



The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies

Mitchell Goldman, Ian Hirsch, James G. Zangrilli, Paul Newbold & Xiao Xu

To cite this article: Mitchell Goldman, Ian Hirsch, James G. Zangrilli, Paul Newbold & Xiao Xu (2017): The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies, Current Medical Research and Opinion, DOI: [10.1080/03007995.2017.1347091](https://doi.org/10.1080/03007995.2017.1347091)

To link to this article: <http://dx.doi.org/10.1080/03007995.2017.1347091>



Accepted author version posted online: 23 Jun 2017.



Submit your article to this journal [↗](#)



Article views: 70



View related articles [↗](#)



View Crossmark data [↗](#)

The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies

Mitchell Goldman¹, Ian Hirsch¹, James G. Zangrilli¹, Paul Newbold², Xiao Xu¹

¹AstraZeneca, Gaithersburg, MD, USA; ²MedImmune LLC, Gaithersburg, MD, USA

Corresponding author: Mitchell Goldman, AstraZeneca, One MedImmune Way, Gaithersburg, MD, USA 20078, E-mail: mitchell.goldman@astrazeneca.com

Transparency

Declaration of funding:

Funding for the SIROCCO and CALIMA studies was provided by AstraZeneca and Kyowa Hakko Kirin. Funding for the analyses was provided by AstraZeneca.

Declaration of financial and other interests:

MG, IH, JGZ, PN, and XX are full-time employees of AstraZeneca/MedImmune LLC. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work, but have no other relevant financial relationships to disclose.

Author contributions:

All authors conceived and designed the study, acquired the data, and accessed, analyzed, and interpreted the data. All authors participated in the development and critical review of the manuscript. All authors provided final approval for publication submission and are accountable for the accuracy and integrity of the work.

Acknowledgments:

The authors would like to thank the investigators, health care providers, research staff, and patients who participated in the SIROCCO and CALIMA studies. Writing and editing support, including preparation of the draft manuscript under the direction and guidance of the authors, incorporating author feedback, and manuscript submission, was provided by Alan Saltzman, PhD, of Endpoint Medical Communications, Conshohocken, PA, USA, and Michael A. Nissen, ELS, of AstraZeneca (Gaithersburg, MD, USA). This support was funded by AstraZeneca.

Abstract

Objective: Benralizumab, an anti-eosinophilic monoclonal antibody, in combination with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (ICS/LABA) significantly reduced asthma exacerbations, improved lung function, and reduced symptoms for patients with severe, uncontrolled asthma with blood eosinophil counts ≥ 300 cells/ μ L in the Phase III SIROCCO and CALIMA studies. To understand the efficacy and safety of benralizumab for patients with eosinophil-driven disease with blood eosinophil counts lower than 300 cells/ μ L, we evaluated the effect of applying an eosinophil cutoff of ≥ 150 cells/ μ L.

Methods: Adult patients with uncontrolled asthma despite high-dosage ICS/LABA $\pm$ additional asthma controller(s) received subcutaneous benralizumab 30 mg every 8 weeks (Q8W; first three doses every 4 weeks) or placebo for 48 (SIROCCO) or 56 (CALIMA) weeks. Efficacy measures including annual exacerbation rate, prebronchodilator FEV₁, and total asthma symptom score were analyzed by baseline blood eosinophil counts ≥ 150 vs. < 150 cells/ μ L.

Results: Benralizumab reduced asthma exacerbation rates by 42% in SIROCCO (rate ratio: 0.58; 95% CI: 0.46–0.74; $p < 0.001$; $n = 325$) and 36% in CALIMA (rate ratio: 0.64; 95% CI: 0.50–0.81; $p < 0.001$; $n = 300$) vs. placebo ($n = 306, 315$) for patients with blood eosinophil counts ≥ 150 cells/ μ L. Benralizumab increased prebronchodilator FEV₁ (both studies, $p \leq 0.002$) and improved total asthma symptom score in SIROCCO ($p = 0.009$) at end of treatment vs. placebo for patients with blood eosinophil counts ≥ 150 cells/ μ L. The overall adverse events frequency was similar between treatment groups and eosinophil count cohorts.

Conclusion: These results support the efficacy and safety of benralizumab for patients with severe asthma and blood eosinophil counts ≥ 150 cells/ μ L.

Key words: Benralizumab, asthma, exacerbations, eosinophils, interleukin-5 receptor, monoclonal antibody

Short title: Blood eosinophil counts and benralizumab efficacy.

