Ann Allergy Asthma Immunol 120 (2018) 504–511

Contents lists available at ScienceDirect

Benralizumab efficacy by atopy status and serum immunoglobulin E for patients with severe, uncontrolled asthma

Bradley E. Chipps, MD [*]; Paul Newbold, PhD [†]; Ian Hirsch, PhD [‡]; Frank Trudo, MD [§]; Mitchell Goldman, MD [‡]

[*] *Capital Allergy and Respiratory Disease Center, Sacramento, California*
[†] *MedImmune LLC, Gaithersburg, Maryland*
[‡] *AstraZeneca, Gaithersburg, Maryland*
[§] *AstraZeneca, Wilmington, Delaware*

ARTICLE INFO

Article history:
Received for publication November 6, 2017.
Received in revised form January 9, 2018.
Accepted for publication January 24, 2018.

ABSTRACT

Background: Patients with severe asthma can have eosinophilic inflammation and/or allergen sensitization. Benralizumab is an anti-eosinophilic monoclonal antibody indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.
Objective: To investigate the efficacy of benralizumab by atopic status and serum immunoglobulin E (IgE) concentrations.
Methods: We analyzed pooled results from the SIROCCO (NCT01928771) and CALIMA (NCT01914757) phase III studies. Patients 12 to 75 years old with severe, uncontrolled asthma on high-dosage inhaled corticosteroids plus long-acting β_2-agonists received 30 mg of subcutaneous benralizumab every 4 weeks or every 8 weeks (first 3 doses every 4 weeks) or placebo every 4 weeks. The analysis stratified patients who did and did not meet similar omalizumab-qualifying criteria of atopy and serum IgE levels 30 to 700 kU/L. Patients also categorized as having high serum IgE (≥150 kU/L) or low serum IgE (<150 kU/L) and as having atopy or no atopy. Efficacy outcomes were for all patients and by blood eosinophil counts and included annual exacerbation rate ratio and pre-bronchodilator forced expiratory volume in 1 second change at treatment end vs placebo.
Results: Benralizumab every 8 weeks decreased exacerbations by 46% (95% confidence interval 26–61, $P = .0002$) and increased forced expiratory volume in 1 second by 0.125 L (95% confidence interval 0.018–0.232, $P = .0218$) vs placebo for patients with at least 300 eosinophils/μL who met the atopy and IgE criteria. For patients with eosinophilia and high or low IgE, treatment with benralizumab every 8 weeks resulted in 42% and 43% decreases in exacerbation rate ($P \leq .0004$) and 0.123- and 0.138-L increases in forced expiratory volume in 1 second ($P \leq .0041$) vs placebo, respectively.
Conclusion: Benralizumab treatment decreased exacerbations and improved lung function for patients with severe, uncontrolled eosinophilic asthma regardless of serum IgE concentrations and atopy status.

Introduction

Asthma affects more than 315 million people worldwide, with approximately 10% having severe or uncontrolled asthma.[1,2] Severe, uncontrolled asthma leads to substantial disease burden, lower health-related quality of life, and increased health care resource usage and costs for patients.[3–5] Patients with severe asthma require high-dosage inhaled corticosteroids (ICSs) in combination with long-acting β_2-agonists (LABAs) for disease control.[6]

Reprints: Bradley E. Chipps, MD, FAAP, FACAAI, FAAAAI, FCCP, American College of Allergy, Asthma & Immunology, Capital Allergy & Respiratory Disease Center, 5609 J Street, Suite C, Sacramento, CA 95819; E-mail: chipps@capitalallergy.com.
Disclosures: Bradley E. Chipps has nothing to declare. Ian Hirsch, Frank Trudo, and Mitchell Goldman are employees of AstraZeneca. Paul Newbold is an employee of MedImmune.
Funding Sources: AstraZeneca.
Trial Registration: SIROCCO, NCT01928771 (https://clinicaltrials.gov/ct2/show/NCT01928771); CALIMA, NCT01914757 (https://clinicaltrials.gov/ct2/show/NCT01914757).

https://doi.org/10.1016/j.anai.2018.01.030

Despite these treatments, asthma remains uncontrolled in many patients, putting them at risk for severe asthma exacerbations.[3] Add-on treatments that have been recommended for patients with severe, uncontrolled asthma include anti-immunoglobulin E (IgE) and anti–interleukin-5 (IL-5) agents and the long-acting muscarinic antagonist tiotropium.[6] Omalizumab (Genentech, Inc, South San Francisco, California) is a humanized anti-IgE monoclonal antibody approved as add-on therapy for patients at least 6 years of age with moderate to severe (United States) or severe (Europe) persistent, uncontrolled asthma with positive skin test or in vitro reactivity to a perennial aeroallergen.[7,8] Omalizumab prevents binding of IgE to mast cells and basophils, decreases free IgE concentrations, and inhibits allergen-induced inflammation (eg, decreasing eosinophils).[9,10] In clinical trials, omalizumab decreased exacerbation frequency, decreased ICS use, and improved lung function for patients with severe allergic asthma compared with placebo.[9,11]

Two monoclonal antibodies against IL-5, mepolizumab and reslizumab, are approved in the United States and Europe as add-on maintenance treatment for patients with severe asthma and an eosinophilic phenotype.[12–14] Eosinophilic inflammation affects approximately 50% of patients with asthma and is associated with increased disease severity, exacerbation frequency, and symptom burden and decreased lung function.[15–17] IL-5 is an important cytokine for eosinophil development, activation, proliferation, and survival that is present in increased blood concentrations for patients with asthma.[18,19]

An additional anti-eosinophilic therapy for severe, uncontrolled asthma is benralizumab, a humanized, afucosylated, anti–IL-5 receptor-α monoclonal antibody. In the United States, benralizumab (Fasenra, AstraZeneca, Cambridge, United Kingdom) is indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.[20] Benralizumab induces the 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.[21,22] Unlike benralizumab, anti–IL-5 therapies decrease eosinophils through a passive mechanism that does not entirely deplete these cells.[12–14] Two phase III trials, SIROCCO (NCT01928771) and CALIMA (NCT01914757), demonstrated that benralizumab in combination with high-dosage ICS and LABA with or without additional controllers significantly decreased asthma exacerbations and improved disease control for patients with severe, uncontrolled asthma and blood eosinophil counts of at least 300 cells/μL vs placebo.[23,24] Further analysis of these studies has confirmed efficacy for patients with blood eosinophil counts of at least 150 cells/μL.[25,26] In addition, the recent ZONDA study demonstrated that benralizumab treatment can substantially decrease daily oral glucocorticoid use for patients with blood eosinophil counts of at least 150 cells/μL who receive long-term glucocorticoid therapy.[27]

Asthma is a heterogenous disease in which factors associated with disease severity and control (including IgE concentrations, atopy status, and eosinophilic inflammation) can differ between patients.[2,28,29] Individual patients can have several factors present, with each factor potentially having a changing influence on their disease.[2,28,29] In a study by Tran et al,[29] 68% to 78% of adults had atopic asthma with blood eosinophil counts of at least 150 cells/μL. Understanding the benefits of targeted therapies for patients with several disease processes is important to identify the appropriate treatment regimen for a particular patient.

In this report, we present an analysis of the pooled efficacy results from the SIROCCO and CALIMA studies for patients with asthma treated with benralizumab who had atopy and serum IgE concentrations of 30 to 700 kU/L, criteria similar to those for patients who might qualify for omalizumab treatment. We also evaluated efficacy for patients based on their serum IgE concentrations, atopy status, and baseline blood eosinophil counts.

Methods

Study Design and Participants

SIROCCO and CALIMA were randomized, double-blinded, parallel-group, placebo-controlled, phase III studies that enrolled patients at 374 and 303 clinical research centers, respectively, in Africa, Asia, Europe, North America, and South America.[23,24] The study design consisted of an enrollment visit (week –4), a 4-week screening and run-in phase, randomization (week 0), a treatment period from weeks 0 to 48 (SIROCCO) or 56 (CALIMA), and a final follow-up visit 8 (SIROCCO) or 4 (CALIMA) weeks after the end of the treatment (EOT) period.

