiring treatment with medium-dosage to high-dosage inhaled corticosteroids (>250 µg [medium] or ≥500 µg [high] fluticasone dry powder formulation or equivalent total daily dosage) plus LABA, for 12 months or more before enrolment, were included. Patients must have also had two or more asthma exacerbations in the 12 months before enrolment that required use of a systemic corticosteroid or temporary increase in the patient's usual maintenance dosage of oral corticosteroids.

Additional inclusion criteria included treatment with inhaled corticosteroids (≥500 µg per day fluticasone propionate dry powder formulation or equivalent total daily dosage) plus LABA for 3 months or more before enrolment, with or without oral corticosteroids and additional asthma controllers; 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; Asthma Control Questionnaire-6[24] (ACQ-6)

score ≥1·5 at enrolment; and post-bronchodilator reversibility in FEV_1 of 12% or greater and 200 mL or greater in FEV_1 within 12 months before enrolment (lung function impairment criteria were included based on treatment guidelines at the time the study protocol was developed; see appendix pp 6–8 for full eligibility criteria). Patients continued receiving their background asthma controller medications at a stable dosage during the study and short-acting β_2-agonists were allowed as rescue medications (see appendix pp 9–11 for restricted asthma medications).

An independent ethics committee or institutional review board for each study centre approved the final study protocol. All patients provided written, informed consent before initiation of any study procedures. The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice guidelines, and the ethics committee at each participating site.

Randomisation and masking

Eligible adult patients from all regions and adolescent patients from outside of the European Union were randomly assigned (1:1:1) to receive 56-week, double-blind treatment with either benralizumab 30 mg once every 4 weeks (Q4W), benralizumab 30 mg once every 4 weeks for the first three doses followed by once every 8 weeks for the remainder of the treatment period (hereafter referred to as the Q8W regimen), or placebo. Patients aged 12–17 years enrolled within the European Union were randomly assigned (1:1) to receive double-blind treatment with benralizumab 30 mg Q8W or placebo to accommodate a request by the Paediatric Committee at the European Medicines Agency to limit drug burden in adolescents.

Patients were assigned to treatment groups using an interactive web-based voice response system. Randomisation was stratified by inhaled corticosteroids dosage at enrolment (high or medium), geographic region, age group (adult or adolescent), and peripheral blood eosinophil count at enrolment (<300 cells per µL or ≥300 cells per µL). Patients were recruited with blood eosinophils 300 cells per µL or greater and less than 300 cells per µL at screening in a ratio of approximately 2:1, respectively, to enrich the study population with patients most likely to have an eosinophilic phenotype and to gain an insight into how patients with lower blood eosinophil counts respond to therapy. The study investigator assigned randomisation codes sequentially in each stratum as patients became eligible for randomisation, until each stratum was full.

To preserve blinding, patients and study centre staff were masked to treatment allocation, placebo solution was visually matched with benralizumab solution, and both placebo and benralizumab were provided in accessorised (needle guards and finger phalanges), pre-filled syringes.

Procedures

Benralizumab (manufactured by AstraZeneca, Gaithersburg, MD, USA) was administered as a 30 mg per mL solution for injection (1 mL). Patients assigned to benralizumab Q4W or placebo received their randomised treatment at study centre visits at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, whereas patients assigned to benralizumab Q8W received benralizumab on weeks 0, 4, 8, 16, 24, 32, 40, and 48, and placebo at intervening visits. The anatomical site of injection was rotated at each visit.

Data were collected from all patients at enrolment, screening, randomisation (week 0), 4-weekly intervals during the treatment period (weeks 4–56), and follow-up (week 60). Study investigators undertook pre-bronchodilator spirometry at screening, then at weeks 0, 4, 8, 16, 24, 32, 40, 48, and 56. Study investigators undertook post-bronchodilator spirometry at screening, and weeks 0, 24, and 56. Patients monitored peak expiratory flow at home using a hand-held spirometer, recorded asthma symptoms, and completed the Asthma Daily Diary,[24] twice a day from the morning of the screening visit (week −3) to the end of the treatment period (week 56). In addition, patients recorded responses to the self-administered ACQ-6[25] and standardised Asthma Quality of Life Questionnaire for 12 years and older[26] (AQLQ[S]+12) once every 2 weeks and once every 4 weeks, respectively, during the treatment period. Patients recorded all responses using an electronic patient-reported outcomes device (see appendix pp 12–13 for procedure and questionnaire details). The Asthma Daily Diary, ACQ-6, and AQLQ(S)+12 have been validated for use in clinical trials.[24–26] At each visit, investigators assessed patients' adherence to lung function measurements and self-assessment questionnaires. Adverse events were also recorded at each study visit.

Outcomes

The primary efficacy endpoint was the annual rate ratio versus placebo of asthma exacerbations for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils 300 cells per µL or greater. The annual exacerbation rate was defined as the total number of exacerbations × 365·25 / total duration of follow-up within the treatment group (days). An asthma exacerbation was defined as a worsening of asthma that led to one of the following: (1) use of systemic corticosteroids for 3 days or more or a temporary increase in a stable, background dosage of oral corticosteroids; (2) an emergency department or urgent care visit (<24 h) due to asthma that required systemic corticosteroids; or (3) an inpatient admission to hospital (≥24 h) due to asthma. Worsening of asthma was defined as any new or

