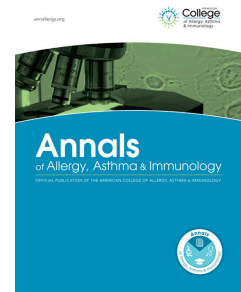


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Benralizumab Efficacy for Patients with Fixed Airflow Obstruction and Severe, Uncontrolled Eosinophilic Asthma

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Abbreviations:

ACQ-6, Asthma Control Questionnaire 6; AQLQ(S)+12, Asthma Quality of Life Questionnaire (standardized) for 12 years and older; CI, confidence interval; ED, emergency department; EOT, end of treatment; FAO, fixed airflow obstruction; FAO+, FAO positive; FAO-, FAO negative; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled

corticosteroids; ITT, intention-to-treat; LABA, long-acting β_2 -agonists; LS, least squares; OCS, oral corticosteroids; Q4W, every 4 weeks; Q8W, every 8 weeks; RR, rate ratio; SD, standard deviation

INTRODUCTION

Fixed airflow obstruction (FAO) is present for approximately 16% of patients with asthma, with a greater FAO incidence for patients with severe disease than for those with less severe disease.^{1,2} Patients with FAO have increased exacerbation frequency, decreased lung function, and greater mortality than patients without FAO.^{3,4} The risk of developing FAO is 2–4-fold greater for patients with increased sputum/blood eosinophil counts than for those with lesser eosinophil counts.^{3–7} Elevated sputum and/or blood eosinophil counts are consensual markers of asthma with an eosinophilic phenotype.^{8,9} Patients with FAO and elevated eosinophil counts have greater exacerbation frequencies and may be at risk of more rapid decreases in lung function than patients with FAO without eosinophilia.⁴ Therefore, agents that reduce eosinophil counts in the airway may be particularly beneficial for patients with asthma who have FAO and an eosinophilic phenotype.

Benralizumab is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody that binds directly to eosinophils and induces rapid apoptosis *in vitro* in the presence of natural killer cells via enhanced antibody-dependent cell-mediated cytotoxicity.^{10,11} For patients with asthma, benralizumab resulted in nearly complete depletion of blood eosinophils after the first dose, with corresponding clearance of eosinophils in bronchial biopsies and sputum.^{10,12,13} In the Phase III SIROCCO (NCT01928771; 48 weeks) and CALIMA (NCT01914757; 56 weeks) trials, benralizumab 30 mg every 4 weeks (Q4W) and the indicated dosage of every 8 weeks (Q8W; first three doses Q4W) significantly reduced exacerbations and improved lung function and asthma symptoms for patients with severe, uncontrolled eosinophilic asthma.^{14,15} In a separate

study, benralizumab 30 mg Q4W and Q8W allowed for significant reduction in daily dosage of oral corticosteroids (OCS) without loss of asthma control for OCS-dependent patients with asthma.¹⁶

In this analysis, we evaluated the efficacy of benralizumab Q8W for patients with severe, uncontrolled eosinophilic asthma based on the presence or absence of FAO at baseline for the pooled SIROCCO and CALIMA study population.

METHODS

Study Design and Participants

SIROCCO and CALIMA were randomized, double-blind, parallel-group, placebo-controlled, Phase III studies.^{14,15} Patients were enrolled at 374 (SIROCCO) and 303 (CALIMA) clinical research centers worldwide. The study design included an enrollment visit (Week -4), 4-week screening/run-in phase, randomization (Week 0), treatment period (Weeks 0–48 [SIROCCO] or 0–56 [CALIMA]), and final follow-up visit 8 (SIROCCO) or 4 (CALIMA) weeks following end of treatment (EOT).

Enrollment criteria for the studies have been published.^{14,15} Male and female patients aged 12–75 years who weighed ≥ 40 kg were included in the studies. Patients had physician-diagnosed asthma that required treatment with medium- to high-dosage inhaled corticosteroids (ICS)/long-acting β_2 -agonists (LABA) for ≥ 12 months before enrollment. Patients with diagnoses of lung diseases other than asthma (including chronic obstructive pulmonary disease) or smoking history of >10 pack-years were excluded. Patients also had ≥ 2 asthma exacerbations within 12 months before enrollment that required either systemic corticosteroid therapy or a temporary increase in usual maintenance OCS dosage. Patients were required to have had documented treatment with high-dosage ICS/LABA (defined as fluticasone propionate >500 mg/d or equivalent total daily dosage) with or without OCS and additional asthma controllers for ≥ 3 months before enrollment. Maximal postbronchodilator forced expiratory volume in 1 second (FEV_1) was assessed at baseline after the administration of four, six, and eight puffs of albuterol (360, 540, and 720 mg) according to Moore et al.¹⁷ Studies were conducted in accordance with the Declaration of

Helsinki, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice guidelines, and the ethics committee at each participating site. All patients provided written informed consent at enrollment.

Treatments

In the SIROCCO and CALIMA trials, patients were randomized 1:1:1 to receive subcutaneous benralizumab 30 mg Q4W, benralizumab 30 mg Q8W (first three doses Q4W), or placebo (Q4W). Treatment was double-blind and lasted for 48 (SIROCCO) or 56 (CALIMA) weeks. In both trials, patients with baseline blood eosinophil counts ≥ 300 cells/ μ L and < 300 cells/ μ L were recruited at a ratio of approximately 2:1, respectively. Except for population demographics and baseline disease state characteristics, efficacy results presented herein will be for the approved Q8W dosing regimen.

Outcomes

In the current *post-hoc* study, analyses were performed with data for patients from the pooled SIROCCO and CALIMA studies who were receiving high-dosage ICS/LABA, representing patients receiving Global Initiative for Asthma Steps 4 and 5 treatment,¹⁸ and had baseline blood eosinophil counts ≥ 300 cells/ μ L. The primary and key secondary endpoints from these trials were analyzed based on patients' FAO statuses, either FAO positive (FAO+) or FAO negative (FAO-). FAO+ was defined as a ratio ($\times 100$) of postbronchodilator FEV₁ to forced vital capacity (FVC) of $< 70\%$, with FAO- defined as $\geq 70\%$. Postbronchodilator reversibility was not accounted for in the definition of FAO+ status. FAO+ and FAO- patients were identified at

baseline. Spirometry measurements were performed at the study centers with equipment provided by a central vendor.