Enrollment criteria for the studies have been published.[23,24] The studies included male and female patients 12 to 75 years old with a weight of at least 40 kg and physician-diagnosed asthma that required treatment with medium- to high-dosage ICS and LABA for at least 12 months before enrollment. Inclusion criteria included at least 2 asthma exacerbations within 12 months before the date of enrollment requiring systemic corticosteroid therapy or a temporary increase in the usual maintenance dosages of oral corticosteroid. Patients also must have had documented treatment of high-dosage ICS and LABA (≥500 μg/d of fluticasone propionate equivalent for CALIMA) with or without oral corticosteroids and additional asthma controllers for at least 3 months before enrollment. Studies were conducted in accordance with the Declaration of Helsinki, the 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.

Treatments

For the 2 studies, patients were randomized 1:1:1 to receive 30 mg of subcutaneous benralizumab once every 4 weeks (Q4W), 30 mg of benralizumab Q4W for the first 3 doses followed by once every 8 weeks for the remainder of the treatment period (Q8W), or placebo Q4W. Treatment was doubly blinded and lasted for 48 (SIROCCO) or 56 (CALIMA) weeks. For the respective studies, patients with baseline blood eosinophil counts of at least 300 cells/μL and lower than 300 cells/μL were recruited at a ratio of approximately 2:1, respectively.

Outcomes

The original primary efficacy variable for the 2 studies was the annual asthma exacerbation rate (AER). For the 2 studies, the primary analysis set included patients receiving high-dosage ICS and LABA with a baseline blood eosinophil count of at least 300 cells/μL. An exacerbation was defined as a worsening of asthma that led to 1 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 depo-injectable dose of corticosteroid, (2) asthma-related emergency department or urgent care visit (<24 hours) that required systemic corticosteroids, or (3) asthma-related inpatient hospitalization (≥24 hours). 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.[23,24] A key secondary endpoint for the primary analysis population evaluated in this study was pre-bronchodilator forced expiratory volume in 1 second (FEV_1), measured by spirometry. Additional secondary end points included Asthma Control Questionnaire 6 (ACQ-6) score and standardized Asthma Quality of

Life Questionnaire for 12 years and older (AQLQ[S]+12) score. The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β-agonist use on a scale of 0 to 6 (low scores represent better control).[30] The AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life scored on a scale of 1 to 7 (low scores represent greater impairment).[31] Details on efficacy measurement methods have been published.[23,24]

In the present study, analyses were performed for patients treated with high-dosage ICS and LABA (defined as ≥500 mg/d of fluticasone or equivalent total daily dosage) from the pooled SIROCCO and CALIMA studies. In 1 analysis, patients who did and did not meet the screening criteria of total serum IgE concentrations of at least 30 to no greater than 700 kU/L, had atopy, and had a baseline weight of 30 to 150 kg were evaluated. Patients were excluded if they had a combined serum IgE concentration range and baseline weight greater than 600 to 700 kU/L and greater than 60 kg, greater than 500 to 600 kU/L and greater than 70 kg, or greater than 300 to 500 kU/L and greater than 90 kg. Atopy was defined as having a positive Phadiatop (Phadia AB/Thermo Fisher Scientific, Uppsala, Sweden) test reaction. The Phadiatop test is a multi-allergen inhalant screening blood test with extracts for house dust mites, cat and dog dander, mold spores, and tree, grass, and weed pollen. For this study, end points evaluated were AER, pre-bronchodilator FEV_1, ACQ-6 score, and AQLQ(S)+12 score.

A second analysis was performed on patients based on whether they had high or low serum IgE concentrations (≥150 or <150 kU/L respectively), chosen post hoc, and atopic or nonatopic status. Outcomes evaluated were AER and pre-bronchodilator FEV_1.

Statistical Analysis

We performed analyses based on the full analysis set according to the intention-to-treat principle for the pooled SIROCCO and CALIMA studies. This set included all randomized patients who received any study treatment, regardless of their protocol adherence and continued participation in the study. The similar design of the 2 studies allowed for the results to be pooled, which allowed us to obtain more accurate estimates of the relations of efficacy end points with combined IgE concentration and atopy screening criteria, serum IgE concentrations, and atopy status. Analyses were performed with SAS 9.2 (SAS Institute, Cary, North Carolina).

We analyzed the exacerbation rates using a negative binomial model, with adjustments for treatment, study, region, oral corticosteroid use at time of randomization, and prior exacerbations. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for different exposure times during which the events occurred. We determined the estimated treatment effect (ie, rate ratio [RR] of benralizumab vs placebo), corresponding 95% confidence intervals (CIs), and 2-sided *P* value for the RR. The AER and corresponding 95% CIs also were calculated. Pre-bronchodilator FEV_1, ACQ-6 score, and AQLQ(S)+12 score were analyzed using a mixed-effects model for repeated measures analysis, with adjustments for treatment, study, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. The EOT visit for each study was included in the model and used as the primary time point. To account for the 2:1 stratification for baseline blood eosinophil counts (≥300 and <300 cells/μL) in analyses using cut points that were lower than 300 cells/μL, we reweighted patients with baseline blood eosinophil counts lower than 300 cells/μL using the ratio of the number of patients with baseline blood eosinophil counts of at least 300 cells/μL to the number of those who had counts lower than 300 cells/μL. We calculated least squares means, treatment differences in least squares means, 95% CIs, and *P* values. Because these analyses were not part of the formal testing strategy, all *P* values were nominal. Locally weighted scatterplot smoothing determination with its corresponding 95% CI was used to determine the relation between serum IgE and blood eosinophil counts.

Results

A total of 824 patients (271 placebo, 256 Q4W, 297 Q8W) had atopy and serum IgE concentrations of at least 30 to fewer than 700 kU/L, meeting criteria similar to those for patients to qualify for omalizumab treatment (Table 1). Demographics and clinical characteristics were similar between patients who met the criteria and those who did not (1,471 patients: 506 placebo, 500 Q4W, 465 Q8W; Table 1). In addition, 1,204 patients (413 placebo, 398 Q4W, 393 Q8W) had high IgE (≥150 kU/L) and 1,053 patients (352 placebo, 349 Q4W, 352 Q8W) had low IgE (<150 kU/L). There were 1,375 patients who had a positive test reaction for atopy (463 placebo, 444 Q4W, 468 Q8W), whereas 883 patients (302 placebo, 301 Q4W, 280 Q8W) had a negative reaction.

A trend for a positive relation between blood eosinophil counts and IgE concentrations was observed for patients with atopy and lower serum IgE concentrations (Fig 1). For patients without atopy and all patients, regardless of their atopy status, a weaker positive relation existed for these variables (Fig 1).

Overall, efficacy on annual AER with the Q8W dosage was similar to that with the Q4W dosage (Table 2, eTable 1). Annual AER improvements of 41% (RR 0.59, 95% CI 0.46–0.76, $P < .0001$) and 37% (RR 0.63, 95% CI 0.50–0.81, $P = .0002$) were observed with benralizumab Q4W and Q8W treatment, respectively, vs placebo for patients who met atopy and serum IgE 30 to 700 kU/L concentration criteria (eTable 1). Similar efficacy on annual AER was observed for patients who did not meet the atopy and IgE 30 to 700 kU/L criteria. Improvements of 37% (RR 0.63, 95% CI 0.52–0.77, $P < .0001$) and 37% (RR 0.63, 95% CI 0.52–0.77, $P < .0001$) were observed with benralizumab Q4W and Q8W treatment, respectively, vs placebo (eTable 1). Improvements in annual AER were more pronounced for patients with blood eosinophil counts of at least 300 cells/μL compared with those with blood eosinophil counts lower than 300 cells/μL and were observed regardless of whether patients did or did not meet the atopy and serum IgE criteria (Table 2, eTable 1). For patients in the primary population with blood eosinophil counts of at least 300 cells/μL who received benralizumab Q8W, annual AER improved vs placebo by 46% (RR 0.54, 95% CI 0.39–0.74, $P = .0002$) for patients who met the 2 criteria and 39% (RR 0.61, 95% CI 0.47–0.78, $P < .0001$) for patients who did not meet the criteria (Table 2).