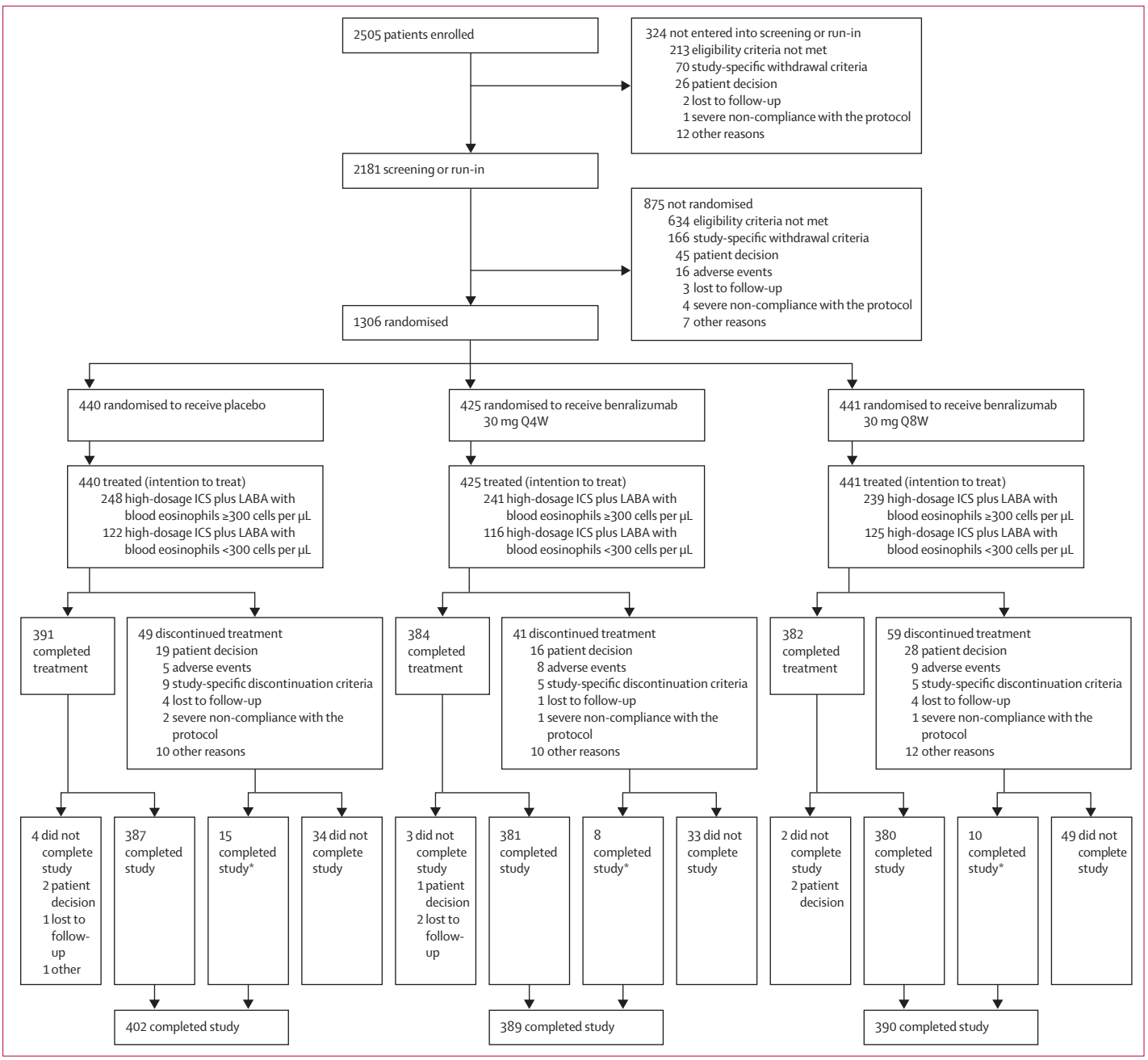

Figure 1: **Trial profile**

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

increased symptoms or signs that were concerning to the patient or related to an Asthma Daily Diary alert (appendix p 14).

Key secondary efficacy endpoints (ie, multiplicity [type I error] protected) were pre-bronchodilator FEV_1 and total asthma symptom score for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils 300 cells per µL or greater. Additional secondary endpoints were time to first asthma exacerbation; annual rate of asthma exacerbations associated with an emergency department visit, urgent care visit, or admission to hospital (defined as an admission to an inpatient facility and/or evaluation and treatment in a health-care facility for 24 h or longer); post-bronchodilator FEV_1; ACQ-6 score; and AQLQ(S)+12 score.

To assess safety, study investigators recorded adverse events from start of treatment to end of treatment.

	All patients (n=1306)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=728)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL (n=363)		
	Placebo (n=440)	Benralizumab 30 mg Q4W (n=425)	Benralizumab 30 mg Q8W (n=441)	Placebo (n=248)	Benralizumab 30 mg Q4W (n=241)	Benralizumab 30 mg Q8W (n=239)	Placebo (n=122)	Benralizumab 30 mg Q4W (n=116)	Benralizumab 30 mg Q8W (n=125)
Age (years)	48·8 (15·1)	50·0 (13·6)	49·0 (14·3)	48·5 (14·1)	50·1 (13·1)	49·6 (13·0)	52·4 (14·4)	51·9 (12·2)	51·1 (13·8)
Age group (years)									
≥12 to <18	23 (5%)	11 (3%)	21 (5%)	7 (3%)	3 (1%)	6 (3%)	5 (4%)	1 (<1%)	4 (3%)
≥18 to 75	417 (95%)	414 (97%)	420 (95%)	241 (97%)	238 (99%)	233 (97%)	117 (96%)	115 (99%)	121 (97%)
Sex									
Male	176 (40%)	155 (36%)	168 (38%)	103 (42%)	82 (34%)	101 (42%)	46 (38%)	45 (39%)	38 (30%)
Female	264 (60%)	270 (64%)	273 (62%)	145 (58%)	159 (66%)	138 (58%)	76 (62%)	71 (61%)	87 (70%)
Race									
White	372 (85%)	360 (85%)	369 (84%)	213 (86%)	209 (87%)	203 (85%)	108 (89%)	99 (85%)	107 (86%)
Black or African American	14 (3%)	10 (2%)	15 (3%)	8 (3%)	5 (2%)	8 (3%)	4 (3%)	3 (3%)	5 (4%)
Asian	53 (12%)	55 (13%)	55 (12%)	27 (11%)	27 (11%)	28 (12%)	10 (8%)	14 (12%)	12 (10%)
Other*	1 (<1%)	0	2 (<1%)	0	0	0	0	0	1 (<1%)
Ethnic group									
Hispanic or Latino	92 (21%)	104 (24%)	104 (24%)	52 (21%)	56 (23%)	52 (22%)	22 (18%)	26 (22%)	27 (22%)
Not Hispanic or Latino	348 (79%)	321 (76%)	337 (76%)	196 (79%)	185 (77%)	187 (78%)	100 (82%)	90 (78%)	98 (78%)
Body-mass index (kg/m^2)†	28·9 (6·5)	28·7 (6·8)	28·8 (6·5)	29·0 (6·1)	29·1 (7·3)	28·6 (6·1)	29·7 (7·4)	28·8 (6·5)	29·8 (7·2)
Missing data	1	0	0	0	0	0	1	0	0
Local eosinophil count (cells per µL)†	371 (0–4494)	370 (20–2420)	400 (0–2600)	510 (300–4494)	500 (300–2420)	500 (300–2600)	190 (0–298)	160 (20–293)	180 (0–295)
Missing data	7	7	6	1	4	3	2	0	2
Central eosinophil count (cells per µL)†	370 (0–4150)	350 (0–2800)	350 (0–2260)	490 (30–4150)	470 (0–2800)	475 (10–2260)	170 (0–700)	150 (10–880)	140 (0–440)
Missing data	11	9	9	8	4	5	3	5	2
Prebronchodilator FEV_1 (L)†	1·771 (0·645)	1·757 (0·602)	1·759 (0·641)	1·815 0·648)	1·75 (0·570)	1·758 (0·622)	1·639 (0·615)	1·717 (0·626)	1·665 (0·616)
Missing data	6	5	1	3	2	0	3	2	1
Prebronchodilator FEV_1 (% predicted normal)†	58·0% (14·9)	58·9% (14·8)	57·9% (14·9)	58·2% (13·9)	59·1% (13·7)	57·0% (14·2)	56·1% (16·3)	57·4% (16·2)	56·7% (15·2)
Missing data	6	5	1	3	2	0	3	2	1
FEV_1/FVC prebronchodilator†	61 (13)	61 (12)	60 (13)	60 (12)	61 (12)	60 (13)	60 (13)	59 (13)	60 (14)
Missing data	6	5	1	3	2	0	3	2	1
Reversibility (%)†	20% (–18 to 814)	20% (–24 to 809)	20% (–13 to 171)	20% (–9 to 133)	20% (–24 to 124)	20% (–13 to 171)	18% (–18 to 814)	21% (–9 to 809)	18% (–10 to 154)
Missing data	13	15	8	5	6	3	7	6	4
ACQ-6 score‡	2·69 (0·92)	2·69 (0·91)	2·75 (0·93)	2·75 (0·94)	2·70 (0·91)	2·80 (0·95)	2·68 (0·89)	2·82 (0·89)	2·87 (0·96)
Time since asthma diagnosis (years)	16·2 (1·2–69·9)	15·8 (1·2–69·2)	16·8 (1·1–64·6)	17·0 (1·3–69·9)	15·6 (1·3–66·2)	16·1 (1·2–58·2)	16·3 (1·2–64·9)	15·0 (1·5–69·2)	18·3 (1·1–64·6)