The primary efficacy outcome for both SIROCCO and CALIMA was annual asthma exacerbation rate. In both studies, the primary analysis set included patients receiving high-dosage ICS/LABA with baseline blood eosinophil counts ≥ 300 cells/ μ L. An exacerbation was defined as worsening of asthma that led to one of the following: 1) use of systemic corticosteroids (or temporary increase in a stable background OCS dosage) for at least 3 days or a single depo-injectable dose of corticosteroids, 2) asthma-related emergency department (ED)/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.^{14,15}

Secondary endpoints evaluated by FAO status were annual rate of exacerbations associated with ED visits or hospitalizations; changes from baseline at EOT for prebronchodilator and postbronchodilator FEV₁ (measured by spirometry), prebronchodilator and postbronchodilator FVC, postbronchodilator FEV₁/FVC, total asthma symptom score, Asthma Control Questionnaire 6 (ACQ-6) score, and Asthma Quality of Life Questionnaire (standardized) for 12 years and older (AQLQ[S]+12) score; and percentages of patients who changed from FAO- to FAO+ or remained FAO+ at EOT. Total asthma symptom score is a composite of daytime and night-time symptoms on a scale of 0–6 overall.^{14,15} ACQ-6 is a six-item questionnaire to assess daytime and night-time symptoms and rescue β -agonist use on a 0–6 scale (small numbers

represent better control). AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life on a 1–7 scale (small numbers represent greater impairment¹⁹). Details on efficacy measurement methods have been published.^{14,15}

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 protocol adherence, and continued participation in the study. The similar design of the two studies allowed for the results to be pooled, which enabled us to obtain more accurate estimates of the relationships between efficacy endpoints and FAO status. Analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC, USA).

Exacerbation rates were calculated via a negative binomial model, with adjustment for study code, treatment, region, OCS use at time of randomization, and either prior exacerbations (for annual exacerbation rate) or any exacerbations resulting in ED visits or hospitalizations in the previous year (for annual asthma exacerbation rate associated with ED visits or hospitalizations) with a rate ratio (RR) of benralizumab vs. placebo at EOT. The corresponding 95% confidence intervals (CIs) and two-sided *p*-values for the RR were determined. 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. Secondary endpoints were determined via a mixed-effects model for repeated measures analysis, with adjustment for study code, treatment, baseline value, region, OCS use at time of randomization, visit, and visit × treatment. Least

122 squares (LS) means, treatment differences in LS means, 95% CIs, and p -values were calculated.

123 Because this analysis was not part of the formal testing strategy, all p -values were nominal.

124

RESULTS

Of 1,493 total patients enrolled in SIROCCO and CALIMA, 63% (n=935; 308 placebo, 314 benralizumab Q4W, 313 benralizumab Q8W) were categorized as FAO+ and 37% (n=558; 193 placebo, 189 benralizumab Q4W, 176 benralizumab Q8W) as FAO- (**Table 1**). FAO+ patients were older, had asthma for a longer period, and were more likely to be former smokers than FAO- patients. Median (range) blood eosinophil counts were 510 cells/ μ L (300–4,494) for FAO+ patients and 490 cells/ μ L (300–3,100) for FAO- patients. Baseline lung function was worse for FAO+ patients than for FAO- patients, and a greater percentage of FAO+ patients required OCS at study entry compared with FAO- patients. The percentage reversibility ranges for FAO+ and FAO- patients overlapped substantially.

Greater reductions in annual asthma exacerbation rate were experienced by FAO+ patients receiving the indicated benralizumab Q8W dosage vs. placebo (RR=0.56, 95% CI=0.44 to 0.71, $p<0.0001$) (**Table 2, Figure 1A**). Similar reductions in exacerbation rate were also achieved by FAO- patients receiving benralizumab Q8W vs. placebo (RR=0.58, 95% CI=0.41 to 0.83, $p=0.0030$) (**Table 2, Figure 1A**). The reduction in asthma exacerbations associated with ED visits or hospitalizations was greater for FAO+ patients receiving benralizumab Q8W vs. placebo (RR=0.55, 95% CI=0.33 to 0.91, $p=0.0195$) than for FAO- patients vs. placebo (RR=0.70, 95% CI=0.33 to 1.48, $p=0.3514$) (**Table 2, Figure 1B**).

Prebronchodilator FEV₁ increased more from baseline to EOT for FAO+ patients receiving benralizumab Q8W vs. placebo (LS mean difference 0.159 L, 95% CI=0.082 to 0.236,

$p<0.0001$) (**Table 3, Figure 2**). An increase in prebronchodilator FEV_1 at EOT from baseline was also observed for FAO- patients receiving benralizumab Q8W vs. placebo (LS mean difference 0.103 L, 95% CI=-0.008 to 0.215, $p=0.0699$) (**Table 3, Figure 2**). Similar improvements were observed at EOT for prebronchodilator FVC as for prebronchodilator FEV_1 with benralizumab vs. placebo (**Table 3**).

Improvements from baseline to EOT in total asthma symptom score, ACQ-6 score, and AQLQ(S)+12 score were greater for FAO+ patients receiving benralizumab Q8W vs. placebo than for FAO- patients (**Table 4**). For benralizumab Q8W vs. placebo, improvements (LS mean difference) for FAO+ patients were -0.30 in total asthma symptom score (95% CI=-0.45 to -0.14, $p=0.0002$), -0.33 in ACQ-6 score (95% CI=-0.49 to -0.17, $p<0.0001$), and 0.33 in AQLQ(S)+12 score (95% CI=0.15 to 0.51, $p=0.0003$) (**Table 4**). For FAO- patients, numerical LS mean differences with benralizumab vs. placebo were observed in total asthma symptom score (-0.08, 95% CI=-0.30 to 0.14, $p=0.4941$), ACQ-6 score (-0.18, 95% CI=-0.40 to 0.04, $p=0.1096$), and AQLQ(S)+12 score (0.17, 95% CI=-0.08 to 0.41, $p=0.1894$) from baseline to EOT (**Table 4**).

Mean postbronchodilator FEV_1 /FVC improved from baseline with benralizumab vs. placebo at EOT for FAO+ patients but not for FAO- patients (**Table 3**). Improvements from baseline to EOT were also observed for FAO+ patients for postbronchodilator FEV_1 and FVC with benralizumab vs. placebo. These improvements were lesser than those obtained for prebronchodilator FEV_1 (0.130 L vs. 0.159 L) and FVC (0.110 L vs. 0.196 L) (**Table 3**). Of

170 patients who were FAO+ at baseline, 5–6% more patients became FAO– with benralizumab
171 treatment compared with placebo at Week 24 or EOT (**Figure 3**).

172

DISCUSSION

We used pooled results from the SIROCCO and CALIMA Phase III studies to evaluate the efficacy of benralizumab for patients with severe, uncontrolled eosinophilic asthma based on their baseline FAO statuses. We found that almost two-thirds of patients with blood eosinophil counts ≥ 300 cells/ μ L had FAO, consistent with reports indicating a strong association between elevated blood eosinophil counts and FAO,³⁻⁷ and responded to benralizumab treatment. Compared with FAO- patients, FAO+ patients tended to be male, were more likely to be former smokers, and had slightly lesser bronchodilator reversibility, longer time since asthma diagnosis, and greater OCS use.