Pre-bronchodilator FEV_1 increased with benralizumab from baseline to EOT, vs placebo, for patients with blood eosinophil counts of at least 300 cells/μL who did and did not meet the atopy and IgE criteria (Table 3, eTable 2). For these patients in the benralizumab Q8W cohort, increases of 0.125 L (95% CI 0.018–0.232, $P = .0218$) and 0.152 L (95% CI 0.076–0.228, $P < .0001$) occurred in pre-bronchodilator FEV_1 vs placebo for patients who did and did not meet the criteria, respectively (Table 3).

Improvements from baseline at EOT were observed for ACQ-6 and AQLQ(S)+12 scores for the benralizumab Q8W cohort vs placebo, irrespective of whether patients with blood eosinophil counts of at least 300 cells/μL and did or did not meet the atopy and IgE criteria (Tables 4 and 5). ACQ-6 scores improved at EOT with benralizumab Q8W treatment vs placebo by –0.34 (95% CI –0.55 to –0.13, $P = .0017$) and –0.26 (95% CI –0.41 to –0.10, $P = .0016$) for patients with blood eosinophil counts of at least 300 cells/μL who did and did not meet the criteria, respectively (Table 4). AQLQ(S)+12 scores increased at EOT vs placebo with benralizumab Q8W treatment by 0.27 (95% CI 0.04–0.50, $P = .0193$) and 0.27 (95% CI 0.10–0.44, $P = .0022$) for patients who did and did not meet the criteria, respectively (Table 5). Similar improvements with benralizumab in ACQ-6 and AQLQ(S)+12 scores in general were not observed for

Table 1
Patient Demographics and Baseline Clinical Characteristics (Full Analysis Set, Pooled)

	Met atopy and IgE 30–700 kU/L criteria[a] (n = 824)	Did not meet atopy and IgE 30–700 kU/L criteria[a] (n = 1,471)	IgE high (≥150 kU/L; n = 1,204)	IgE low (n = 1,053)	Atopy (n = 1,375)	No atopy (n = 883)
Age (y), mean (SD)	47.3 (14.2)	50.7 (13.6)	47.7 (14.5)	51.4 (13.1)	46.8 (14.6)	53.5 (12.0)
Sex, n (%)						
Men	308 (37)	515 (35)	488 (41)	316 (30)	551 (40)	256 (29)
Women	516 (63)	956 (65)	716 (59)	737 (70)	824 (60)	627 (71)
Race, n (%)						
White	611 (74)	1,202 (82)	887 (74)	896 (85)	1,018 (74)	768 (87)
Black or African-American	34 (4)	45 (3)	52 (4)	26 (2)	63 (5)	15 (2)
Asian	122 (15)	150 (10)	176 (15)	92 (9)	196 (14)	72 (8)
Other[b]	57 (7)	74 (5)	89 (7)	39 (4)	98 (7)	28 (3)
Body mass index (kg/m^2), mean (SD)[c]	28.5 (6.4)	29.2 (6.9)	28.7 (6.8)	29.3 (6.8)	29.0 (7.0)	28.9 (6.3)
Eosinophil count (cells/μL), median (range)[c]	350 (0–3,440)	400 (0–4,494)	420 (0–4,494)	320 (0–3,440)	384 (0–3,640)	370 (0–4,494)
FEV_1 pre-bronchodilator (L), mean (SD)[c]	1.754 (0.607)	1.671 (0.587)	1.748 (0.614)	1.650 (0.568)	1.775 (0.615)	1.588 (0.541)
FEV_1 pre-bronchodilator (% predicted normal), mean (SD)[c,d]	57.9 (14.2)	56.7 (14.8)	57.5 (14.6)	56.9 (14.5)	58.0 (14.4)	56.0 (14.7)
Reversibility (%), median (range)[c]	20.0 (–26.4 to 813.8)	19.1 (–24.3 to 808.5)	19.6 (–12.8 to 170.5)	20.0 (–26.4 to 813.8)	20.2 (–26.4 to 813.8)	18.6 (–12.1 to 808.5)
Exacerbations in previous 12 mo (n), mean (SD)	2.8 (1.9)	2.8 (1.5)	2.8 (1.6)	2.8 (1.7)	2.8 (1.6)	2.8 (1.7)
ACQ-6 score, mean (SD)[e]	2.7 (0.9)	2.8 (0.9)	2.8 (0.9)	2.8 (0.9)	2.7 (0.9)	2.9 (0.9)
AQLQ(S)+12 score, mean (SD)[c,f]	4.0 (1.0)	3.9 (1.0)	4.0 (1.0)	3.9 (1.0)	4.0 (1.0)	3.8 (1.0)
Atopy by Phadiatop test, n (%)	824 (100)	551 (37)	963 (80)	405 (38)	1,375 (100)	0 (0)
IgE (kU/L), median (range)[c]	182.5 (31.1–645.5)	160.9 (2.0–46,983.8)	423.4 (150.0–46,983.8)	57.3 (2.0–149.8)	305.1 (3.7–46,983.8)	70.6 (2.0–10,999.4)
Nasal polyps, n (%)	124 (15)	293 (20)	221 (18)	195 (19)	207 (15)	209 (24)
Maintenance OCS use, n (%)	104 (13)	205 (14)	134 (11)	170 (16)	155 (11)	148 (17)

Abbreviations: ACQ-6, Asthma Control Questionnaire 6; AQLQ(S)+12, Standardized Asthma Quality of Life Questionnaire for 12 years and older; IgE, immunoglobulin E; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroid.

[a]Atopy (by Phadiatop test) and serum IgE concentration of 30 to 700 kU/L criteria.

[b]Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other.

[c]Data not available for all randomized patients.

[d]Percentage of predicted normal is FEV_1 expressed as a percentage of the normal value for a person of the same sex, age, and height.

[e]The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β-agonist use on a scale of 0 to 6 (low scores represent better control).

[f]The AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life scored on a scale of 1 to 7 (high scores indicate better asthma-related quality of life).

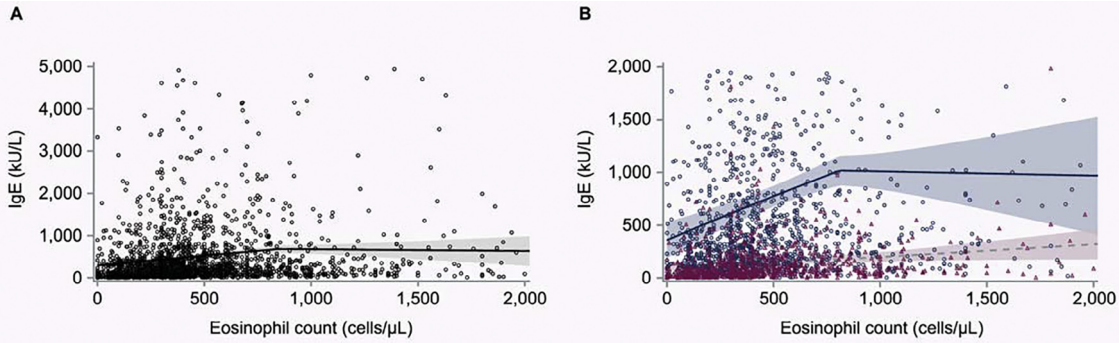

Figure 1. Relation of serum immunoglobulin E (IgE) concentrations with blood eosinophil counts based on atopy status (full analysis set, pooled). Baseline serum IgE concentrations vs eosinophil counts for (*A*) all patients (*black circles*) and (*B*) patients who had (*blue circles*) or did not have (*red triangles*) atopy. Locally weighted scatterplot smoothing line and corresponding 95% confidence interval are presented.

patients with blood eosinophil counts lower than 300 cells/μL (eTables 3 and 4).