(Table 1 continues on next page)

Statistical analysis

The anticipated total sample size was approximately 1296 patients. The study was powered for the primary efficacy analysis of adult and adolescent patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophil counts 300 cells per µL or greater. Approximately 228 patients needed to be randomised to each treatment group (totalling roughly 684 patients) to achieve 90% power to detect a 40% reduction in the annual asthma exacerbation rate in this patient population for both benralizumab dosage versus placebo. The sample size calculation assumed

	All patients (n=1306)			High-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL (n=728)			High-dosage ICS plus LABA with baseline blood eosinophils <300 cells per µL (n=363)		
	Placebo (n=440)	Benralizumab 30 mg Q4W (n=425)	Benralizumab 30 mg Q8W (n=441)	Placebo (n=248)	Benralizumab 30 mg Q4W (n=241)	Benralizumab 30 mg Q8W (n=239)	Placebo (n=122)	Benralizumab 30 mg Q4W (n=116)	Benralizumab 30 mg Q8W (n=125)
(Continued from previous page)									
Number of exacerbations in the past 12 months	2·7 (1·6)	2·7 (1·9)	2·7 (1·4)	2·8 (1·7)	2·8 (1·7)	2·7 (1·3)	2·7 (1·9)	2·6 (1.6)	2·7 (1·7)
Number resulting in emergency department visit	0·3 (1.2)	0·3 (0·8)	0·2 (0.7)	0·4 (1·4)	0·3 (0·9)	0·2 (0·6)	0·2 (0·8)	0·2 (0·5)	0·2 (0·6)
Patients with ≥1 exacerbations resulting in emergency department visit	62 (14%)	60 (14%)	56 (13%)	36 (15%)	35 (15%)	31 (13%)	18 (15%)	15 (13%)	13 (10%)
Number resulting in hospital admission	0·3 (0·8)	0·2 (0·5)	0·3 (0·7)	0·3 (0·7)	0·2 (0·5)	0·3 (0·6)	0·3 (1.0)	0·3 (0·6)	0·2 (0·6)
Patients with ≥1 exacerbations resulting in hospital admission	72 (16%)	65 (15%)	78 (18%)	44 (18%)	42 (17%)	43 (18%)	21 (17%)	20 (17%)	18 (14%)
Total asthma symptom score†	2·71 (1·04)	2·73 (1·02)	2·79 (1·06)	2·71 (1·06)	2·69 (0·98)	2·76 (1·06)	2·69 (1·02)	2·81 (1·09)	2·87 (1·06)
Missing data	1	1	2	1	0	1	0	1	1
Diagnosis of allergic rhinitis	248 (56%)	242 (57%)	227 (51%)	147 (59%)	136 (56%)	125 (52%)	59 (48%)	68 (59%)	58 (46%)
Nasal polyps	73 (17%)	59 (14%)	65 (15%)	55 (22%)	40 (17%)	53 (22%)	12 (10%)	12 (10%)	8 (6%)
Atopic (based on Phadiatop test)	286 (65%)	264 (62%)	278 (63%)	164 (66%)	151 (63%)	149 (62%)	69 (57%)	62 (53%)	75 (60%)
History of omalizumab treatment†	14 (3%)	12 (3%)	12 (3%)	9 (4%)	7 (3%)	7 (3%)	5 (4%)	4 (3%)	3 (2%)
Missing data	1	1	3	0	0	2	1	1	1
AQLQ(S)+12 score†§	3·96 (1·03)	3·98 (0·96)	3·85 (1·02)	3·93 (1·04)	3·99 (0·98)	3·87 (1·05)	4·03 (1·01)	3·95 (0·93)	3·82 (0·97)
Missing data	13	13	13	8	7	7	2	4	2
Smoking history									
Never	349 (79%)	325 (76%)	348 (79%)	203 (82%)	175 (73%)	185 (77%)	89 (73%)	91 (78%)	99 (79%)
Current	2 (<1%)	0	3 (<1%)	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
Former	89 (20%)	100 (24%)	90 (20%)	44 (18%)	66 (27%)	53 (22%)	33 (27%)	25 (22%)	25 (20%)
Smoking pack year (years)¶	5 (0–9)	5 (0–9)	5 (0–45)	4 (0–9)	5 (0–9)	4·5 (0–45)	5 (0–9)	5 (0–9)	5 (0–9)

Data are mean (SD), median (range), or n (%). ACQ-6=Asthma Control Questionnaire-6. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. ICS=inhaled corticosteroids. LABA=long-acting β_2-agonist. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W). *Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other. †Data not available for all randomised patients. ‡The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β_2-agonist use on a 0–6 scale (low numbers represent better control). §The AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale (greater numbers indicate better quality of life). ¶For current and former smokers.

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

two-sided 4% α-level tests (see appendix p 16 for rationale), an annual placebo exacerbation rate of 0·88 events per patient based on published data, and an exposure–response analysis of phase 2B study data,[23,27] and a negative binomial shape parameter of 0·9. To maintain a 2:1 ratio of patients with blood eosinophil counts of 300 cells per µL or greater and less than 300 cells per µL, we aimed to enrol 114 patients receiving high-dosage inhaled corticosteroids plus LABA with blood eosinophil counts less than 300 cells per µL per treatment group. Lastly, approximately 270 patients receiving medium-dosage inhaled corticosteroids plus LABA were expected to be recruited.