Introduction

Severe, uncontrolled asthma affects approximately 5–10% of an estimated 315 million patients with asthma worldwide.^{1,2} Severe asthma requires medium-/high-dosage inhaled corticosteroids/long-acting β_2 -agonists (ICS/LABA) with add-on therapies (e.g., oral corticosteroids, anti-immunoglobulin E [omalizumab] or anti-interleukin-5 [IL-5] agents) to control the disease. For many patients, the disease remains uncontrolled despite such extensive treatment,³ placing them at risk of severe asthma exacerbations.⁴ Thus, a significant unmet medical need remains. Patients with severe, uncontrolled asthma have increased morbidity, reduced health-related quality of life, and increased health care resource use, and therefore need additional therapeutic options.^{4–7}

Eosinophilic inflammation is evident in approximately half of patients with asthma and is associated with increased disease severity, exacerbation frequency, and symptom burden, as well as with decreased lung function.^{8–10} IL-5, a critical cytokine for eosinophil development, activation, and survival, is present in increased concentrations in patients with asthma.^{11,12} Current asthma treatment guidelines recommend add-on anti-IL-5 therapy for patients with severe, uncontrolled, eosinophilic asthma.³ Blood eosinophil count is one of the predictive biomarkers of eosinophilic asthma. However, blood eosinophil count cutoff criteria have varied from study to study and a clear definition of blood eosinophilia has not been established. Eosinophil counts can fluctuate with circadian rhythm and exposure to systemic steroids.¹³ Furthermore, patients with low blood eosinophil counts may still have eosinophil-driven disease and would benefit from therapies that target eosinophilic inflammation.

Benralizumab is a humanized, afucosylated, anti-eosinophilic monoclonal antibody against IL-5 receptor α , which is expressed on the surface of eosinophils and basophils.^{14,15} Benralizumab is under development for patients with severe, uncontrolled, eosinophilic asthma. Benralizumab induces direct, rapid, and nearly complete depletion of eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity, an apoptotic process of eosinophil elimination involving natural killer cells.¹⁶ In this respect, benralizumab differs from the two marketed anti-IL-5 antibodies (mepolizumab and reslizumab) that bind IL-5 and result in passive, indirect eosinophil reduction.^{17–19} In two Phase III studies, SIROCCO and CALIMA, adding subcutaneous benralizumab 30 mg every 4 weeks (Q4W) or every 8 weeks (Q8W; Q4W for the first three doses) to ICS/LABA significantly reduced asthma exacerbations, increased lung function (forced expiratory volume in 1 second [FEV₁]), improved symptom control, and depleted blood eosinophils for patients with severe, uncontrolled asthma and a screening blood eosinophil count of ≥ 300 cells/ μ L.^{20,21} Both benralizumab dosing regimens reduced the frequency of exacerbations relative to that with placebo for patients with blood eosinophil counts < 300 cells/ μ L in CALIMA and with the benralizumab Q4W regimen in SIROCCO.^{20,21}

Mepolizumab and reslizumab, the two marketed anti-IL-5 antibodies indicated for severe asthma, have been studied in patients with blood eosinophil counts ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L in the prior year and with ≥ 400 cells/ μ L, respectively.^{17–19} In contrast, the Phase III benralizumab trials included patients irrespective of blood eosinophil count, so it was possible to assess efficacy across a range of blood eosinophils. Of note, benralizumab demonstrated efficacy for patients with a screening blood

eosinophil count <300 cells/ μ L.^{20,21} The aim of the current study was to further characterize the patient population most likely to benefit from benralizumab treatment. To this end, our analysis examined the efficacy and safety results from the SIROCCO and CALIMA studies for patients aged ≥ 18 years with severe, uncontrolled asthma with blood eosinophil counts ≥ 150 cells/ μ L vs. <150 cells/ μ L.

Methods

Study design and participants

The SIROCCO (NCT01928771) and CALIMA (NCT01914757) studies were randomized, double-blind, parallel-group, placebo-controlled, Phase III studies that enrolled patients at 303 and 374 clinical research centers, respectively, in Africa, Asia, Europe, North America, and South America.^{20,21} The study design comprised an enrollment visit (Week -4), a 4-week screening/run-in phase, randomization (Week 0), a treatment period from Weeks 0 to 48 (SIROCCO) or 56 (CALIMA), and a final follow-up visit 4 weeks following the end of treatment period.