In addition, benralizumab decreased exacerbation frequency and improved lung function for patients with high (≥150 kU/L) or low (<150 kU/L) serum IgE concentrations and with blood eosinophil counts of at least 300 cells/μL (Table 6). Annual AER improved by 42% (RR 0.58, 95% CI 0.45–0.75, $P < .0001$) and 43% (RR 0.57, 95% CI 0.41–0.78, $P = .0004$) vs placebo for patients with high and low IgE concentrations, respectively, with blood eosinophil counts of at least 300 cells/μL and receiving benralizumab Q8W. For this same cohort, pre-bronchodilator FEV_1 increased at EOT from baseline by 0.123 L (95% CI 0.041–0.205 L, $P = .0034$) and 0.138 L (95% CI 0.044–0.233, $P = .0041$) for patients with high and low IgE concentrations, respectively, and receiving benralizumab Q8W vs placebo (Table 6). Patients with blood eosinophil counts lower than 300 cells/μL did not achieve a similar level of exacerbation decrease or lung function improvement with benralizumab (eTable 5).

Table 2
Annual Exacerbation Rates for Patients Who Did and Did Not Meet Atopy and Serum IgE Criteria and Blood Eosinophil Counts ≥300 Cells/μL (Full Analysis Set, Pooled)[a]

	Met atopy and IgE 30–700 kU/L criteria[b] (n = 824)			Did not meet atopy and IgE 30–700 kU/L criteria[b] (n = 1,471)		
	Placebo (n = 271)	Benralizumab Q4W (n = 256)	Benralizumab Q8W (n = 297)	Placebo (n = 506)	Benralizumab Q4W (n = 500)	Benralizumab Q8W (n = 465)
Patients analyzed, n	179	153	185	336	363	321
Rate estimate (95% CI)	1.25 (1.01–1.54)	0.62 (0.47–0.81)	0.67 (0.52–0.86)	1.07 (0.91–1.26)	0.69 (0.58–0.82)	0.65 (0.54–0.78)
Absolute difference estimate vs placebo (95% CI)	—	–0.63 (–0.93 to –0.32)	–0.58 (–0.89 to –0.27)	—	–0.38 (–0.59 to –0.17)	–0.42 (–0.63 to –0.21)
Rate ratio vs placebo (95% CI)	—	0.50 (0.36–0.69)	0.54 (0.39–0.74)	—	0.64 (0.51–0.81)	0.61 (0.47–0.78)
Nominal *P* vs placebo	—	<.0001	.0002	—	.0002	<.0001

Abbreviations: CI, confidence interval; IgE, immunoglobulin E; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).
[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β_2-agonist treatment cohorts of the SIROCCO and CALIMA studies. Estimates were calculated using a negative binomial model, with adjustment for study code, treatment, region, oral corticosteroid use at time of randomization, and prior exacerbations. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 cells/μL and <300 cells/μL).
[b]Atopy (by Phadiatop test) and serum IgE concentration of 30 to 700 kU/L criteria.

Table 3
Pre-bronchodilator Forced Expiratory Volume in 1 Second (Liters) Change (Baseline–EOT) for Patients Who Did and Did Not Meet Atopy and Serum IgE Criteria and Blood Eosinophil Counts ≥300 Cells/μL (Full Analysis Set, Pooled)[a]

	Met atopy and IgE 30–700 kU/L criteria[b] (n = 824)			Did not meet atopy and IgE 30–700 kU/L criteria[b] (n = 1,471)		
	Placebo (n = 271)	Benralizumab Q4W (n = 256)	Benralizumab Q8W (n = 297)	Placebo (n = 506)	Benralizumab Q4W (n = 500)	Benralizumab Q8W (n = 465)
Patients in analysis, n	178	149	184	327	360	318
Patients with EOT data, n	155	135	161	299	317	285
LS mean change	0.238	0.367	0.363	0.217	0.330	0.369
LS mean difference vs placebo (95% CI)	—	0.129 (0.017–0.241)	0.125 (0.018–0.232)	—	0.114 (0.040–0.187)	0.152 (0.076–0.228)
Nominal *P* vs placebo	—	.0244	.0218	—	.0024	<.0001

Abbreviations: CI, confidence interval; EOT, end of treatment; IgE, immunoglobulin E; LS, least squares; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).
[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β_2-agonist treatment cohorts of the SIROCCO and CALIMA studies. Pre-bronchodilator forced expiratory volume in 1 second change is from baseline (ie, last value before randomization) to EOT (SIROCCO: week 48; CALIMA: week 56). Estimates were calculated by using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 cells/μL and <300 cells/μL).
[b]Atopy (by Phadiatop test) and serum IgE concentration of 30 to 700 kU/L criteria.

Table 4
ACQ-6 Change (Baseline–EOT) for Patients Who Did and Did Not Meet Atopy and Serum IgE Criteria and Blood Eosinophil Counts ≥300 cells/μL (Full Analysis Set, Pooled)[a]

	Met atopy and IgE 30–700 kU/L criteria[b] (n = 824)			Did not meet atopy and IgE 30–700 kU/L criteria[b] (n = 1,471)		
	Placebo (n = 271)	Benralizumab Q4W (n = 256)	Benralizumab Q8W (n = 297)	Placebo (n = 506)	Benralizumab Q4W (n = 500)	Benralizumab Q8W (n = 465)
Patients in analysis, n	179	152	185	335	363	317
Patients with EOT data, n	130	118	139	253	272	237
LS mean change	–1.07	–1.40	–1.41	–1.22	–1.34	–1.47
LS mean difference vs placebo (95% CI)	—	–0.33 (–0.55 to –0.11)	–0.34 (–0.55 to –0.13)	—	–0.12 (–0.28 to 0.03)	–0.26 (–0.41 to –0.10)
Nominal *P* vs placebo	—	.0038	.0017	—	.1111	.0016

Abbreviations: ACQ-6, Asthma Control Questionnaire 6; CI, confidence interval; EOT, end of treatment; IgE, immunoglobulin E; LS, least squares; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).
[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β_2-agonist treatment cohorts of the SIROCCO and CALIMA studies. ACQ-6 change is from baseline (ie, last value before randomization) to EOT (SIROCCO: week 48; CALIMA: week 56). Estimates were calculated using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 cells/μL and <300 cells/μL).
[b]Atopy (by Phadiatop test) and serum IgE concentration of 30 to 700 kU/L criteria.

Table 5
AQLQ(S)+12 Change (Baseline–EOT) by Patients Who Did and Did Not Meet Atopy and Serum IgE Criteria and Blood Eosinophil Counts ≥300 cells/μL (Full Analysis Set, Pooled)[a]

	Met atopy and IgE 30–700 kU/L criteria[b] (n = 824)			Did not meet atopy and IgE 30–700 kU/L criteria[b] (n = 1,471)		
	Placebo (n = 271)	Benralizumab Q4W (n = 256)	Benralizumab Q8W (n = 297)	Placebo (n = 506)	Benralizumab Q4W (n = 500)	Benralizumab Q8W (n = 465)
Patients in analysis, n	176	147	176	318	347	306
Patients with EOT data, n	128	115	133	243	263	234
LS mean change	1.23	1.51	1.5	1.32	1.43	1.59
LS mean difference vs placebo (95% CI)	—	0.28 (0.04–0.52)	0.27 (0.04–0.50)	—	0.11 (–0.06 to 0.27)	0.27 (0.10–0.44)
Nominal *P* vs placebo	—	.0207	.0193	—	.2057	.0022

Abbreviations: AQLQ(S)+12, Standardized Asthma Quality of Life Questionnaire for 12 years and older; CI, confidence interval; EOT, end of treatment; IgE, immunoglobulin E; LS, least squares; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).
[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β_2-agonist treatment cohorts of the SIROCCO and CALIMA studies. AQLQ(S)+12 change is from baseline (ie, last value before randomization) to EOT (SIROCCO: week 48; CALIMA: week 56). Estimates were calculated using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 cells/μL and <300 cells/μL).
[b]Atopy (by Phadiatop test) and serum IgE concentration of 30 to 700 kU/L criteria.