FAO+ patients experienced improvements with benralizumab in asthma exacerbation rates, including those associated with ED visits or hospitalizations; lung function; asthma symptoms; and health-related quality of life compared with placebo. Overall, these results indicate that despite the greater risk of exacerbations and decreased lung function for FAO+ patients relative to FAO- patients,^{3,4} these patients have comparable, if not better, responses with benralizumab. It is tempting to hypothesize that these improvements suggest normalization of the remodeled airway for FAO+ patients. However, this would require confirmation by direct (e.g., biopsy) or indirect (e.g., imaging) assessments and remains to be seen.

Improvements in exacerbation frequency and lung function with benralizumab Q8W were also observed for FAO- patients compared with placebo, with a similar treatment effect noted on annual asthma exacerbation rate for FAO+ patients. The reduced effect of benralizumab on lung

function improvements for FAO⁻ patients vs. FAO⁺ patients most likely reflected lesser airflow obstruction and, thus, the opportunity for improvement for FAO⁻ patients. For asthma symptoms and health-related quality of life, a numerical difference between benralizumab Q8W and placebo at EOT relative to baseline was achieved but was smaller than that obtained by FAO⁺ patients. This difference may be attributable, in part, to the greater placebo effect observed for FAO⁻ patients compared with FAO⁺ patients.

A limitation of the current study was that pooled analyses were not part of the general testing strategy. Because of this, all comparator results of benralizumab vs. placebo use nominal *p*-values, and no formal statistical significance can be inferred. Another limitation is that classification of FAO was based on a single test at randomization. The use of a maximal bronchodilation procedure (after appropriate medication hold) for patients with severe asthma treated repeatedly over the long term with high-dosage ICS and basing our conclusions on a relatively large FAO subpopulation help mitigate the influence of individual variability.

In summary, benralizumab treatment improves exacerbation frequency, lung function, asthma symptoms, and health-related quality of life for FAO⁺ patients with severe, uncontrolled eosinophilic asthma. The presence of FAO can help guide clinicians considering benralizumab for the treatment of these patients.

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TABLES

Table 1. Patient Demographics and Baseline Clinical Characteristics (Full Analysis Set, Baseline Eosinophil Counts ≥ 300 cells/ μ L)

	FAO+ (n=935)^a	FAO- (n=558)^a
Age [years], mean (SD)	51.3 (12.5)	44.7 (14.9)
Sex, n (%)		
Male	384 (41)	175 (31)
Female	551 (59)	383 (69)
Race, n (%)		
White	745 (80)	416 (75)
Black or African-American	29 (3)	19 (3)
Asian	114 (12)	77 (14)
Other ^b	47 (5)	46 (8)
Body mass index [kg/m ²], mean (SD) ^c	28.6 (6.1)	28.7 (7.2)
Eosinophil count [cells/ μ L], median (range) ^c	510 (300–4,494)	490 (300–3,100)
Prebronchodilator FEV ₁ [L], mean (SD) ^c	1.569 (0.569)	1.961 (0.568)
Prebronchodilator FEV ₁ [% predicted normal], mean (SD) ^{c,d}	52.0 (13.6)	65.2 (11.3)
Reversibility [%], median (range) ^c	18.6 (–26.4–156.8)	22.1 (–24.3–170.5)
Postbronchodilator FEV ₁ /FVC, mean (SD)	0.575 (0.095)	0.781 (0.057)
Postbronchodilator FEV ₁ [L], mean (SD)	1.91 (0.66)	2.50 (0.74)
Number of exacerbations in previous 12 months, mean (SD)	3.0 (1.9)	2.7 (1.4)
Patients with exacerbations leading to hospitalizations in previous 12 months, n (%)	218 (23)	103 (19)
Time since asthma diagnosis [years], median (range)	16.8 (1.1–69.9)	13.3 (1.1–64.0)
ACQ-6 score, mean (SD) ^e	2.8 (0.9)	2.7 (1.0)
AQLQ(S)+12 score, mean (SD) ^{c,f}	3.9 (1.0)	4.0 (1.0)
Total asthma symptom score, mean (SD) ^c	2.7 (1.0)	2.7 (1.1)
OCS use, n (%)	150 (16)	52 (9)
Nasal polyps, n (%)	230 (25)	98 (18)
Atopic (based on Phadiatop test), n (%)	560 (60)	361 (65)
IgE [kU/L], mean (SD) ^c	586.6 (1,299.3)	672.0 (2,338.2)
Smoking status, n (%)		
Never	707 (76)	473 (85)
Current	0 (0)	4 (1)
Former	228 (24)	81 (15)

ACQ-6, Asthma Control Questionnaire 6; AQLQ(S)+12, Asthma Quality of Life Questionnaire

(standardized) for 12 years and older; FAO, fixed airflow obstruction; FEV₁, forced expiratory

volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; OCS, oral

corticosteroids; SD, standard deviation.

^aFAO+ and FAO– are defined as <70% or $\geq 70\%$ of a ratio ($\times 100$) of postbronchodilator FEV₁ to

FVC, respectively, at baseline. ^bNative Hawaiian or other Pacific Islander, American Indian or

Alaska Native, and Other. ^cData not available for all randomized patients. ^dPercentage predicted normal is FEV₁ expressed as a percentage of the normal value for a person of the same sex, age, and height. ^eACQ-6 is a six-item questionnaire to assess daytime and night-time symptoms and rescue β -agonist use on a 0–6 scale (small numbers represent better control). ^fAQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life on a 1–7 scale (small numbers represent greater impairment).

Table 2. Effect of Benralizumab on Annual Asthma Exacerbation Rate by FAO Status^a**(Full Analysis Set, Baseline Eosinophil Counts ≥ 300 cells/ μ L)**

	FAO+		FAO–	
	Placebo (n=308)	Benralizumab Q8W (n=313)	Placebo (n=193)	Benralizumab Q8W (n=176)
Annual asthma exacerbation rate^b				
Number of patients analyzed	308	313	193	176
Rate estimate (95% CI)	1.32 (1.13 to 1.55)	0.74 (0.61 to 0.88)	0.86 (0.69 to 1.08)	0.50 (0.38 to 0.66)
Absolute difference estimate vs. placebo (95% CI)	–	–0.59 (–0.83 to –0.34)	–	–0.36 (–0.60 to –0.12)
Rate ratio vs. placebo (95% CI)	–	0.56 (0.44 to 0.71)	–	0.58 (0.41 to 0.83)
Nominal <i>p</i> vs. placebo	–	<0.0001	–	0.0030
Annual asthma exacerbation rate associated with ED visits or hospitalizations^b				
Number of patients analyzed	308	313	193	176
Rate estimate (95% CI)	0.13 (0.09 to 0.18)	0.07 (0.05 to 0.11)	0.10 (0.06 to 0.16)	0.07 (0.04 to 0.13)
Absolute difference estimate vs. placebo (95% CI)	–	–0.06 (–0.11 to –0.01)	–	–0.03 (–0.09 to 0.03)
Rate ratio vs. placebo (95% CI)	–	0.55 (0.33 to 0.91)	–	0.70 (0.33 to 1.48)
Nominal <i>p</i> vs. placebo	–	0.0195	–	0.3514

CI, confidence interval; ED, emergency department; FAO, fixed airflow obstruction; FEV₁,

forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids;

ITT, intention-to-treat; LABA, long-acting β_2 -agonists; OCS, oral corticosteroids; Q8W, every 8 weeks (first three doses every 4 weeks).