Exacerbation rates for each of the benralizumab treatment groups were compared with the exacerbation

	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=248)	Benralizumab 30 mg Q4W (n=241)	Benralizumab 30 mg Q8W (n=239)	Placebo (n=122)	Benralizumab 30 mg Q4W (n=116)	Benralizumab 30 mg Q8W (n=125)
Annual asthma exacerbation rate over 56 weeks*						
Number of patients analysed (baseline and at least one post-baseline assessment)	248	241	239	122	116	125
Rate estimate	0·93 (0·77–1·12)	0·60 (0·48–0·74)	0·66 (0·54–0·82)	1·21 (0·96–1·52)	0·78 (0·59–1·02)	0·73 (0·55–0·95)
Absolute difference estimate	..	−0·33 (−0·54 to −0·12)	−0·26 (−0·48 to −0·04)	..	−0·43 (−0·78 to −0·08)	−0·48 (−0·82 to −0·14)
Rate ratio *vs* placebo	..	0·64 (0·49–0·85)	0·72 (0·54–0·95)	..	0·64 (0·45–0·92)	0·60 (0·42–0·86)
p value *vs* placebo	..	0·0018	0·0188	..	0·0150	0·0048
Prebronchodilator FEV_1 (L)†						
Number of patients analysed (baseline and at least one post-baseline assessment)	244	238	238	116	114	121
LS mean change§	0·215; 221	0·340; 216	0·330; 211	0·156; 99	0·219; 101	0·140; 98
LS mean difference *vs* placebo	..	0·125 (0·037–0·213)	0·116 (0·028–0·204)	..	0·064 (−0·049 to 0·176)	−0·015 (−0·127 to 0·096)
p value *vs* placebo	..	0·0054	0·0102	..	0·2676	0·7863
Total asthma symptom score†‡						
Number of patients analysed (baseline and at least one post-baseline assessment)	247	241	237	122	115	124
LS mean change§	−1·16; 187	−1·28; 184	−1·40; 185	−0·95; 89	−1·11; 88	−0·95; 85
LS mean difference *vs* placebo	..	−0·12 (−0·32 to 0·07)	−0·23 (−0·43 to −0·04)	..	−0·16 (−0·44 to 0·13)	0·01 (−0·28 to 0·29)
p value *vs* placebo	..	0·2241	0·0186	..	0·2868	0·9663

Data for the primary endpoint are rate estimate (95% CI) or rate ratio (95% CI). Data for the secondary endpoint are mean change from baseline at week 56; n or mean difference (95% CI). FEV_1=forced expiratory volume in 1 s. LS=least squares. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).
*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. ‡Key secondary endpoint; composite of daytime and night-time symptoms scored 0–6 overall (a decrease in score indicates improvement). §Numbers after semicolon are patients at 56 weeks.

***Table 2*: Asthma exacerbations, lung function outcomes, and asthma symptoms by baseline eosinophil counts (full analysis set)**

rate in the placebo group using a negative binomial model. The response variable in the model was the number of asthma exacerbations experienced by a patient during the 56-week treatment period. The model included covariates of treatment group, region, number of exacerbations in the previous year, and the use of maintenance oral corticosteroids at the time of randomisation. The estimated treatment effect (ie, the rate ratio of benralizumab *vs* placebo), corresponding 95% CI, and two-sided p value for the rate ratio were determined. The annual exacerbation rate and corresponding 95% CI within each treatment group were also calculated.

Change from baseline in pre-bronchodilator FEV_1 and total asthma symptom score at week 56 was compared between each of the benralizumab treatment groups and the placebo group using a mixed-effects model for repeated measures analysis, with adjustment for treatment, region, baseline value, oral corticosteroids use at the time of randomisation, visit, and visit×treatment. Change from baseline to week 56 in ACQ-6 and AQLQ(S)+12 scores was analysed using the same method. Results are presented in terms of least squares means, treatment differences in least squares means, 95% CIs, and p values. Time to first exacerbation was analysed using a Cox proportional hazards model and was fitted to data with covariates of treatment, region, number of exacerbations in the year before the study, and the use of maintenance oral corticosteroids at the time of randomisation. Data are presented as hazard ratios (HR), 95% CI, and p values.

To account for multiplicity in testing the primary and key secondary endpoints in the primary analysis population, a multiple testing procedure was followed to control the overall type I error rate, according to a gatekeeping procedure (see appendix p 16). We calculated

the annual exacerbation rate for each dosing regimen and tested at the family-wise error rate of 0·04 using a Hochberg procedure. If both results were significant at this level, key secondary endpoints for each dosing regimen were tested at the family-wise error rate of 0·05, maintaining an overall type I error rate of 0·05 using a Holm procedure.

Prespecified subgroup analyses were conducted to assess the exacerbation rate in patient subgroups of clinical relevance (see appendix p 15 for subgroups). We also conducted a post-hoc analysis to assess further the treatment effect of the number of exacerbations experienced by patients in the previous year (2, ≥3) using a separate negative binomial model with adjustment for treatment, region, and oral corticosteroids use at the time of randomisation. The model for the three or more previous exacerbations subgroup was adjusted for the number of previous exacerbations.

All efficacy analyses were done using an intention-to-treat approach based on the full analysis set. The full analysis set considered patients according to their assigned treatment regimen and included all randomised patients who received any study treatment, regardless of their protocol adherence and continued participation in the study. The safety analysis set considered patients based on the actual treatment regimen they received and included all patients who received at least one dose of study treatment. All data were analysed with SAS System version 9.2 (SAS Institute Inc, Cary, NC, USA).

The study was overseen by an independent drug safety monitoring board, and two adjudication committees (asthma adjudication, and MACE and malignancy adjudication; appendix p 17).

This study is registered with ClinicalTrials.gov, number NCT01914757.

Role of the funding source

JMF, ERB, and the funders of the study participated in the study design. All authors participated in data collection, data analysis, data interpretation, or writing of the manuscript. All authors gave approval to submit for publication.

Results

Between Aug 21, 2013, and March 16, 2015, we recruited 2505 patients. 2181 entered screening and run-in and 1306 were randomised (figure 1). All randomised patients received study treatment: 425 patients were randomly assigned to and received benralizumab 30 mg Q4W, 441 patients to benralizumab 30 mg Q8W, and 440 patients to placebo. Of these, 1157 (89%) patients completed and 149 (11%) patients discontinued treatment, 116 of whom also discontinued the study. The most common reason for treatment withdrawal was patient decision (63 [42%] of 149), and reasons for withdrawal were balanced across treatment groups. All 1306 patients randomised were included in the full analysis set and safety analysis set. Within the full analysis set, 728 patients were receiving high-dosage inhaled corticosteroids plus LABA and had baseline blood eosinophil counts ≥300 cells per µL and were eligible for the primary efficacy analysis: 241 patients in the benralizumab Q4W group, 239 patients in the benralizumab Q8W group, and 248 patients in the placebo group (figure 1). Patient demographics and baseline clinical characteristics were balanced across study groups (table 1; concomitant maintenance asthma medications at baseline are provided in the appendix p 18).