Enrollment criteria for the studies have been previously published.^{20,21} The study included male and female patients aged 12 to 75 years, with a weight of ≥ 40 kg, and with physician-diagnosed asthma that required treatment with medium- to high-dosage ICS/LABA (defined as fluticasone ≥ 500 μ g/day or equivalent total daily dosage) for ≥ 12 months prior to enrollment. In this current analysis, only patients aged ≥ 18 years treated with high-dosage ICS/LABA (defined as fluticasone >500 μ g/day or equivalent total daily dosage) were evaluated. Patients must have had at least two asthma exacerbations requiring systemic corticosteroid therapy or a temporary increase in their usual maintenance dosages of oral corticosteroids within 12 months prior to enrollment. Patients must have had documented treatment of ICS/LABA with or without oral corticosteroids or additional asthma controllers for ≥ 3 months prior to enrollment. 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.

Patients from all regions were randomized 1:1:1 to receive either subcutaneous benralizumab 30 mg Q4W, benralizumab 30 mg Q8W, or placebo Q4W. Treatment was double blind and lasted for 48 (SIROCCO) or 56 weeks (CALIMA). Patients with blood eosinophil counts ≥ 300 cells/ μ L and <300 cells/ μ L were recruited at screening in a ratio of approximately 2:1, respectively.

Because there was no apparent safety or efficacy benefit to more frequent benralizumab dosing in either the SIROCCO or CALIMA studies, only benralizumab 30 mg Q8W was explored further in the current analysis.^{20,21} The Q8W regimen has indicated greater numerical trends (statistical tests not evaluated) toward efficacy benefits and a smaller drug burden compared with the Q4W regimen.^{20,21}

Outcomes

The primary efficacy endpoint was annual asthma exacerbation rate. Annual asthma exacerbation rate was calculated as the total number of exacerbations $\times$ 365.25/total duration of follow up within the treatment group (days). An exacerbation was defined as a worsening of asthma that led to one of the following: 1) use of systemic corticosteroids (or temporary increase in a stable oral corticosteroids background dosage) for at least 3 days or a single, injected dose of corticosteroids, 2) emergency department (ED)/urgent care visit (<24 hours) related to asthma that required systemic corticosteroids, or 3) inpatient hospitalization ($\geq$ 24 hours) related to asthma. Worsening of asthma was defined as any new or increased symptoms or signs that were concerning to the patient or related to an Asthma Daily Diary alert.^{20,21}

Key secondary endpoints (i.e., multiplicity [type-1 error]–protected endpoints) included prebronchodilator FEV₁ and total asthma symptom score. FEV₁ was measured by spirometry at the study center with equipment provided by a central vendor. Spirometry was performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines by the investigator or authorized delegate.²² Asthma symptom scores were derived from night-time and daytime symptom recordings by patients each morning and evening, respectively, with electronic patient-reported outcome devices. Symptoms were reported on a 4-point response scale (0–3), with 0 indicating no symptoms. In addition, symptom severity was rated from 1 (low) to 3 (high). Total asthma symptom score was a sum of night-time and morning scores, with a maximum score of 6.

Additional secondary endpoints were Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) score and Asthma Control Questionnaire 6 (ACQ-6) score. The AQLQ(S)+12 questionnaire measured the health-related quality of life experienced by patients aged $\geq$ 12 years with asthma.²³ Four separate domains were part of the questionnaire: symptoms, activity limitations, emotional function, and environmental stimuli. Patients were asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score was calculated as the mean response to all questions. The ACQ-6 assessed asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheezing) and short-acting bronchodilator use.²⁴ Patients were asked to recall their experiences during the previous week and to score each of the questions on a 7-point scale ranging from 0 (totally controlled) to 6 (severely uncontrolled). The overall score was calculated as the mean response to all questions. For the AQLQ(S)+12 and ACQ-6, total score changes of $\geq$ 0.5 were considered clinically meaningful. Electronic patient-reported outcome devices were used to record AQLQ(S)+12 and ACQ-6 assessments. Safety outcomes included adverse events and serious adverse events.

Statistical analysis

To account for the 2:1 stratification for baseline blood eosinophil counts ($\geq$ 300 cells/ μ L and <300 cells/ μ L) we reweighted patients with baseline blood eosinophil counts <300 cells/ μ L using the ratio of the number of patients who had baseline blood eosinophil counts $\geq$ 300 cells/ μ L to the number of those who had <300 cells/ μ L. The analysis of treatment outcomes by blood eosinophil counts $\geq$ 150 cells/ μ L

and <150 cells/ μL was not part of the formal testing strategy; therefore, all p -values were nominal. Exacerbation rates were calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomization, and prior exacerbations. The estimated treatment effect (rate ratio of benralizumab vs. placebo at end of treatment), corresponding 95% CI, and two-sided p -value for the rate ratio were determined. Secondary endpoints were determined using a mixed-effects model for repeated measures analysis with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit $\times$ treatment. Based on these analyses, covariate adjusted or least squares means, treatment differences in least squares means, 95% confidence intervals (CIs), and p -values were calculated.