Table 6
Annual Exacerbation Rates and Pre-bronchodilator FEV_1 (Liters) Change (Baseline–EOT) by Baseline Serum IgE Concentrations and Blood Eosinophil Counts ≥300 cells/μL (Full Analysis Set, Pooled)[a]

	IgE high (≥150 kU/L; n = 1,204)			IgE low (<150 kU/L; n = 1,053)		
	Placebo (n = 413)	Benralizumab Q4W (n = 398)	Benralizumab Q8W (n = 393)	Placebo (n = 352)	Benralizumab Q4W (n = 349)	Benralizumab Q8W (n = 352)
Annual asthma exacerbation rates						
Patients analyzed, n	304	304	297	206	207	199
Rate estimate (95% CI)	1.09 (0.92–1.29)	0.69 (0.58–0.84)	0.63 (0.52–0.77)	1.21 (0.99–1.47)	0.65 (0.52–0.82)	0.68 (0.54–0.87)
Absolute difference estimate vs placebo (95% CI)	—	–0.39 (–0.62 to –0.17)	–0.46 (–0.68 to –0.24)	—	–0.56 (–0.84 to –0.27)	–0.52 (–0.82 to –0.23)
Rate ratio vs placebo (95% CI)	—	0.64 (0.50–0.82)	0.58 (0.45–0.75)	—	0.54 (0.40–0.73)	0.57 (0.41–0.78)
Nominal *P* vs placebo	—	.0004	<.0001	—	<.0001	.0004
Pre-bronchodilator FEV_1 change						
Patients in analysis, n	301	299	296	200	205	197
Patients with EOT data, n	268	267	264	182	181	174
LS mean change	0.247	0.367	0.370	0.200	0.297	0.338
LS mean difference vs placebo (95% CI)	—	0.120 (0.038–0.202)	0.123 (0.041–0.205)	—	0.098 (0.004–0.191)	0.138 (0.044–0.233)
Nominal *P* vs placebo	—	.0042	.0034	—	.0405	.0041

Abbreviations: CI, confidence interval; EOT, end of treatment; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; LS, least squares; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).
[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β_2-agonist treatment cohorts of the SIROCCO and CALIMA studies. For annual asthma exacerbation rate change, estimates were calculated using a negative binomial model, with adjustment for study code, treatment, region, oral corticosteroid use at time of randomization, and prior exacerbations. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred. FEV_1 change is from baseline (ie, last value before randomization) to EOT (SIROCCO: week 48; CALIMA: week 56). For FEV_1, estimates were calculated using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 cells/μL and <300 cells/μL).

Table 7
Annual Exacerbation Rates and Pre-bronchodilator FEV_1 (Liters) Change (Baseline–EOT) by Baseline Atopy Status and Blood Eosinophil Counts ≥300 cells/μL (Full Analysis Set, Pooled)[a]

	With atopy (n = 1,375)			Without atopy (n = 883)		
	Placebo (n = 463)	Benralizumab Q4W (n = 444)	Benralizumab Q8W (n = 468)	Placebo (n = 302)	Benralizumab Q4W (n = 301)	Benralizumab Q8W (n = 280)
Annual asthma exacerbation rates						
Patients analyzed, n	316	307	318	193	201	181
Rate estimate (95% CI)	1.10 (0.94–1.30)	0.71 (0.59–0.85)	0.66 (0.55–0.80)	1.15 (0.95–1.41)	0.60 (0.48–0.76)	0.62 (0.49–0.79)
Absolute difference estimate vs placebo (95% CI)	—	−0.40 (−0.62 to −0.17)	−0.44 (−0.66 to −0.22)	—	−0.55 (−0.82 to −0.28)	−0.53 (−0.81 to −0.26)
Rate ratio vs placebo (95% CI)	—	0.64 (0.50–0.82)	0.60 (0.47–0.77)	—	0.52 (0.39–0.71)	0.54 (0.39–0.74)
Nominal *P* vs placebo	—	.0004	<.0001	—	<.0001	.0001
Pre-bronchodilator FEV_1 change						
Patients in analysis, n	314	303	316	186	198	180
Patients with EOT data, n	276	269	279	173	176	162
LS mean change	0.236	0.339	0.349	0.201	0.348	0.382
LS mean difference vs placebo (95% CI)	—	0.103 (0.022–0.184)	0.114 (0.033–0.194)	—	0.148 (0.053–0.242)	0.181 (0.085–0.278)
Nominal *P* vs placebo	—	.0124	.0056	—	.0021	.0002

Abbreviations: CI, confidence interval; EOT, end of treatment; FEV_1, forced expiratory volume in 1 second; LS, least squares; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).

[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β_2-agonist treatment cohorts of the SIROCCO and CALIMA studies. For annual asthma exacerbation rate change, estimates were calculated using a negative binomial model, with adjustment for study code, treatment, region, oral corticosteroid use at time of randomization, and prior exacerbations. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred. FEV_1 change is from baseline (ie, last value before randomization) to EOT (SIROCCO: week 48; CALIMA: week 56). For FEV_1, estimates were calculated using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 cells/μL and <300 cells/μL).

Similar improvements in exacerbation frequency and lung function with benralizumab Q8W were observed in patients with and without atopy (Table 7). For patients who had atopy and blood eosinophil counts of at least 300 cells/μL, annual AER improved by 40% (RR 0.60, 95% CI 0.47–0.77, $P < .0001$), and pre-bronchodilator FEV_1 increased by 0.114 L (95% CI 0.033–0.194, $P = .0056$) with benralizumab Q8W vs placebo (Table 7). For patients who did not have atopy and had blood eosinophil counts of at least 300 cells/μL, annual AER improved by 46% (RR 0.54, 95% CI 0.39–0.74, $P = .0001$), and pre-bronchodilator FEV_1 increased by 0.181 L (95% CI 0.085–0.278, $P = .0002$) with benralizumab Q8W vs placebo (Table 7). Improvements in exacerbation rate and lung function with benralizumab in general were lower for patients with blood eosinophil counts lower than 300 cells/μL (eTable 6).

Discussion

Patients who have severe, uncontrolled asthma can have a number of factors associated with the pathology and progression of their disease.[2,28] For example, patients with severe allergic asthma can present with high blood and sputum eosinophil counts and high IgE concentrations, and patients with eosinophilic asthma can present with T-helper cell type 2 biomarkers such as IL-5 and IL-13.[2,28] In some cases these factors can be related to each other, such as high IL-5 concentrations and blood eosinophil counts, although other factors might not be directly related. Treatment approaches that target 1 mechanism could complement an approach that targets a second mechanism. Alternatively, using only 1 treatment approach might be less effective for patients who have several factors influencing disease activity. Patients who are treated with agents targeting 1 mechanism of action eventually could develop resistance that requires treatment with a second agent targeting a different mechanism of action. Therefore, it is important to understand the ability of agents targeting 1 mechanism of action to control disease symptoms for patients with asthma that stems from several etiologies.

In the present study, we evaluated the efficacy of benralizumab for patients with severe, uncontrolled eosinophilic asthma who had atopy and high IgE serum concentrations at study entry. We used pooled data from the SIROCCO and CALIMA studies, which demonstrated that benralizumab in combination with ICS and LABA decreased exacerbations by as much as 51% ($P < .0001$), increased pre-bronchodilator FEV_1 by as much as 0.159 L ($P = .0006$), and improved health-related quality of life for patients with blood eosinophil counts of at least 300 cells/μL.[23,24] The present study confirmed and expanded these results by demonstrating that benralizumab in combination with ICS and LABA decreased exacerbation frequency, increased lung function, and improved health-related quality of life for patients with severe, uncontrolled eosinophilic asthma who met the criteria of atopy and IgE 30 to 700 kU/L. These criteria are similar to those for patients who might qualify for omalizumab treatment. The improvements of decreased exacerbation frequency, increased lung function, and better health-related quality of life for patients with blood eosinophil counts of at least 300 cells/μL were similar for patients who did not meet these criteria of atopy and IgE 30 to 700 kU/L. Furthermore, similar improvements were observed for exacerbation frequency and lung function for patients with eosinophilia, regardless of whether they had high or low IgE concentrations or did or did not have atopy. The improvements were greater for patients with blood eosinophil counts of at least 300 cells/μL vs those with counts lower than 300 cells/μL. Consistent with results from the SIROCCO and CALIMA studies,[23,24] the benralizumab Q8W regimen was equal to, if not better than, the Q4W regimen in decreasing exacerbations and improving lung function. Another notable finding was a trend for better efficacy with respect to increased lung function for patients who had low serum IgE or did not have atopy. The reasons for this finding are unknown.