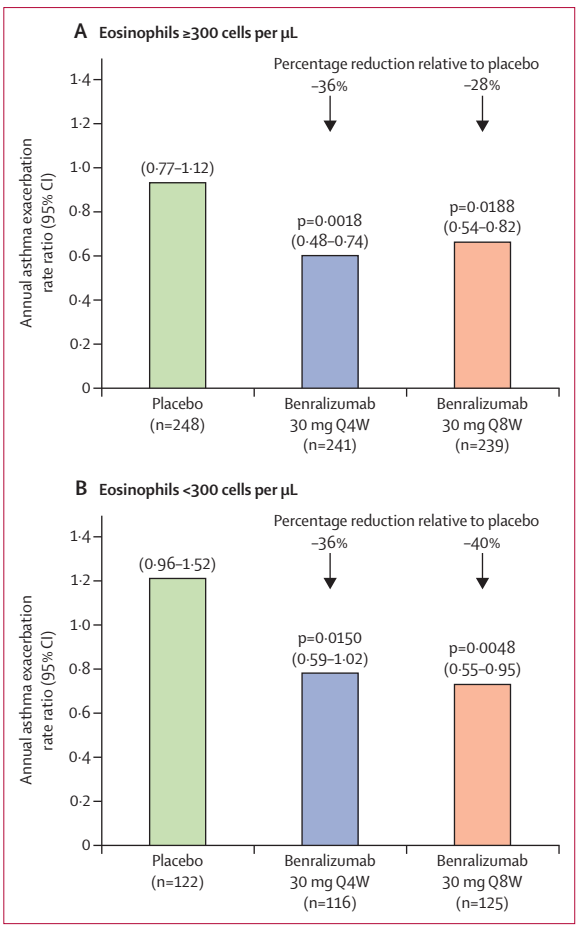

Figure 2: **Annual asthma exacerbation rate reductions at 56 weeks for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils (A) 300 cells per µL or greater and (B) less than 300 cells per µL (full analysis set)**

Estimates calculated using a negative binomial model with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations. ICS=inhaled corticosteroids. LABA=long-acting β_2-agonist. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).

For the primary endpoint, 56 weeks of treatment with benralizumab resulted in significant reductions in the annual rate of asthma exacerbations, compared with placebo, for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils ≥300 cells per µL (table 2). Annual exacerbation rates were approximately 36% (rate ratio 0·64 [95% CI

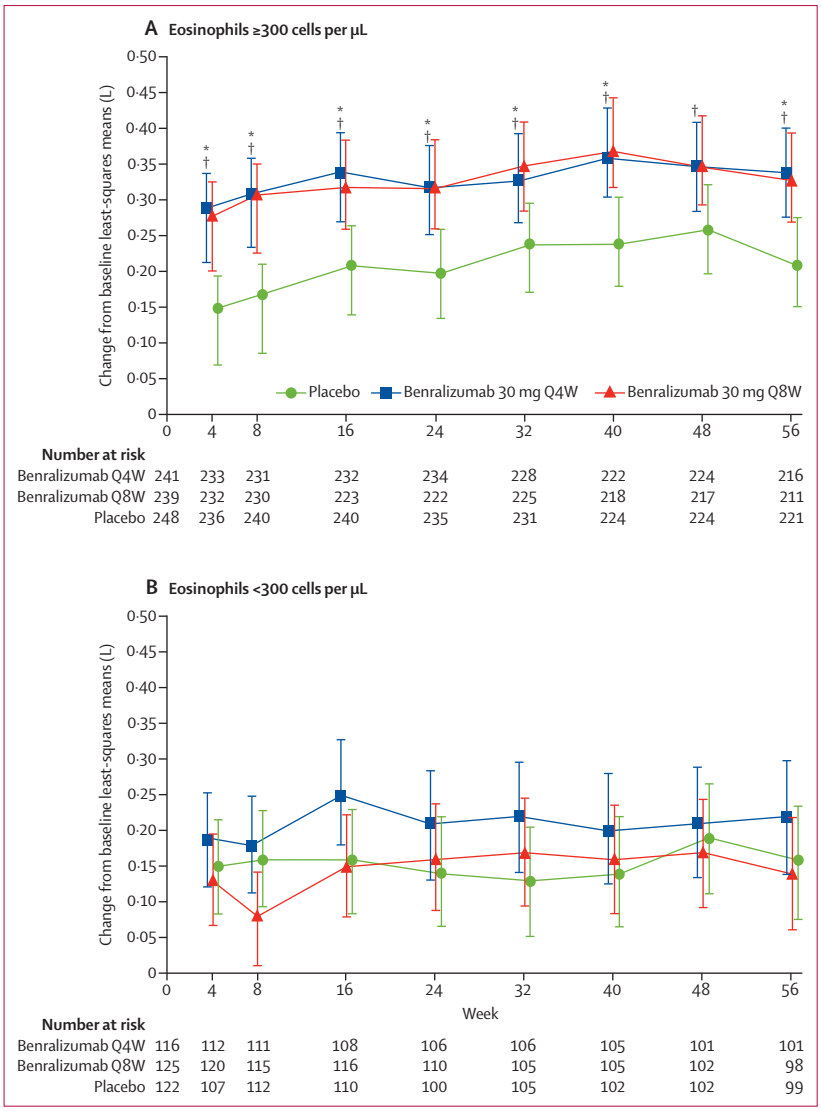

***Figure* 3: Change from baseline in pre-bronchodilator FEV_1 for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils (A) 300 cells per µL or greater and (B) less than 300 cells per µL (full analysis set)**

FEV_1=forced expiratory volume in 1 s. ICS=inhaled corticosteroids. LABA=long-acting β_2-agonist. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W). *p<0·05 for benralizumab Q4W versus placebo treatment comparison. †p<0·05 for benralizumab Q8W versus placebo treatment comparison.

0·49–0·85], p=0·0018) and 28% (0·72 [0·54–0·95], p=0·0188) lower than with placebo for patients treated with the benralizumab Q4W and Q8W regimens, respectively (figure 2).

For the key secondary endpoints, 56 weeks of treatment with benralizumab Q4W and Q8W resulted in significant increases in pre-bronchodilator FEV_1, compared with placebo for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils ≥300 cells per µL (table 2). Improvements in pre-bronchodilator FEV_1 were present within 4 weeks of treatment start and were maintained throughout the entire treatment period (figure 3).

The benralizumab Q8W regimen resulted in a significant reduction in total asthma symptom score at week 56 relative to baseline (table 2), compared with placebo, for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils ≥300 cells per µL. Total asthma symptom score was lower for benralizumab-treated patients than for patients who received placebo at most timepoints throughout the treatment period (see appendix p 20 for time course). Mean changes in total asthma symptom scores did not differ at most timepoints during the treatment period between patients treated with the benralizumab Q4W regimen and those who received placebo in this patient subpopulation (table 2; see appendix p 20 for time course).

For additional secondary endpoints for patients with baseline blood eosinophils ≥300 cells per µL who were receiving high-dosage inhaled corticosteroids plus LABA, both benralizumab dosing regimens increased the time to first asthma exacerbation compared with placebo (Q4W HR 0·61 [95% CI 0·46–0·80], p=0·0004; Q8W HR 0·73 [0·55–0·95], p=0·0182; see appendix p 21 for plots of time to first exacerbation). During the 56-week period, the curves for cumulative number of exacerbations for the benralizumab treated and placebo cohorts diverged as early as 4 weeks (first sampling time point; see appendix p 22 for plots of cumulative number of exacerbations). The annual rate of asthma exacerbations that required an emergency department visit or admission to hospital did not differ between the benralizumab and placebo treatment groups (Q4W rate ratio 0·93 [95% CI 0·48–1·82], p=0·8366; Q8W rate ratio 1·23 [0·64–2·35], p=0·5381; appendix p 23). In addition, benralizumab treatment did not alter the time to first asthma exacerbation requiring an emergency department visit or admission to hospital (Q4W HR 1·01 [95% CI 0·50–2·02], p=0·9766; Q8W HR 1·41 [0·73–2·76], p=0·3011). Both benralizumab regimens versus placebo increased post-bronchodilator FEV_1 at week 56 relative to baseline (appendix p 19).