The efficacy of subcutaneous benralizumab 30 mg was analyzed by blood eosinophil count <150 cells/ μL and ≥ 150 cells/ μL for the Q8W dosing arm in adult patients on high-dosage ICS/LABA for both SIROCCO and CALIMA studies. The full analysis set, including all patients randomized and receiving either benralizumab or placebo, irrespective of protocol adherence or continued study participation, was used for the analyses. Statistical calculations were performed using SAS version 9.2.

Results

These analyses evaluated adult patients with severe, uncontrolled asthma and screening blood eosinophil counts ≥ 150 cells/ μL and < 150 cells/ μL who had received benralizumab Q8W or placebo plus high-dosage ICS/LABA in the SIROCCO (≥ 150 cells/ μL $n=631$; < 150 cells/ μL $n=122$; total $n=753$) and CALIMA (≥ 150 cells/ μL $n=615$; < 150 cells/ μL $n=88$; total $n=703$) studies. Demographics and baseline clinical characteristics for the adult patients in the SIROCCO and CALIMA studies for the respective eosinophil count groups were similar except for nasal polyposis, which was present at a greater frequency in the ≥ 150 cells/ μL subgroup than in the < 150 cells/ μL subgroup (Table 1).

Reductions in annual exacerbation rate with benralizumab versus placebo were seen for adult patients with baseline blood eosinophil counts ≥ 150 cells/ μL in the SIROCCO (42%; rate ratio [95% CI]: 0.58 [0.46 to 0.74]; $p<0.001$) and CALIMA (36%; rate ratio [95% CI]: 0.64 [0.50 to 0.81]; $p<0.001$) studies (Table 2). Numerical differences in annual exacerbation rates favoring treatment were observed between the benralizumab and placebo groups for patients with baseline blood eosinophil counts < 150 cells/ μL in both studies. In the SIROCCO study, a decrease was observed in the annual exacerbation rate for exacerbations leading to emergency room visits or hospitalizations with benralizumab versus placebo for patients with baseline blood eosinophil counts ≥ 150 cells/ μL (rate ratio vs. placebo 0.54 [95% CI: 0.32 to 0.90; $p=0.018$]).

Benralizumab treatment resulted in increases in prebronchodilator FEV_1 at end of treatment for patients with baseline blood eosinophils ≥ 150 cells/ μL in both studies (Table 3). The least squares mean treatment differences versus placebo were 0.163 L (95% CI: 0.087 to 0.239; $p<0.001$) for the SIROCCO study and 0.116 L (95% CI: 0.041 to 0.191; $p=0.002$) for the CALIMA study. Improvements in FEV_1 for patients with baseline blood eosinophils ≥ 150 cells/ μL who received benralizumab were observed after the first dose by the first 4-week assessment in both studies ($p<0.05$; Figure 1). A greater reduction versus placebo in total asthma symptom score was achieved in the SIROCCO study (-0.23 points, 95% CI: -0.41 to -0.06 ; $p=0.009$) and in the CALIMA study (-0.16 points, 95% CI: -0.33 to 0.01 ; $p=0.073$), representing 13–19% greater improvement, for patients with baseline blood eosinophil counts ≥ 150 cells/ μL (Table 3). Numerical improvements in FEV_1 and total asthma symptom score between the benralizumab and placebo groups were observed only in the SIROCCO study for patients with baseline blood eosinophil counts < 150 cells/ μL .

For adult patients with blood eosinophil counts ≥ 150 cells/ μL , benralizumab treatment increased AQLQ(S)+12 scores relative to placebo in the SIROCCO (0.19; 95% CI: 0.01 to 0.37; $p=0.036$) and CALIMA studies (0.20; 95% CI: 0.02 to 0.38; $p=0.029$; Table 4). Decreases in ACQ-6 scores in comparison with placebo were observed in both the SIROCCO (-0.15 ; 95% CI: -0.31 to 0.02 ; $p=0.084$) and CALIMA studies (-0.22 ; 95% CI: -0.39 to -0.06 ; $p=0.008$; Table 4) for patients with blood eosinophil counts ≥ 150 cells/ μL . Improvements in AQLQ(S)+12 and ACQ-6 scores with benralizumab treatment relative to placebo were observed only in the SIROCCO study ($p\leq 0.056$) for patients with blood eosinophil counts < 150 cells/ μL .