Data are for the pooled ITT population from the high-dosage ICS/LABA treatment cohorts of the SIROCCO and CALIMA studies.

^aFAO+ and FAO– are defined as <70% or $\geq 70\%$ of a ratio ($\times 100$) of postbronchodilator FEV₁ to FVC, respectively, at baseline. ^bEstimates calculated via a negative binomial model, with adjustment for study code, treatment, region, OCS use at time of randomization, and either prior exacerbations (for annual exacerbation rate) or any exacerbations resulting in ED visits or

hospitalizations in the previous year (for annual asthma exacerbation rate associated with ED visits or hospitalizations). 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.

Table 3. Effect of Benralizumab on Lung Function by FAO Status^a (Full Analysis Set, Baseline Eosinophil Counts ≥ 300 cells/ μ L)

	FAO+		FAO-	
	Placebo (n=308)	Benralizumab Q8W (n=313)	Placebo (n=193)	Benralizumab Q8W (n=176)
Prebronchodilator FEV ₁ [L] (EOT-baseline) ^b				
Number of patients in analysis	304	312	190	175
Number of patients with EOT data	277	284	168	148
LS mean change	0.184	0.343	0.293	0.396
LS mean difference vs. placebo (95% CI)	–	0.159 (0.082 to 0.236)	–	0.103 (–0.008 to 0.215)
Nominal <i>p</i> vs. placebo	–	<0.0001	–	0.0699
Postbronchodilator FEV ₁ [L] (EOT-baseline) ^b				
Number of patients in analysis	302	297	182	165
Number of patients with EOT data	280	282	171	154
LS mean change	0.134	0.263	0.045	0.101
LS mean difference vs. placebo (95% CI)	–	0.130 (0.051 to 0.208)	–	0.056 (–0.034 to 0.146)
Nominal <i>p</i> vs. placebo	–	0.0013	–	0.2204
Prebronchodilator FVC [L] (EOT-baseline) ^b				
Number of patients in analysis	304	312	190	175
Number of patients with EOT data	277	284	168	148
LS mean change	0.172	0.369	0.314	0.439
LS mean difference vs. placebo (95% CI)	–	0.196 (0.108 to 0.285)	–	0.125 (–0.002 to 0.252)
Nominal <i>p</i> vs. placebo	–	<0.0001	–	0.0542
Postbronchodilator FVC [L] (EOT-baseline) ^b				
Number of patients in analysis	302	297	182	165
Number of patients with EOT data	280	282	171	154
LS mean change	0.092	0.202	0.089	0.136
LS mean difference vs. placebo (95% CI)	–	0.110 (0.032 to 0.188)	–	0.047 (–0.049 to 0.143)
Nominal <i>p</i> vs. placebo	–	0.0059	–	0.3337
Postbronchodilator FEV ₁ /FVC (EOT-baseline) ^b				
Number of patients in analysis	302	297	182	165
Number of patients with EOT data	280	282	171	154
LS mean change	0.0222	0.0430	–0.0093	–0.0101
LS mean difference vs. placebo (95% CI)	–	0.0208 (0.0068 to 0.0348)	–	–0.0008 (–0.0184 to 0.0169)
Nominal <i>p</i> vs. placebo	–	0.0037	–	0.9321

CI, confidence interval; EOT, end of treatment; FAO, fixed airflow obstruction; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; ITT, intention-to-treat; LABA, long-acting β_2 -agonists; LS, least squares; Q8W, every 8 weeks (first three doses every 4 weeks); OCS, oral corticosteroids.

Data are for the pooled ITT population from the high-dosage ICS/LABA treatment cohorts of the SIROCCO and CALIMA studies. Change is from baseline (i.e., last value before randomization) to EOT (SIROCCO: Week 48; CALIMA: Week 56).

^aFAO+ and FAO- are defined as $<70\%$ or $\geq 70\%$ of a ratio ($\times 100$) of postbronchodilator FEV₁ to FVC, respectively, at baseline. ^bEstimates calculated via a repeated measures model, with adjustment for study code, treatment, baseline value, region, OCS use at time of randomization, visit, and visit $\times$ treatment.

Table 4. Effect of Benralizumab on Asthma Symptoms, Asthma Control, and Health-Related Quality of Life by FAO Status^a (Full Analysis Set, Baseline Eosinophil Counts ≥ 300 cells/ μ L)

	FAO+		FAO-	
	Placebo (n=308)	Benralizumab Q8W (n=311)	Placebo (n=193)	Benralizumab Q8W (n=176)
Total asthma symptom score (EOT–baseline); baseline values (mean [SD]): FAO+: 2.7 (1.0), FAO–: 2.7 (1.1)				
Number of patients in analysis	308	311	192	172
Number of patients with EOT data	230	250	129	102
LS mean change	–1.05	–1.34	–1.26	–1.33
LS mean difference vs. placebo	–	–0.30	–	–0.08
(95% CI)		(–0.45 to –0.14)		(–0.30 to 0.14)
Nominal <i>p</i> vs. placebo	–	0.0002	–	0.4941
ACQ-6 (EOT–baseline); baseline values (mean [SD]): FAO+: 2.8 (0.9), FAO–: 2.7 (1.0)				
Number of patients in analysis	308	311	192	175
Number of patients with EOT data	232	245	140	119
LS mean change	–1.14	–1.47	–1.23	–1.41
LS mean difference vs. placebo	–	–0.33	–	–0.18
(95% CI)		(–0.49 to –0.17)		(–0.40 to 0.04)
Nominal <i>p</i> vs. placebo	–	<0.0001	–	0.1096
AQLQ(S)+12 (EOT–baseline); baseline values (mean [SD]): FAO+: 3.9 (1.0), FAO–: 4.0 (1.0)				
Number of patients in analysis	299	300	181	166
Number of patients with EOT data	225	239	135	116
LS mean change	1.21	1.55	1.39	1.55
LS mean difference vs. placebo	–	0.33	–	0.17
(95% CI)		(0.15 to 0.51)		(–0.08 to 0.41)
Nominal <i>p</i> vs. placebo	–	0.0003	–	0.1894