The efficacy of agents that target the IL-5 pathway for patients who might qualify for omalizumab treatment has been evaluated for mepolizumab, a marketed anti–IL-5 antibody indicated for severe asthma.[12,13,32,33] A post hoc analysis was performed with patients from the MENSA study, which evaluated mepolizumab as adjunctive therapy for severe asthma, and the SIRIUS study, which assessed decrease in steroid use for patients receiving mepolizumab.[32] In that analysis, similar decreases in the rate of exacerbations were ob-

served for patients previously treated or not treated with omalizumab (57% vs 47%, respectively, for MENSA; and 33% vs 29%, respectively, for SIRIUS).[32] However, although lung function improvements were similar between these groups in the SIRIUS study, they were greater for patients who had not previously received omalizumab in the MENSA study.[32] Decrease in oral corticosteroid use with mepolizumab treatment was similar for patients regardless of their prior omalizumab use.[32] Because differences exist between the 2 studies, such as patient populations and prior treatment with omalizumab, it is not possible to compare the results of the 2 studies directly. Nevertheless, our present findings with benralizumab further support the use of therapies that target eosinophils for patients with allergic asthma who might qualify for omalizumab treatment.

Our study has some limitations. Because the pooled analyses were not part of the general testing strategy, all comparator results of benralizumab vs placebo use nominal *P* values and no formal statistical significance can be inferred. Another limitation of this study is that the atopy and IgE concentration criteria that we applied were not identical to the criteria indicated for the use of omalizumab. For example, patients in the present study were defined as having atopy if they had positive test reactions to a Phadiatop test, which is a multi-allergen inhalant screening blood test that includes seasonal and perennial allergens (ie, extracts for house dust mites, cat and dog dander, mold spores, and tree, grass, and weed pollen). The Phadiatop test is not all inclusive and could have missed positivity to an allergen not tested. In contrast, patients who qualify for omalizumab can have positive skin test or in vitro reactivity to a perennial aeroallergen.[7,8] Nevertheless, our findings are useful for understanding the efficacy of benralizumab for patients with atopy and increased IgE concentrations.

Benralizumab treatment can be efficacious for patients with severe, uncontrolled eosinophilic asthma regardless of total serum IgE concentrations and atopy status. These results provide clinicians with additional options for patients with severe asthma who present with several factors associated with disease severity, including eosinophilia, atopy, and high IgE concentrations.

Acknowledgments

We thank Yanping Wu (AstraZeneca, Gaithersburg, Maryland) for her statistical analysis support. Writing and editing support, including preparation of the draft report under the direction and guidance of the authors, incorporating author feedback, and manuscript submission, was provided by Alan Saltzman, PhD (JK Associates, Inc., Conshohocken, Pennsylvania) and Michael A. Nissen, ELS (AstraZeneca).

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2018.01.030.

References

[1] To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health*. 2012; 12:204.
[2] Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43: 343–373.
[3] O'Byrne PM, Pedersen S, Schatz M, et al. The poorly explored impact of uncontrolled asthma. *Chest*. 2013;143:511–523.
[4] Fernandes AG, Souza-Machado C, Coelho RC, et al. Risk factors for death in patients with severe asthma. *J Bras Pneumol*. 2014;40:364–372.
[5] Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. *Asthma Res Pract*. 2017;3:1.
[6] Global Initiative for Asthma. Global strategy for asthma management and prevention; 2017. http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed September 26, 2017.
[7] Genentech, Inc (South San Francisco, CA). Xolair prescribing information; 2017. https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed September 26, 2017.
[8] Genentech, Inc (South San Francisco, CA). Xolair summary of product characteristics; 2016. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf. Accessed September 26, 2017.
[9] Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108:184–190.
[10] Boulet LP, Chapman KR, Cote J, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med*. 1997;155:1835–1840.
[11] Corren J, Casale T, Deniz Y, et al. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. *J Allergy Clin Immunol*. 2003;111:87–90.
[12] Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371:1198–1207.
[13] Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012; 380:651–659.
[14] Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3:355–366.
[15] Pavord ID. Eosinophilic phenotypes of airway disease. *Ann Am Thorac Soc*. 2013; 10(suppl):S143–S149.
[16] Price D, Wilson AM, Chisholm A, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. *J Asthma Allergy*. 2016;9:1–12.
[17] Talini D, Novelli F, Bacci E, et al. Sputum eosinophilia is a determinant of FEV1 decline in occupational asthma: results of an observational study. *BMJ Open*. 2015;5:e005748.
[18] Tan LD, Bratt JM, Godor D, et al. Benralizumab: a unique IL-5 inhibitor for severe asthma. *J Asthma Allergy*. 2016;9:71–81.
[19] Patterson MF, Borish L, Kennedy JL. The past, present, and future of monoclonal antibodies to IL-5 and eosinophilic asthma: a review. *J Asthma Allergy*. 2015; 8:125–134.
[20] (FASENRA™) benralizumab prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf. Published November 2017. Accessed 15 December 2017.
[21] Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol*. 2010;125:1344–1353, e1342.
[22] Pham TH, Damera G, Newbold P, et al. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med*. 2016;111:21–29.
[23] Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115–2127.
[24] FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2128–2141.
[25] Goldman M, Hirsch I, Zangrilli JG, et al. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies. *Curr Med Res Opin*. 2017;33:1605–1613.
[26] FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies [published online ahead of print September 8, 2017]. *Lancet Respir Med*. 2018;6(1):51–64 doi:10.1016/S2213-2600(17)30344-2.
[27] Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376:2448–2458.
[28] Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. *Clin Exp Allergy*. 2012;42:650–658.
[29] Tran TN, Zeiger RS, Peters SP, et al. Overlap of atopic, eosinophilic, and TH2-high asthma phenotypes in a general population with current asthma. *Ann Allergy Asthma Immunol*. 2016;116:37–42.
[30] Juniper EF, Svensson K, Mork AC, et al. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99:553–558.
[31] Juniper EF, Svensson K, Mork AC, et al. Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. *Health Qual Life Outcomes*. 2005;3:58.
[32] Magnan A, Bourdin A, Prazma CM, et al. Treatment response with mepolizumab in severe eosinophilic asthma patients with previous omalizumab treatment. *Allergy*. 2016;71:1335–1344.
[33] Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189–1197.

Supplementary Data

eTable 1
Annual Exacerbation Rates for Patients Who Did and Did Not Meet Atopy and Serum IgE Criteria (All Patients and Patients With Blood Eosinophil Counts <300 Cells/μL; Full Analysis Set, Pooled)[a]

	Met atopy and IgE 30–700 kU/L criteria[b] (n = 824)			Did not meet atopy and IgE 30–700 kU/L criteria[b] (n = 1,471)		
	Placebo (n = 271)	Benralizumab Q4W (n = 256)	Benralizumab Q8W (n = 297)	Placebo (n = 506)	Benralizumab Q4W (n = 500)	Benralizumab Q8W (n = 465)
All patients						
Patients analyzed, n	271	256	297	506	500	465
Rate estimate (95% CI)	1.27 (1.08–1.49)	0.75 (0.62–0.91)	0.80 (0.67–0.96)	1.12 (0.99–1.27)	0.71 (0.62–0.82)	0.71 (0.61–0.83)
Absolute difference estimate vs placebo (95% CI)	—	–0.51 (–0.76 to –0.26)	–0.47 (–0.72 to –0.21)	—	–0.41 (–0.59 to –0.24)	–0.41 (–0.59 to –0.23)
Rate ratio vs placebo (95% CI)	—	0.59 (0.46–0.76)	0.63 (0.50–0.81)	—	0.63 (0.52–0.77)	0.63 (0.52–0.77)
Nominal *P* vs placebo	—	<.0001	.0002	—	<.0001	<.0001
<300 cells/μL						
Patients analyzed, n	92	103	112	170	137	144
Rate estimate (95% CI)	1.28 (0.99–1.65)	0.89 (0.68–1.16)	0.94 (0.72–1.22)	1.17 (0.95–1.45)	0.76 (0.58–0.99)	0.80 (0.62–1.04)
Absolute difference estimate vs placebo (95% CI)	—	–0.39 (–0.79 to 0.01)	–0.34 (–0.75 to 0.07)	—	–0.42 (–0.73 to –0.10)	–0.37 (–0.69 to –0.05)
Rate ratio vs placebo (95% CI)	—	0.69 (0.48–1.00)	0.74 (0.51–1.06)	—	0.64 (0.46–0.90)	0.69 (0.49–0.96)
Nominal *P* vs placebo	—	.0502	.1003	—	.0111	.0257