Benralizumab treatment improved ACQ-6 scores at week 56 relative to baseline for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils ≥300 cells per µL, compared with placebo (table 3). AQLQ(S)+12 scores at week 56 relative to baseline also improved for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils ≥300 cells per µL treated with the benralizumab Q8W regimen compared with placebo, but not for patients treated with the Q4W regimen (table 3).

In an exploratory analysis of the effect of benralizumab on blood eosinophil counts for the subpopulation of patients who were receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils ≥300 cells per µL, anti-eosinophil therapy reduced blood eosinophils from baseline (Q4W median 470 cells per µL [IQR 320–720]; Q8W 480 cells per µL

	High-dosage ICS plus LABA + baseline blood eosinophils ≥300 cells per μL			High-dosage ICS plus LABA + baseline blood eosinophils <300 cells per μL		
	Placebo (n=248)	Benralizumab 30 mg Q4W (n=241)	Benralizumab 30 mg Q8W (n=239)	Placebo (n=122)	Benralizumab 30 mg Q4W (n=116)	Benralizumab 30 mg Q8W (n=125)
ACQ-6 score*†						
Number of patients analysed (baseline and at least one post-baseline assessment)	247	241	239	122	116	125
LS mean change‡	–1·19; 197	–1·38; 192	–1·44; 185	–0·89; 92	–1·14; 88	–1·00; 83
LS mean difference *vs* placebo	..	–0·19 (–0·38 to –0·01)	–0·25 (–0·44 to –0·07)	..	–0·24 (–0·51 to 0·03)	–0·10 (–0·37 to 0·16)
p value *vs* placebo	..	0·0425	0·0082	..	0·0776	0·4488
AQLQ(S)+12 score*§						
Number of patients analysed (baseline and at least one post-baseline assessment)	240	233	230	..	..	..
LS mean change‡	1·31; 191	1·47; 186	1·56; 180	..	..	..
LS mean difference *vs* placebo	..	0·16 (–0·04 to 0·37)	0·24 (0·04 to 0·45)	..	..	..
p value *vs* placebo	..	0·1194	0·0194	..	..	..

Data are mean change from baseline at week 56; n or mean difference (95% CI). We did not do a formal statistical analysis of the data from the <300 cells per μL group for AQLQ(S)+12 score. ACQ-6=Asthma Control Questionnaire-6. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. ICS=inhaled corticosteroids. LABA=long-acting β_2-agonist. LS=least squares. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W). *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. †The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β_2-agonist use on a 0–6 scale (low numbers represent better control). ‡Numbers after semicolon are patients at 56 weeks. §The AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale (high numbers indicate better quality of life).

***Table* 3: Improvements in health-related quality of life and productivity with benralizumab treatment at week 56 (full analysis set)**

[350–700]) through week 4 (Q4W and Q8W median 0 cells per μL [0–10]), and week 56 (Q4W and Q8W median 0 cells per μL [0–10]). By comparison, blood eosinophil counts remained generally stable between baseline and end of treatment for patients in this group who received placebo (appendix p 24).

Reduced annual exacerbation rates and blood eosinophil counts were also achieved with 56 weeks of benralizumab treatment versus placebo for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophil counts <300 cells per μL (table 2; figure 2; see appendix p 24 for on-treatment blood eosinophil counts). However, pre-bronchodilator FEV_1 did not improve for patients treated with benralizumab in this patient group (table 2; figure 3). No apparent treatment differences were observed in change from baseline total asthma symptom score for either benralizumab dosing regimen versus placebo for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline eosinophil counts less than 300 cells per μL (table 2). Annual exacerbation rates, pre-bronchodilator FEV_1, and total asthma symptom scores were not affected by benralizumab treatment for the subset of patients receiving medium-dosage inhaled corticosteroids plus LABA with blood eosinophils ≥300 cells per μL at baseline (appendix p 25).

Data obtained in prespecified subgroup analyses suggested that geographic region and baseline asthma severity, as indicated by the number of exacerbations experienced by patients in the previous year, might have influenced the magnitude of treatment effect (see appendix p 26 for full subgroup analysis). The regions with the smallest treatment effects were eastern Europe (Q4W rate ratio 0·89 [95% CI 0·55–1·44]; Q8W rate ratio 1·00 [0·62–1·62]), and rest of world (South America; Q4W rate ratio 0·69 [0·37–1·28]; Q8W rate ratio 1·04 [0·58–1·88]). In these two regions, the percentages of patients who had experienced two exacerbations in the previous year were substantially greater than the percentages of patients who had experienced three or more previous exacerbations (see appendix p 27 for baseline patient demographics and clinical characteristics by geographic region). A possible treatment effect of baseline asthma severity was examined further in a post-hoc analysis. For patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils ≥300 cells per μL who had experienced two exacerbations in the previous year, annual exacerbation rates did not differ between the placebo group and the benralizumab treatment groups (see appendix p 28 for exacerbation rate ratios). For patients who had

	Placebo (n=440)	Benralizumab 30 mg Q4W (n=438)	Benralizumab 30 mg Q8W (n=428)
Any adverse event	342 (78%)	322 (74%)	320 (75%)
Any drug-related adverse event	36 (8%)	51 (12%)	54 (13%)
Any adverse event leading to treatment discontinuation	4 (<1%)	8 (2%)	10 (2%)
Any adverse event leading to death	0	2 (<1%)	2 (<1%)
Any serious adverse event	60 (14%)	45 (10%)	40 (9%)
Adverse event in >3% of patients*			
Nasopharyngitis	92 (21%)	90 (21%)	79 (18%)
Asthma	68 (15%)	61 (14%)	47 (11%)
Bronchitis	52 (12%)	40 (9%)	44 (10%)
Upper respiratory tract infection	41 (9%)	29 (7%)	36 (8%)
Headache	32 (7%)	33 (8%)	34 (8%)
Sinusitis	37 (8%)	21 (5%)	20 (5%)
Influenza	24 (5%)	22 (5%)	14 (3%)
Rhinitis allergic	23 (5%)	20 (5%)	16 (4%)
Hypertension	21 (5%)	12 (3%)	18 (4%)
Rhinitis	17 (4%)	12 (3%)	17 (4%)
Back pain	16 (4%)	16 (4%)	11 (3%)
Acute sinusitis	14 (3%)	6 (1%)	5 (1%)
Arthralgia	9 (2%)	8 (2%)	14 (3%)
Cough	8 (2%)	10 (2%)	14 (3%)
Pharyngitis	7 (2%)	16 (4%)	10 (2%)
Pyrexia	6 (1%)	16 (4%)	12 (3%)
Injection-site reactions	8 (2%)	11 (3%)	9 (2%)
Hypersensitivity	17 (4%)	13 (3%)	13 (3%)
Drug-related hypersensitivity	2 (<1%)	2 (<1%)	4 (<1%)

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 therapy visit. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W). *Medical Dictionary for Regulatory Activities version 18.1.