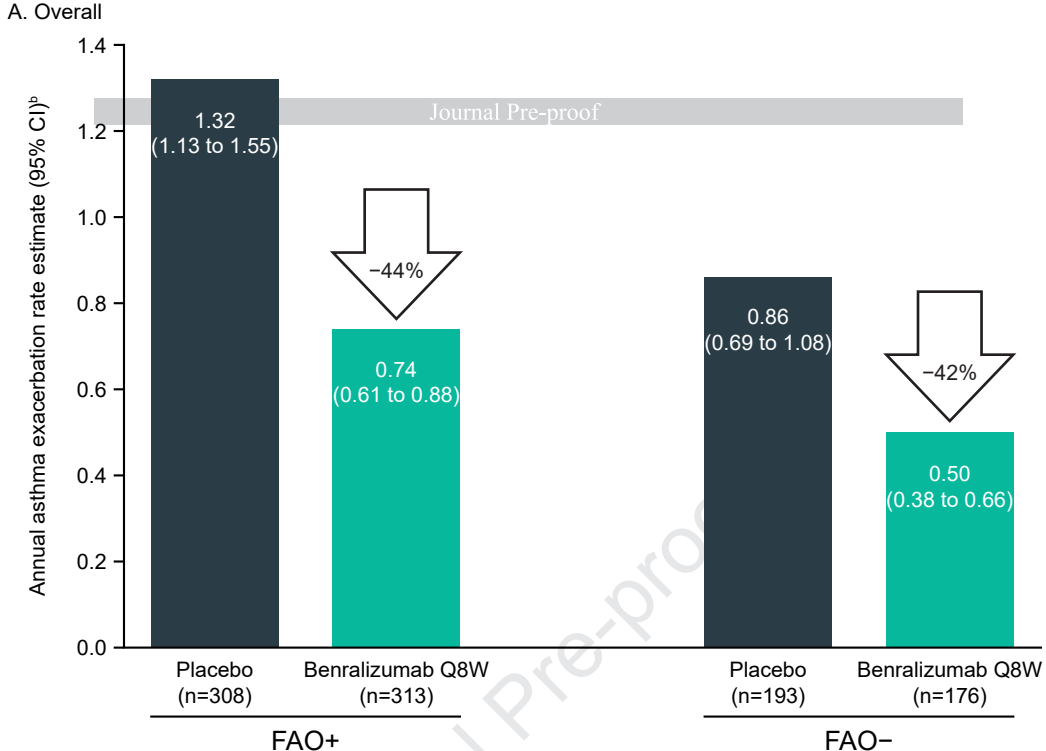
ACQ-6, Asthma Control Questionnaire 6; AQLQ(S)+12, Asthma Quality of Life Questionnaire

(standardized) for 12 years and older; CI, confidence interval; EOT, end of treatment; FAO, fixed airflow obstruction; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; ITT, intention-to-treat; LABA, long-acting β_2 -agonists; LS, least squares; Q8W, every 8 weeks (first three doses every 4 weeks); OCS, oral corticosteroids.

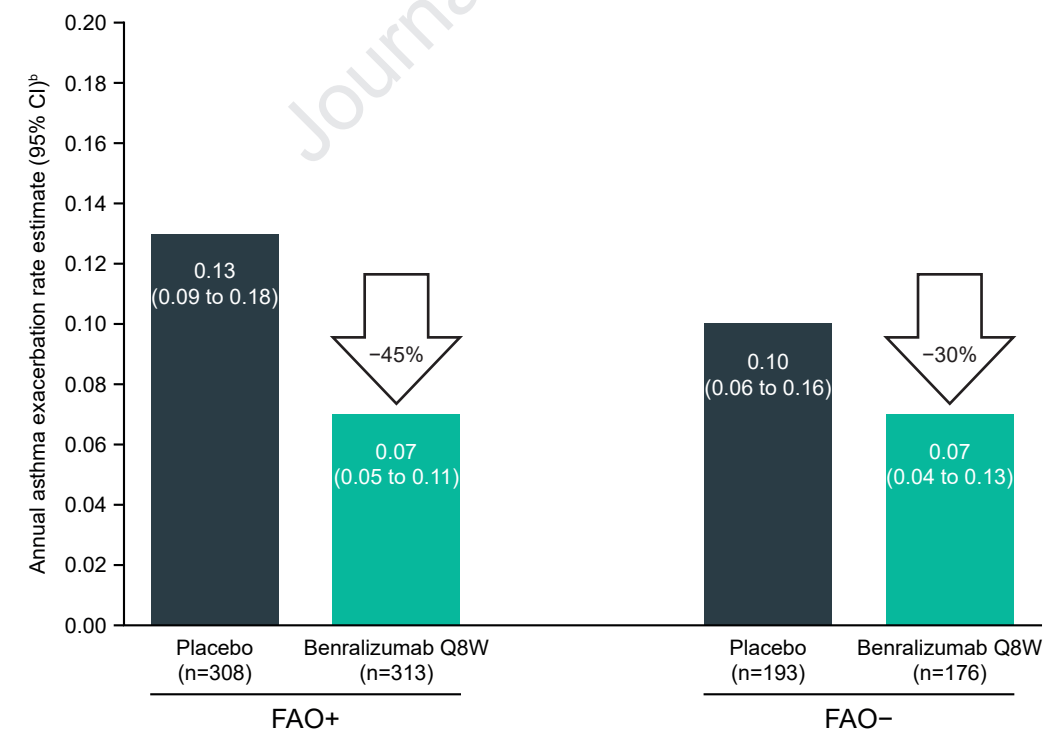
Data are for the pooled ITT population from the high-dosage ICS/LABA treatment cohorts of the SIROCCO and CALIMA studies. Change is from baseline (i.e., last value before randomization) to EOT (SIROCCO: Week 48; CALIMA: Week 56). Estimates calculated via a repeated

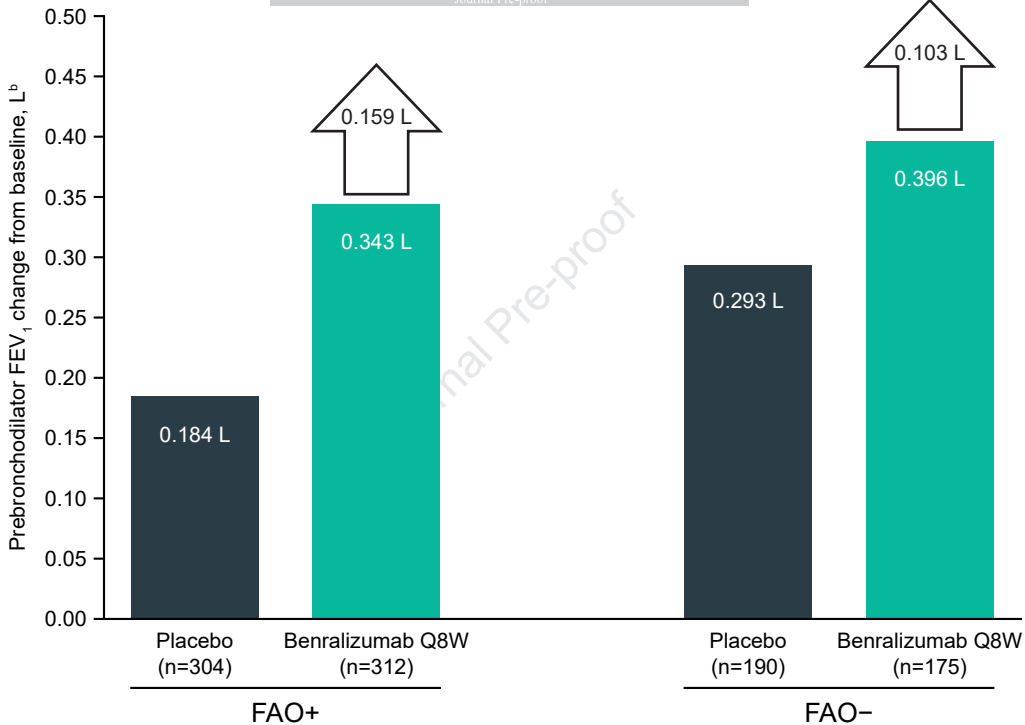
measures model, with adjustment for study code, treatment, baseline value, region, OCS use at time of randomization, visit, and visit $\times$ treatment.