Abbreviations: CI, confidence interval; IgE, immunoglobulin E; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).
[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β_2-agonist treatment cohorts of the SIROCCO and CALIMA studies. Estimates were calculated using a negative binomial model, with adjustment for study code, treatment, region, oral corticosteroid use at time of randomization, and prior exacerbations. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 and <300 cells/μL).
[b]Atopy (by Phadiatop test) and serum IgE concentration of 30 to 700 kU/L criteria.

eTable 2
Pre-bronchodilator Forced Expiratory Volume in 1 Second (Liters) Change (Baseline–EOT) for Patients Who Did and Did Not Meet Atopy and Serum IgE Criteria (All Patients and Patients With Blood Eosinophil Counts <300 Cells/μL; Full Analysis Set, Pooled)[a]

	Met atopy and IgE 30–700 kU/L criteria[b] (n = 824)			Did not meet atopy and IgE 30–700 kU/L criteria[b] (n = 1,471)		
	Placebo (n = 271)	Benralizumab Q4W (n = 256)	Benralizumab Q8W (n = 297)	Placebo (n = 506)	Benralizumab Q4W (n = 500)	Benralizumab Q8W (n = 465)
All patients						
Patients in analysis, n	269	249	294	490	494	458
Patients with EOT data, n	233	222	257	445	436	406
LS mean change	0.222	0.246	0.277	0.168	0.265	0.289
LS mean difference vs placebo (95% CI)	—	0.024 (–0.59 to 0.108)	0.055 (–0.025 to 0.136)	—	0.097 (0.041–0.154)	0.121 (0.063–0.178)
Nominal *P* vs placebo	—	.5661	.1791	—	.0008	<.0001
<300 cells/μL						
Patients in analysis, n	91	100	110	163	134	140
Patients with EOT data, n	78	87	96	146	119	121
LS mean change	0.208	0.160	0.201	0.124	0.176	0.198
LS mean difference vs placebo (95% CI)	—	–0.048 (–0.175 to 0.079)	–0.007 (–0.130 to 0.117)	—	0.053 (–0.038 to 0.144)	0.074 (–0.016 to 0.165)
Nominal *P* vs placebo	—	.4595	.9173	—	.2566	.1064

Abbreviations: CI, confidence interval; EOT, end of treatment; IgE, immunoglobulin E; LS, least squares; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).
[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β2-agonist treatment cohorts of the SIROCCO and CALIMA studies. Pre-bronchodilator forced expiratory volume in 1 second change is from baseline (ie, last value before randomization) to EOT (SIROCCO: week 48; CALIMA: week 56). Estimates were calculated using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 and <300 cells/μL).
[b]Atopy (by Phadiatop test) and serum IgE concentration of 30 to 700 kU/L criteria.

eTable 3
ACQ-6 Change (Baseline–EOT) for Patients Who Did and Did Not Meet Atopy and Serum IgE Criteria (All Patients and Patients With Blood Eosinophil Counts <300 Cells/μL; Full Analysis Set, Pooled)[a]

	Met atopy and IgE 30–700 kU/L criteria[b] (n = 824)			Did not meet atopy and IgE 30–700 kU/L criteria[b] (n = 1,471)		
	Placebo (n = 271)	Benralizumab Q4W (n = 256)	Benralizumab Q8W (n = 297)	Placebo (n = 506)	Benralizumab Q4W (n = 500)	Benralizumab Q8W (n = 465)
All patients						
Patients in analysis, n	271	255	297	503	500	460
Patients with EOT data, n	197	192	217	375	375	336
LS mean change	–1.04	–1.24	–1.21	–1.01	–1.15	–1.26
LS mean difference vs placebo (95% CI)	—	–0.19 (–0.37 to –0.02)	–0.17 (–0.34 to –0.00)	—	–0.14 (–0.27 to –0.01)	–0.25 (–0.38 to –0.12)
Nominal *P* vs placebo	—	.0293	.0483	—	.0351	.0002
<300 cells/μL						
Patients in analysis, n	92	103	112	168	137	143
Patients with EOT data, n	67	74	78	122	103	99
LS mean change	–1.01	–1.12	–1.05	–0.81	–0.91	–1.03
LS mean difference vs placebo (95% CI)	—	–0.11 (–0.38 to 0.17)	–0.03 (–0.31 to 0.24)	—	–0.10 (–0.33 to 0.13)	–0.22 (–0.45 to 0.01)
Nominal *P* vs placebo	—	.4515	.8047	—	.3969	.0583

Abbreviations: ACQ-6, Asthma Control Questionnaire 6; CI, confidence interval; EOT, end of treatment; IgE, immunoglobulin E; LS, least squares; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).
[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β2-agonist treatment cohorts of the SIROCCO and CALIMA studies. ACQ-6 change is from baseline (ie, last value before randomization) to EOT (SIROCCO: week 48; CALIMA: week 56). Estimates were calculated using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 and <300 cells/μL).
[b]Atopy (by Phadiatop test) and serum IgE concentration of 30 to 700 kU/L criteria.

eTable 4
AQLQ(S)+12 Change (Baseline–EOT) by Patients Who Did and Did Not Meet Atopy and Serum IgE Criteria (All Patients and Patients With Blood Eosinophil Counts <300 Cells/μL; Full Analysis Set, Pooled)[a]

	Met atopy and IgE 30–700 kU/L criteria[b] (n = 824)			Did not meet atopy and IgE 30–700 kU/L criteria[b] (n = 1,471)		
	Placebo (n = 271)	Benralizumab Q4W (n = 256)	Benralizumab Q8W (n = 297)	Placebo (n = 506)	Benralizumab Q4W (n = 500)	Benralizumab Q8W (n = 465)
All patients						
Patients in analysis, n	268	247	285	480	478	445
Patients with EOT data, n	195	188	209	364	363	329
LS mean change	1.14	1.32	1.24	1.1	1.2	1.38
LS mean difference vs placebo (95% CI)	—	0.18 (–0.01 to 0.36)	0.1 (–0.08 to 0.28)	—	0.1 (–0.04 to 0.24)	0.28 (0.14–0.42)
Nominal *P* vs placebo	—	.0568	.2803	—	.1609	.0001
<300 cells/μL						
Patients in analysis, n	92	100	109	162	131	139
Patients with EOT data, n	67	73	76	121	100	95
LS mean change	–1.05	1.17	1.02	0.89	0.92	1.16
LS mean difference vs placebo (95% CI)	—	0.12 (–0.17 to 0.41)	–0.03 (–0.31 to 0.25)	—	0.02 (–0.22 to 0.27)	0.27 (0.02–0.51)
Nominal *P* vs placebo	—	.4300	.8340	—	.8576	.0326

Abbreviations: AQLQ(S)+12, Standardized Asthma Quality of Life Questionnaire for 12 years and older; CI, confidence interval; EOT, end of treatment; IgE, immunoglobulin E; LS, least squares; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).
[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β2-agonist treatment cohorts of the SIROCCO and CALIMA studies. AQLQ(S)+12 change is from baseline (ie, last value before randomization) to EOT (SIROCCO: week 48; CALIMA: week 56). Estimates were calculated using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 and <300 cells/μL).
[b]Atopy (by Phadiatop test) and serum IgE concentration of 30 to 700 kU/L criteria.