Table 4: **Adverse events, injection-site reactions, and hypersensitivity during the on-treatment period (all patients [n=1306])**

experienced three or more exacerbations in the previous year, the annual rates of asthma exacerbations were 45% lower in the benralizumab Q4W group (crude rate 0·90, treatment effect 0·55 [95% CI 0·37–0·81], p=0·0028, n=92) and 51% lower in the benralizumab Q8W group (crude rate 0·75, treatment effect 0·49 [95% CI 0·33–0·74], p=0·0008, n=95) than in the placebo group (crude rate 1·71, n=97; appendix p 28). This analysis also indicated substantially greater improvements in FEV_1, ACQ-6, AQLQ(S)+12, and total asthma symptom scores for these patients.

Most (984 [75%]) patients had adverse events during the on-treatment period (see appendix p 29 for safety results based on baseline blood eosinophil counts). Fewer patients treated with benralizumab (642 [74%] of 866) versus placebo (342 [78%] of 440) experienced adverse events. The most common adverse event was nasopharyngitis (20%). Adverse events were considered to be related to study treatment in 141 (11%) patients, 22 (2%) patients experienced adverse events that led to discontinuation of treatment, and four (<1%) patients died as a result of adverse events (table 4). Adverse events were considered to be mild in 317 (24%) patients, moderate in 551 (42%) patients, and severe in 116 (9%) patients, when classified according to their maximum intensity during the on-treatment period.

28 (2%) patients had injection-site reactions and 43 (3%) patients had hypersensitivity adverse events (table 4). The most common hypersensitivity adverse event was urticaria (22 [2%]). Incidences of injection-site reactions and hypersensitivity were similar between all treatment groups. A positive anti-drug antibody response was reported for 127 (15%) of 866 patients receiving benralizumab (see appendix p 30 for full immunogenicity results).

During the on-treatment period, 145 (11%) patients experienced serious adverse events (table 4). Fewer patients treated with benralizumab (85 [10%] of 866) versus placebo (60 [14%] of 440) experienced serious adverse events. The most commonly reported serious adverse event during the on-treatment period was worsening asthma for 21 (5%) patients treated with benralizumab Q4W, 18 (4%) patients treated with benralizumab Q8W, and 23 (5%) patients who received placebo. Investigators considered serious adverse events to be related to study treatment in four (<1%) patients: one patient treated with benralizumab Q4W experienced urticaria, two patients treated with benralizumab Q8W experienced serious adverse events of asthma and herpes zoster (n=1 each), and one patient receiving placebo experienced non-cardiac chest pain. Ten (<1%) patients discontinued treatment because of serious adverse events: five patients treated with benralizumab Q4W, two patients treated with benralizumab Q8W, and three patients who received placebo.

Four (<1%) patients died during the on-treatment period (table 4). Causes of death included suicide, road traffic accident, death (unknown cause), and colon neoplasm (n=1 each). In addition, two patients died during the post-treatment period. Both patients had acute myocardial infarctions (n=1 each in the Q4W and placebo groups). None of the deaths were considered to be related to the study treatments.

Discussion

The results of the CALIMA study showed that 56 weeks of add-on therapy with benralizumab 30 mg Q4W and Q8W significantly reduced the annual rate of asthma exacerbations by up to 36% for patients with severe asthma and elevated blood eosinophils that were

inadequately controlled on existing standard of care therapy. Both benralizumab dosing regimens also significantly improved lung function and, when administered every 8 weeks, significantly improved patient-reported total asthma symptom scores relative to baseline and placebo. Furthermore, benralizumab rapidly depleted blood eosinophils to the limits of detection. Together, these findings are consistent with the established mechanism of action of benralizumab[18] and validate the approach of targeting the interleukin-5 receptor α to deplete blood eosinophils and improve clinical outcomes for this difficult-to-treat group of patients.

Our findings confirm and support results from the phase 3 SIROCCO study,[28] in which 48 weeks of add-on benralizumab 30 mg (Q4W and Q8W) resulted in substantial improvements in asthma exacerbations, lung function, and symptom control for patients with severe, uncontrolled asthma with baseline blood eosinophils 300 cells per μL or greater (table 5). Despite similar trial designs and target patient groups included in the primary analyses, reductions in exacerbation rates seemed to be greater in the SIROCCO study than in the CALIMA study. A potential explanation for this difference in efficacy between the trials is not completely clear. However, subgroup analyses suggested that heterogeneity in regional exacerbation rates in CALIMA might have contributed to the size of treatment effect of benralizumab to a greater extent in CALIMA than in SIROCCO. This finding was substantially the consequence of patients from the eastern Europe and rest of world (ie, South America) regions who had fewer exacerbations in the year before study entry (ie, less severe baseline disease) compared with patients from the other regions, and because these patients had a very low rate of exacerbations during the treatment period, irrespective of benralizumab regimen. In support of this explanation, we found that patients who had experienced three or more exacerbations in the previous year (ie, greater asthma severity at baseline), and who were under-represented in the eastern Europe and rest of world (South America) regions, had the greatest effects of benralizumab treatment. Exacerbation reductions in this subgroup of CALIMA patients (three or more exacerbations in year before study) mirror annual asthma exacerbation rate reduction results of the SIROCCO study—ie, 45% and 51% for the Q4W and Q8W regimens, respectively, in both studies.[28]

In addition to regional heterogeneity and exacerbation history, the efficacy results of the CALIMA trial seemed to be affected by a strong placebo response. At baseline, the exacerbation rate of the placebo group of the primary analysis population was 2·7, which had fallen to 0·93 by the end of treatment. This response could have led to an underestimation of the treatment benefit of benralizumab in CALIMA.

Our findings confirm and extend results obtained in earlier clinical studies of benralizumab. In CALIMA, 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 showing such depletion to occur as early as day 1,[21–23] which is consistent with the potent depletion of eosinophils seen in CALIMA. In the phase 2B dose-ranging study, depletion of eosinophil counts was associated with a 41% (80% CI 11–60) reduction in the annual exacerbation rate, as well as improved lung function and symptom control, for patients with severe, uncontrolled asthma treated with 52 weeks benralizumab 100 mg Q8W, compared with placebo. Moreover, the reduction in exacerbation rate relative to placebo was 57% (80% CI 33–72) for the subset of patients with baseline blood eosinophils 300 cells per μL or greater. The results from CALIMA and SIROCCO allow more confident predictions of benralizumab efficacy in this patient subpopulation, as well as estimates of treatment benefits for patients receiving high-dosage inhaled corticosteroids plus LABA with baseline blood eosinophils less than 300 cells per μL. These results also provide support for assessments of benralizumab in the treatment of other diseases with an eosinophilic component.