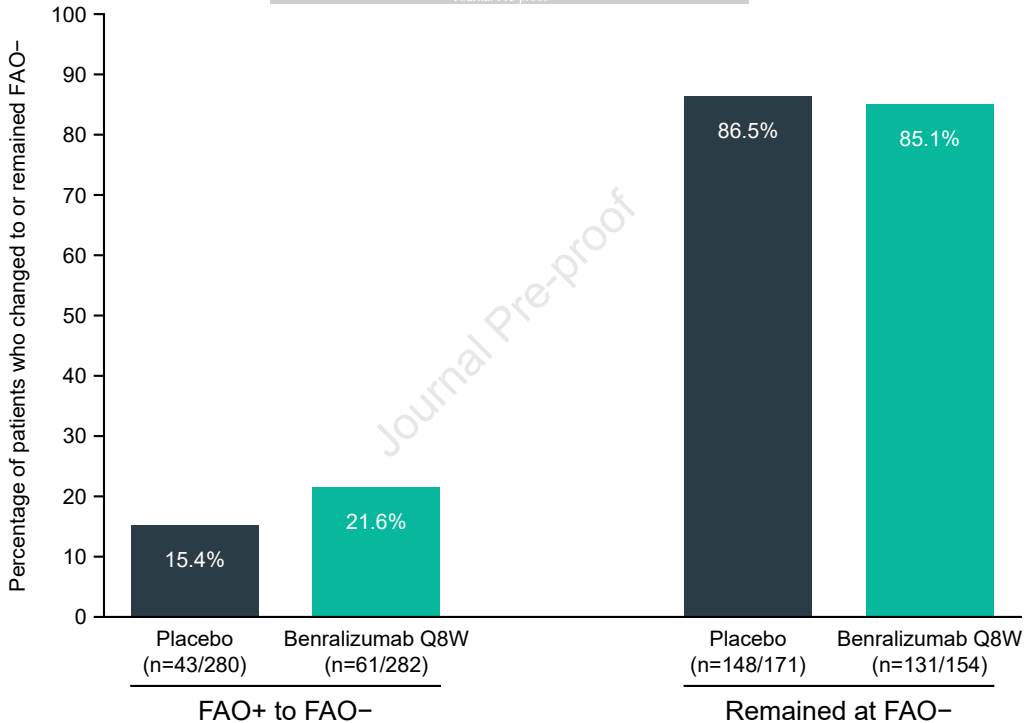
^aFAO+ and FAO- are defined as $<70\%$ or $\geq 70\%$ of a ratio ($\times 100$) of postbronchodilator FEV₁ to FVC, respectively, at baseline.



B. Associated with ED Visits or Hospitalizations







INTRODUCTION

Fixed airflow obstruction (FAO) is present for approximately 16% of patients with asthma, with a greater FAO incidence for patients with severe disease than for those with less severe disease.^{1,2} Patients with FAO have increased exacerbation frequency, decreased lung function, and greater mortality than patients without FAO.^{3,4} The risk of developing FAO is 2–4-fold greater for patients with increased sputum/blood eosinophil counts than for those with lesser eosinophil counts.^{3–7} Elevated sputum and/or blood eosinophil counts are consensual markers of asthma with an eosinophilic phenotype.^{8,9} Patients with FAO and elevated eosinophil counts have greater exacerbation frequencies and may be at risk of more rapid decreases in lung function than patients with FAO without eosinophilia.⁴ Therefore, agents that reduce eosinophil counts in the airway may be particularly beneficial for patients with asthma who have FAO and an eosinophilic phenotype.

Benralizumab is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody that binds directly to eosinophils and induces rapid apoptosis *in vitro* in the presence of natural killer cells via enhanced antibody-dependent cell-mediated cytotoxicity.^{10,11} For patients with asthma, benralizumab resulted in nearly complete depletion of blood eosinophils after the first dose, with corresponding clearance of eosinophils in bronchial biopsies and sputum.^{10,12,13} In the Phase III SIROCCO (NCT01928771; 48 weeks) and CALIMA (NCT01914757; 56 weeks) trials, benralizumab 30 mg every 4 weeks (Q4W) and the indicated dosage of every 8 weeks (Q8W; first three doses Q4W) significantly reduced exacerbations and improved lung function and asthma symptoms for patients with severe, uncontrolled eosinophilic asthma.^{14,15} In a separate

study, benralizumab 30 mg Q4W and Q8W allowed for significant reduction in daily dosage of oral corticosteroids (OCS) without loss of asthma control for OCS-dependent patients with asthma.¹⁶

In this analysis, we evaluated the efficacy of benralizumab Q8W for patients with severe, uncontrolled eosinophilic asthma based on the presence or absence of FAO at baseline for the pooled SIROCCO and CALIMA study population.

METHODS

Study Design and Participants

SIROCCO and CALIMA were randomized, double-blind, parallel-group, placebo-controlled, Phase III studies.^{14,15} Patients were enrolled at 374 (SIROCCO) and 303 (CALIMA) clinical research centers worldwide. The study design included an enrollment visit (Week -4), 4-week screening/run-in phase, randomization (Week 0), treatment period (Weeks 0–48 [SIROCCO] or 0–56 [CALIMA]), and final follow-up visit 8 (SIROCCO) or 4 (CALIMA) weeks following end of treatment (EOT).

Enrollment criteria for the studies have been published.^{14,15} Male and female patients aged 12–75 years who weighed ≥ 40 kg were included in the studies. Patients had physician-diagnosed asthma that required treatment with medium- to high-dosage inhaled corticosteroids (ICS)/long-acting β_2 -agonists (LABA) for ≥ 12 months before enrollment. Patients with diagnoses of lung diseases other than asthma (including chronic obstructive pulmonary disease) or smoking history of >10 pack-years were excluded. Patients also had ≥ 2 asthma exacerbations within 12 months before enrollment that required either systemic corticosteroid therapy or a temporary increase in usual maintenance OCS dosage. Patients were required to have had documented treatment with high-dosage ICS/LABA (defined as fluticasone propionate >500 mg/d or equivalent total daily dosage) with or without OCS and additional asthma controllers for ≥ 3 months before enrollment. Maximal postbronchodilator forced expiratory volume in 1 second (FEV_1) was assessed at baseline after the administration of four, six, and eight puffs of albuterol (360, 540, and 720 mg) according to Moore et al.¹⁷ Studies were conducted in accordance with the Declaration of

Helsinki, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice guidelines, and the ethics committee at each participating site. All patients provided written informed consent at enrollment.