eTable 5
Annual Exacerbation Rates and Pre-bronchodilator FEV_1 (Liters) Change (Baseline–EOT) by Baseline Serum IgE Concentrations (All Patients and Patients With Blood Eosinophil Counts <300 Cells/μL; Full Analysis Set, Pooled)[a]

	IgE high (≥150 kU/L; n = 1,204)			IgE low (<150 kU/L; n = 1,053)		
	Placebo (n = 413)	Benralizumab Q4W (n = 398)	Benralizumab Q8W (n = 393)	Placebo (n = 352)	Benralizumab Q4W (n = 349)	Benralizumab Q8W (n = 352)
Annual asthma exacerbation rates						
All patients						
Patients analyzed, n	413	398	393	352	349	352
Rate estimate (95% CI)	1.13 (0.98–1.30)	0.70 (0.59–0.82)	0.70 (0.59–0.82)	1.21 (1.05–1.40)	0.78 (0.66–0.92)	0.79 (0.67–0.93)
Absolute difference estimate vs placebo (95% CI)	—	–0.43 (–0.63 to –0.24)	–0.43 (–0.63 to –0.23)	—	–0.43 (–0.65 to –0.21)	–0.43 (–0.65 to –0.21)
Rate ratio vs placebo (95% CI)	—	0.62 (0.50–0.76)	0.62 (0.50–0.77)	—	0.64 (0.52–0.80)	0.65 (0.52–0.81)
Nominal *P* vs placebo	—	<.0001	<.0001	—	<.0001	.0001
<300 cells/μL						
Patients analyzed, n	109	94	96	146	142	153
Rate estimate (95% CI)	1.17 (0.89–1.53)	0.68 (0.49–0.94)	0.85 (0.62–1.17)	1.20 (0.97–1.48)	0.93 (0.74–1.17)	0.88 (0.70–1.10)
Absolute difference estimate vs placebo (95% CI)	—	–0.49 (–0.87 to –0.11)	–0.32 (–0.73 to 0.10)	—	–0.27 (–0.60 to 0.06)	–0.32 (–0.64 to 0.00)
Rate ratio vs placebo (95% CI)	—	0.58 (0.38–0.88)	0.73 (0.48–1.11)	—	0.77 (0.57–1.06)	0.73 (0.54–1.00)
Nominal *P* vs placebo	—	.0111	.1401	—	.1055	.0482
Pre-bronchodilator FEV_1 change						
All patients						
Patients in analysis, n	408	392	391	341	342	345
Patients with EOT data, n	368	351	347	302	299	301
LS mean change	0.215	0.277	0.293	0.169	0.233	0.273
LS mean difference vs placebo (95% CI)	—	0.062 (–0.005 to 0.129)	0.078 (0.011–0.145)	—	0.064 (–0.002 to 0.131)	0.105 (0.039–0.171)
Nominal *P* vs placebo	—	.0689	.0232	—	.0583	.0019
<300 cells/μL						
Patients in analysis, n	107	93	95	141	137	148
Patients with EOT data, n	100	84	83	120	118	127
LS mean change	0.181	0.139	0.162	0.150	0.181	0.232
LS mean difference vs placebo (95% CI)	—	–0.041 (–0.160 to 0.078)	–0.018 (–0.138 to 0.101)	—	0.031 (–0.065 to 0.128)	0.082 (–0.013 to 0.177)
Nominal *P* vs placebo	—	.4963	.7624	—	.5248	.0902

Abbreviations: CI, confidence interval; EOT, end of treatment; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; LS, least squares; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).
[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β2-agonist treatment cohorts of the SIROCCO and CALIMA studies. For annual asthma exacerbation rate change, estimates were calculated using a negative binomial model, with adjustment for study code, treatment, region, oral corticosteroid use at time of randomization, and prior exacerbations. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred. FEV_1 change is from baseline (ie, last value before randomization) to EOT (SIROCCO: week 48; CALIMA: week 56). For FEV_1, estimates were calculated by using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 and <300 cells/μL).

eTable 6

Annual Exacerbation Rates and Pre-bronchodilator FEV_1 (Liters) Change (Baseline–EOT) by Baseline Atopy Status (All Patients and Patients With Blood Eosinophil Counts <300 Cells/μL; Full Analysis Set, Pooled)[a]

	With atopy (n = 1,375)			Without atopy (n = 883)		
	Placebo (n = 463)	Benralizumab Q4W (n = 444)	Benralizumab Q8W (n = 468)	Placebo (n = 302)	Benralizumab Q4W (n = 301)	Benralizumab Q8W (n = 280)
Annual asthma exacerbation rates						
All patients						
Patients analyzed, n	463	444	468	302	301	280
Rate estimate (95% CI)	1.15 (1.01–1.31)	0.76 (0.66–0.88)	0.76 (0.65–0.88)	1.19 (1.02–1.39)	0.67 (0.56–0.80)	0.69 (0.57–0.83)
Absolute difference estimate vs placebo (95% CI)	—	–0.39 (–0.58 to –0.20)	–0.39 (–0.58 to –0.20)	—	–0.52 (–0.74 to –0.30)	–0.50 (–0.73 to –0.28)
Rate ratio vs placebo (95% CI)	—	0.66 (0.54–0.81)	0.66 (0.54–0.81)	—	0.56 (0.44–0.71)	0.58 (0.45–0.74)
Nominal *P* vs placebo	—	<.0001	<.0001	—	<.0001	<.0001
<300 cells/μL						
Patients analyzed, n	147	137	150	109	100	99
Rate estimate (95% CI)	1.22 (0.98–1.51)	0.84 (0.65–1.07)	0.90 (0.71–1.14)	1.16 (0.91–1.49)	0.77 (0.57–1.03)	0.75 (0.56–1.00)
Absolute difference estimate vs placebo (95% CI)	—	–0.38 (–0.72 to –0.05)	–0.32 (–0.66 to 0.02)	—	–0.40 (–0.76 to –0.03)	–0.42 (–0.77 to –0.06)
Rate ratio vs placebo (95% CI)	—	0.69 (0.50–0.95)	0.74 (0.54–1.02)	—	0.66 (0.45–0.97)	0.64 (0.44–0.94)
Nominal *P* vs placebo	—	.0230	.0630	—	.0329	.0212
Pre-bronchodilator FEV_1 change						
All patients						
Patients in analysis, n	459	437	464	290	295	275
Patients with EOT data, n	404	387	404	265	261	247
LS mean change	0.221	0.260	0.290	0.142	0.259	0.276
LS mean difference vs placebo (95% CI)	—	0.039 (–0.024 to 0.103)	0.069 (0.007–0.131)	—	0.117 (0.046–0.187)	0.134 (0.062–0.205)
Nominal *P* vs placebo	—	.2233	.0301	—	.0012	.0002
<300 cells/μL						
Patients in analysis, n	145	134	148	104	97	95
Patients with EOT data, n	128	118	125	92	85	85
LS mean change	0.211	0.174	0.220	0.087	0.168	0.182
LS mean difference vs placebo (95% CI)	—	–0.037 (–0.141 to 0.068)	0.009 (–0.093 to 0.111)	—	0.081 (–0.025 to 0.188)	0.095 (–0.011 to 0.202)
Nominal *P* vs placebo	—	.4907	.8677	—	.1342	.0794

Abbreviations: CI, confidence interval; EOT, end of treatment; FEV_1, forced expiratory volume in 1 second; LS, least squares; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses every 4 weeks).

[a]Data are from the pooled intention-to-treat population from the high-dosage inhaled corticosteroid and long-acting β2-agonist treatment cohorts of the SIROCCO and CALIMA studies. For annual asthma exacerbation rate change, estimates were calculated using a negative binomial model, with adjustment for study code, treatment, region, oral corticosteroid use at time of randomization, and prior exacerbations. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred. FEV_1 change is from baseline (ie, last value before randomization) to EOT (SIROCCO: week 48; CALIMA: week 56). For FEV_1, estimates were calculated using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. Where appropriate, estimates were reweighted to account for the 2:1 stratification for baseline blood eosinophil counts (≥300 and <300 cells/μL).