The results obtained in the CALIMA trial add to a growing body of data that supports the use of anti-interleukin-5 pathway drugs in the management of patients with severe, uncontrolled asthma. By contrast with benralizumab, which acts directly on the eosinophil interleukin-5 receptor to cause eosinophil apoptosis, reslizumab and mepolizumab target the interleukin-5 molecule, thereby leading to passive reduction of eosinophils. One advantage of the former approach is that benralizumab could circumvent the induction of increased cytokine production associated with anti-cytokine antibodies.[29] A further advantage is that the direct action of benralizumab results in greater depletions of blood eosinophils than the indirect action of medications that target the interleukin-5 ligand.[18]

In phase 3 studies, reslizumab and mepolizumab treatment resulted in substantial reductions in

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

FEV_1=forced expiratory volume in 1 s. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W). *See Bleecker and colleagues.[28] †All results are differences from placebo; week 56 results presented for CALIMA and week 48 results presented for SIROCCO. ‡Reduced score indicates improvement. §Non-significant.

***Table* 5: Efficacy results for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per μL in the CALIMA and SIROCCO studies*†**

exacerbation rates with attendant reductions in circulating eosinophils.[13–16] Although direct comparison of different biologics is not possible in the absence of dedicated, head-to-head comparative trials, improvements in exacerbation rates seem to be comparable to those reported for patients treated with reslizumab or mepolizumab. However, these findings should be viewed in light of the asthma profiles of the patients recruited into the respective studies, who probably had more severe asthma at baseline than did patients enrolled in CALIMA. The reslizumab studies focused on patients with greater eosinophil counts (ie, baseline blood eosinophils in excess of 400 cells per µL) who might be expected to be more responsive to therapy.[13] Patients were recruited to the DREAM and MENSA mepolizumab studies with greater baseline inhaled corticosteroid dosages than patients in CALIMA (ie, ≥880 µg *vs* ≥500 µg fluticasone formulation or equivalent, respectively), which indicates more severe asthma.[14–16] Moreover, patients enrolled in mepolizumab studies had greater baseline and on-treatment exacerbation rates than patients enrolled in CALIMA,[14–16] which indicates a more severe exacerbation phenotype. The improvements in exacerbation rates indicated by the post-hoc analysis of CALIMA patients with a more severe exacerbation history (ie, three or more exacerbations in the previous year), mirror efficacy results obtained for the overall population in the SIROCCO study,[28] as well as the mepolizumab and reslizumab studies.[13–16]

Increases in lung function with benralizumab treatment seemed to be comparable or greater than those observed for mepolizumab and reslizumab,[13,15] with improvements observed as early as 4 weeks, the first timepoint assessed. We also found small improvements in ACQ-6 and AQLQ(S)+12 scores for patients treated with the benralizumab Q8W regimen, which are consistent with results obtained for mepolizumab and reslizumab.[13,15] However, the clinical benefit of small improvements such as these is uncertain.

In addition to drugs that target the interleukin-5 pathway, other biologic agents are in clinical development for the treatment of uncontrolled asthma. Dupilumab is a human anti-interleukin-4 receptor α monoclonal antibody that inhibits interleukin-4 and interleukin-13 signalling. This agent has increased lung function and reduced severe exacerbations for patients with uncontrolled, persistent asthma in a phase 2 study.[30]

Benralizumab was well tolerated, as shown by the low discontinuation rate and an anticipated safety profile in the CALIMA study based on the results of the phase 2B study.[23] Few adverse events were considered to be drug related, and discontinuations due to benralizumab were uncommon. Anti-drug antibody responses were infrequent, and there was no indication that positive anti-drug antibody responses were associated with hypersensitivity or affected efficacy outcomes.

Our study has some limitations. CALIMA enrolment enriched the study population of patients with baseline blood eosinophils 300 cells per µL or greater (via 2:1 randomisation). Therefore, this study was not designed to compare outcomes for patients with baseline blood eosinophils 300 cells per µL or greater with patients with lower blood eosinophil counts. In addition, the CALIMA study was not powered to detect differences between the two benralizumab dosing regimens. Patients enrolled in CALIMA and SIROCCO were eligible to join the 2-year BORA safety extension study (NCT02258542). This study will provide data for the longer term use of benralizumab, which cannot be provided by CALIMA or SIROCCO. Finally, because of small sample sizes, we were unable to assess whether benralizumab resulted in efficacy for different patient subgroups of interest (eg, black or African American, adolescent, and atopic patients).

The results obtained from this study, together with those obtained in SIROCCO, provide strong evidence of the clinical value of benralizumab treatment in the management of patients with severe or uncontrolled asthma and blood eosinophils 300 cells per µL or greater. Benralizumab, an anti-eosinophil monoclonal antibody that targets the interleukin-5 receptor α, represents a new mechanism of action to address the unmet needs of these patients.

Contributors

JMF, ERB, and MG conceived and designed the study. PB, SS, GG, MA, VW, and MG collected the data. All authors had access to and analysed and interpreted the data. All authors participated in the development and critical review of the report. All authors provided final approval for publication submission and are accountable for the accuracy and integrity of the work.

Declaration of interests

JMF is a member of advisory boards for AstraZeneca, Novartis, Teva, ALK, and Boehringer Ingelheim; and has also been paid honoraria for lecturing at symposia organised by these companies. 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; and has also served as a paid consultant for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, GSK, Forest, Novartis, Regeneron, and Sanofi. PN is a member of advisory boards for AstraZeneca, Sanofi, Teva, and Roche; and has also received honoraria from these companies and from Novartis and Boehringer Ingelheim for lectures at symposia. SK reports being a member of advisory boards for AstraZeneca, Teva, Roche, and Novartis and has received honoraria from these companies for lectures at symposia. KO declares no competing interests. ML received honoraria for lectures and advisory boards from ALK Abelló, Allergopharma, AstraZeneca, Bencard, Berlin-Chemie, Boehringer Ingelheim, Boston Scientific, Chiesi, GSK, Janssen-Cilag, MSD, Mundipharma, Novartis, Nycomed/Takeda, Sanofi, TEVA, and UCB. GTF reports grants and personal fees from Novartis, AstraZeneca, Pearl Therapeutics, and Sunovian, as well as grants from Forest and personal fees from GlaxoSmithKline. WWB reports personal fees from Novartis, Genentech, Roche, Boehringer Ingelheim, Sanofi, AstraZeneca, Teva, 3M, Boston Scientific, Circassia, ICON, and GlaxoSmithKline, outside of the submitted work. PB, GG, MA, VW, and MG are employees of AstraZeneca. SS is an employee of Optimum Statistics Inc and provided statistical analyses and support under contract to AstraZeneca, through inVentiv Health Clinical.

Acknowledgments

Funding for this study was provided by AstraZeneca and Kyowa Hakko Kirin. We would like to thank the investigators, health-care providers, research staff, and patients who participated in the CALIMA study.

We would like to acknowledge Mark Odorisio (AstraZeneca, Gaithersburg, MD, USA), Nick Adye (AstraZeneca, Cambridge, UK), and Irma Dzhindzhikhashvili (AstraZeneca, Warsaw, Poland) for their clinical operations leadership in this study. We also thank Ian Hirsch (AstraZeneca, Gaithersburg, MD, USA) for biometrics management and support of statistical analyses and programming. Writing and editing assistance, including preparation of a draft report under the direction and guidance of the authors, incorporating author feedback, and manuscript submission, was provided by Neil M Thomas (Endpoint Medical Communications, Brighton, UK) and Michael A Nissen (AstraZeneca). This support was funded by AstraZeneca.

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