Treatments

In the SIROCCO and CALIMA trials, patients were randomized 1:1:1 to receive subcutaneous benralizumab 30 mg Q4W, benralizumab 30 mg Q8W (first three doses Q4W), or placebo (Q4W). Treatment was double-blind and lasted for 48 (SIROCCO) or 56 (CALIMA) weeks. In both trials, patients with baseline blood eosinophil counts ≥ 300 cells/ μ L and < 300 cells/ μ L were recruited at a ratio of approximately 2:1, respectively. Except for population demographics and baseline disease state characteristics, efficacy results presented herein will be for the approved Q8W dosing regimen.

Outcomes

In the current *post-hoc* study, analyses were performed with data for patients from the pooled SIROCCO and CALIMA studies who were receiving high-dosage ICS/LABA, representing patients receiving Global Initiative for Asthma Steps 4 and 5 treatment,¹⁸ and had baseline blood eosinophil counts ≥ 300 cells/ μ L. The primary and key secondary endpoints from these trials were analyzed based on patients' FAO statuses, either FAO positive (FAO+) or FAO negative (FAO-). FAO+ was defined as a ratio ($\times 100$) of postbronchodilator FEV₁ to forced vital capacity (FVC) of $< 70\%$, with FAO- defined as $\geq 70\%$. Postbronchodilator reversibility was not accounted for in the definition of FAO+ status. FAO+ and FAO- patients were identified at

baseline. Spirometry measurements were performed at the study centers with equipment provided by a central vendor.

The primary efficacy outcome for both SIROCCO and CALIMA was annual asthma exacerbation rate. In both studies, the primary analysis set included patients receiving high-dosage ICS/LABA with baseline blood eosinophil counts ≥ 300 cells/ μ L. An exacerbation was defined as worsening of asthma that led to one of the following: 1) use of systemic corticosteroids (or temporary increase in a stable background OCS dosage) for at least 3 days or a single depo-injectable dose of corticosteroids, 2) asthma-related emergency department (ED)/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.^{14,15}

Secondary endpoints evaluated by FAO status were annual rate of exacerbations associated with ED visits or hospitalizations; changes from baseline at EOT for prebronchodilator and postbronchodilator FEV₁ (measured by spirometry), prebronchodilator and postbronchodilator FVC, postbronchodilator FEV₁/FVC, total asthma symptom score, Asthma Control Questionnaire 6 (ACQ-6) score, and Asthma Quality of Life Questionnaire (standardized) for 12 years and older (AQLQ[S]+12) score; and percentages of patients who changed from FAO- to FAO+ or remained FAO+ at EOT. Total asthma symptom score is a composite of daytime and night-time symptoms on a scale of 0–6 overall.^{14,15} ACQ-6 is a six-item questionnaire to assess daytime and night-time symptoms and rescue β -agonist use on a 0–6 scale (small numbers

represent better control). AQLQ(S)+12 is a 32-item questionnaire to assess asthma-related quality of life on a 1–7 scale (small numbers represent greater impairment¹⁹). Details on efficacy measurement methods have been published.^{14,15}

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 protocol adherence, and continued participation in the study. The similar design of the two studies allowed for the results to be pooled, which enabled us to obtain more accurate estimates of the relationships between efficacy endpoints and FAO status. Analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC, USA).

Exacerbation rates were calculated via a negative binomial model, with adjustment for study code, treatment, region, OCS use at time of randomization, and either prior exacerbations (for annual exacerbation rate) or any exacerbations resulting in ED visits or hospitalizations in the previous year (for annual asthma exacerbation rate associated with ED visits or hospitalizations) with a rate ratio (RR) of benralizumab vs. placebo at EOT. The corresponding 95% confidence intervals (CIs) and two-sided *p*-values for the RR were determined. 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. Secondary endpoints were determined via a mixed-effects model for repeated measures analysis, with adjustment for study code, treatment, baseline value, region, OCS use at time of randomization, visit, and visit × treatment. Least

122 squares (LS) means, treatment differences in LS means, 95% CIs, and p -values were calculated.

123 Because this analysis was not part of the formal testing strategy, all p -values were nominal.

124

RESULTS

Of 1,493 total patients enrolled in SIROCCO and CALIMA, 63% (n=935; 308 placebo, 314 benralizumab Q4W, 313 benralizumab Q8W) were categorized as FAO+ and 37% (n=558; 193 placebo, 189 benralizumab Q4W, 176 benralizumab Q8W) as FAO- (**Table 1**). FAO+ patients were older, had asthma for a longer period, and were more likely to be former smokers than FAO- patients. Median (range) blood eosinophil counts were 510 cells/ μ L (300–4,494) for FAO+ patients and 490 cells/ μ L (300–3,100) for FAO- patients. Baseline lung function was worse for FAO+ patients than for FAO- patients, and a greater percentage of FAO+ patients required OCS at study entry compared with FAO- patients. The percentage reversibility ranges for FAO+ and FAO- patients overlapped substantially.

Greater reductions in annual asthma exacerbation rate were experienced by FAO+ patients receiving the indicated benralizumab Q8W dosage vs. placebo (RR=0.56, 95% CI=0.44 to 0.71, $p<0.0001$) (**Table 2, Figure 1A**). Similar reductions in exacerbation rate were also achieved by FAO- patients receiving benralizumab Q8W vs. placebo (RR=0.58, 95% CI=0.41 to 0.83, $p=0.0030$) (**Table 2, Figure 1A**). The reduction in asthma exacerbations associated with ED visits or hospitalizations was greater for FAO+ patients receiving benralizumab Q8W vs. placebo (RR=0.55, 95% CI=0.33 to 0.91, $p=0.0195$) than for FAO- patients vs. placebo (RR=0.70, 95% CI=0.33 to 1.48, $p=0.3514$) (**Table 2, Figure 1B**).

Prebronchodilator FEV₁ increased more from baseline to EOT for FAO+ patients receiving benralizumab Q8W vs. placebo (LS mean difference 0.159 L, 95% CI=0.082 to 0.236,

$p<0.0001$) (**Table 3, Figure 2**). An increase in prebronchodilator FEV₁ at EOT from baseline was also observed for FAO- patients receiving benralizumab Q8W vs. placebo (LS mean difference 0.103 L, 95% CI=-0.008 to 0.215, $p=0.0699$) (**Table 3, Figure 2**). Similar improvements were observed at EOT for prebronchodilator FVC as for prebronchodilator FEV₁ with benralizumab vs. placebo (**Table 3**).

Improvements from baseline to EOT in total asthma symptom score, ACQ-6 score, and AQLQ(S)+12 score were greater for FAO+ patients receiving benralizumab Q8W vs. placebo than for FAO- patients (**Table 4**). For benralizumab Q8W vs. placebo, improvements (LS mean difference) for FAO+ patients were -0.30 in total asthma symptom score (95% CI=-0.45 to -0.14, $p=0.0002$), -0.33 in ACQ-6 score (95% CI=-0.49 to -0.17, $p<0.0001$), and 0.33 in AQLQ(S)+12 score (95% CI=0.15 to 0.51, $p=0.0003$) (**Table 4**). For FAO- patients, numerical LS mean differences with benralizumab vs. placebo were observed in total asthma symptom score (-0.08, 95% CI=-0.30 to 0.14, $p=0.4941$), ACQ-6 score (-0.18, 95% CI=-0.40 to 0.04, $p=0.1096$), and AQLQ(S)+12 score (0.17, 95% CI=-0.08 to 0.41, $p=0.1894$) from baseline to EOT (**Table 4**).

Mean postbronchodilator FEV₁/FVC improved from baseline with benralizumab vs. placebo at EOT for FAO+ patients but not for FAO- patients (**Table 3**). Improvements from baseline to EOT were also observed for FAO+ patients for postbronchodilator FEV₁ and FVC with benralizumab vs. placebo. These improvements were lesser than those obtained for prebronchodilator FEV₁ (0.130 L vs. 0.159 L) and FVC (0.110 L vs. 0.196 L) (**Table 3**). Of

170 patients who were FAO+ at baseline, 5–6% more patients became FAO– with benralizumab
171 treatment compared with placebo at Week 24 or EOT (**Figure 3**).

172

DISCUSSION

We used pooled results from the SIROCCO and CALIMA Phase III studies to evaluate the efficacy of benralizumab for patients with severe, uncontrolled eosinophilic asthma based on their baseline FAO statuses. We found that almost two-thirds of patients with blood eosinophil counts ≥ 300 cells/ μ L had FAO, consistent with reports indicating a strong association between elevated blood eosinophil counts and FAO,³⁻⁷ and responded to benralizumab treatment. Compared with FAO- patients, FAO+ patients tended to be male, were more likely to be former smokers, and had slightly lesser bronchodilator reversibility, longer time since asthma diagnosis, and greater OCS use.

FAO+ patients experienced improvements with benralizumab in asthma exacerbation rates, including those associated with ED visits or hospitalizations; lung function; asthma symptoms; and health-related quality of life compared with placebo. Overall, these results indicate that despite the greater risk of exacerbations and decreased lung function for FAO+ patients relative to FAO- patients,^{3,4} these patients have comparable, if not better, responses with benralizumab. It is tempting to hypothesize that these improvements suggest normalization of the remodeled airway for FAO+ patients. However, this would require confirmation by direct (e.g., biopsy) or indirect (e.g., imaging) assessments and remains to be seen.

Improvements in exacerbation frequency and lung function with benralizumab Q8W were also observed for FAO- patients compared with placebo, with a similar treatment effect noted on annual asthma exacerbation rate for FAO+ patients. The reduced effect of benralizumab on lung

function improvements for FAO⁻ patients vs. FAO⁺ patients most likely reflected lesser airflow obstruction and, thus, the opportunity for improvement for FAO⁻ patients. For asthma symptoms and health-related quality of life, a numerical difference between benralizumab Q8W and placebo at EOT relative to baseline was achieved but was smaller than that obtained by FAO⁺ patients. This difference may be attributable, in part, to the greater placebo effect observed for FAO⁻ patients compared with FAO⁺ patients.

A limitation of the current study was that pooled analyses were not part of the general testing strategy. Because of this, all comparator results of benralizumab vs. placebo use nominal *p*-values, and no formal statistical significance can be inferred. Another limitation is that classification of FAO was based on a single test at randomization. The use of a maximal bronchodilation procedure (after appropriate medication hold) for patients with severe asthma treated repeatedly over the long term with high-dosage ICS and basing our conclusions on a relatively large FAO subpopulation help mitigate the influence of individual variability.

In summary, benralizumab treatment improves exacerbation frequency, lung function, asthma symptoms, and health-related quality of life for FAO⁺ patients with severe, uncontrolled eosinophilic asthma. The presence of FAO can help guide clinicians considering benralizumab for the treatment of these patients.

FIGURE LEGEND**Figure 1. Effect of Benralizumab on Annual Exacerbation Rates by FAO Status^a (Full Analysis Set, Baseline Eosinophil Counts ≥ 300 cells/ μ L)**

CI, confidence interval; ED, emergency department; FAO, forced airflow obstruction; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonists; OCS, oral corticosteroids; Q8W, every 8 weeks (first three doses every 4 weeks).

Patients receiving high-dosage ICS/LABA.

^aFAO+ and FAO- are defined as $<70\%$ or $\geq 70\%$ of a ratio ($\times 100$) of postbronchodilator FEV₁ to FVC, respectively, at baseline. ^bEstimates calculated via a negative binomial model, with adjustment for study code, treatment, region, OCS use at time of randomization, and either prior exacerbations (for annual exacerbation rate) or any exacerbations resulting in ED visits or hospitalizations in the previous year (for annual asthma exacerbation rate associated with ED visits or hospitalizations). 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.

**Figure 2. Effect of Benralizumab on Prebronchodilator FEV₁ by FAO Status^a at EOT
(Full Analysis Set, Baseline Eosinophil Counts ≥ 300 cells/ μ L)**

EOT, end of treatment; FAO, forced airflow obstruction; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonists; OCS, oral corticosteroids; Q8W, every 8 weeks (first three doses every 4 weeks).

Patients receiving high-dosage ICS/LABA.

^aFAO+ and FAO- are defined as $<70\%$ or $\geq 70\%$ of a ratio ($\times 100$) of postbronchodilator FEV₁ to FVC, respectively, at baseline. ^bEstimates calculated via a negative binomial model, with adjustment for study code, treatment, baseline value, region, OCS use at time of randomization, visit, and visit $\times$ treatment.

Figure 3. Change in FAO Status^a from Baseline to EOT with Benralizumab (Full Analysis Set, Baseline Eosinophil Counts ≥ 300 cells/ μ L)

EOT, end of treatment; FAO, forced airflow obstruction; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonists; Q8W, every 8 weeks (first three doses every 4 weeks).

Patients receiving high-dosage ICS/LABA. Presented in the columns are percentages of patients who changed to or remained FAO⁻. n represents the number of FAO⁻ patients at EOT/total number of FAO⁺ patients (left) or FAO⁻ patients (right) at baseline.

^aFAO⁺ and FAO⁻ are defined as $<70\%$ or $\geq 70\%$ of a ratio ($\times 100$) of postbronchodilator FEV₁ to FVC, respectively, at baseline.