Adverse events during the on-study period were reported by similar percentages of patients who received benralizumab or placebo for either blood eosinophil subgroup for both SIROCCO and CALIMA studies (72–79% for benralizumab cohorts, Table 5). For patients with blood eosinophil counts ≥ 150 cells/ μL who received benralizumab, the most common adverse events were asthma worsening (SIROCCO and CALIMA, 12% each) and nasopharyngitis (SIROCCO, 11%; CALIMA, 20%). For patients with blood eosinophil counts < 150 cells/ μL who received benralizumab, the most common adverse events were asthma worsening (15%), nasopharyngitis (10%), and upper respiratory tract infection (10%) for the SIROCCO study and nasopharyngitis (29%) and upper respiratory tract infection (15%) for the CALIMA study. Serious adverse events were reported by similar or lesser percentages of patients who received benralizumab versus placebo for either blood eosinophil subgroup. For both blood eosinophil count subgroups, percentages of patients with injection-site reactions were similar between the benralizumab and placebo cohorts (2–4% for the benralizumab cohorts). Percentages of patients experiencing hypersensitivity adverse events were similar or lesser for the benralizumab cohorts versus placebo cohorts.

Discussion

In the SIROCCO and CALIMA studies, benralizumab 30 mg administered Q8W in combination with high-dosage ICS/LABA significantly improved annual exacerbation rates, prebronchodilator FEV₁, and total asthma symptom scores compared with placebo for patients with severe, uncontrolled asthma with baseline blood eosinophil counts ≥ 300 cells/ μ L.^{20,21} The results of the current analyses extend the efficacy profile for benralizumab to patients with severe, uncontrolled asthma with baseline blood eosinophil counts ≥ 150 cells/ μ L. With benralizumab treatment, these patients had consistent improvements in exacerbation reduction, in lung function based on FEV₁, and in disease-specific quality of life based on AQLQ score. Recently, the ZONDA study demonstrated that benralizumab treatment substantially reduced oral glucocorticoid use for patients with blood eosinophil counts ≥ 150 cells/ μ L, further supporting potential use of this agent in this patient population.²⁵

Numerical differences in these measures were observed for the subset of patients with blood eosinophil counts < 150 cells/ μ L. However, the number of patients in this subgroup was small, and the results were less consistent than those for patients with baseline blood eosinophil counts ≥ 150 cells/ μ L. For patients with severe, uncontrolled asthma with blood eosinophil counts < 150 cells/ μ L for whom the possibility of eosinophil-mediated airway inflammation remains high, health care providers should consider the use of sputum or other airway assessments.²⁶

Mepolizumab (administered Q4W), an anti-IL-5 monoclonal antibody, has been studied for patients with severe, eosinophilic asthma defined by an eosinophil inclusion criterion of ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L in the previous 12 months. In the combined mepolizumab Phase III DREAM¹⁸ and MENSA¹⁷ studies, the asthma exacerbation rate ratio of mepolizumab versus placebo was 0.48 (95% CI: 0.39 to 0.58) for patients with blood eosinophil counts ≥ 150 cells/ μ L. For prebronchodilator FEV₁, improvement with mepolizumab for the combined studies versus placebo was 0.064 L (95% CI: 0.001 to 0.127) for patients with blood eosinophil counts of ≥ 150 cells/ μ L. Our ability to compare results from the mepolizumab studies and the current study directly is limited because of differences in baseline characteristics. However, both studies show that their respective agents reduce exacerbation frequency and improve lung function for patients with severe, uncontrolled asthma with blood eosinophil counts ≥ 150 cells/ μ L.

The gold-standard diagnosis of eosinophilic asthma relies on the demonstration of eosinophilic inflammation in the airways based on bronchial biopsies or induced sputum.²⁷ These methods are invasive and require specialized training, and are not feasible for routine clinical practice. Of a range of different biomarkers, blood eosinophil counts offer the greatest diagnostic accuracy for sputum eosinophilia, with increasing specificity as blood eosinophil counts increase.^{28,29} However, given the natural variability of blood eosinophil counts (even within 24 hours) and their sensitivity to corticosteroids, low blood eosinophil counts may belie clinically significant eosinophilic airway inflammation.^{13,30,31} The results of the current analyses underscore the potential limitations of defining probable responders to eosinophil depletion therapy based on a blood eosinophil count of ≥ 300 cells/ μ L.

alone. More detailed characterizations of the eosinophilic phenotype beyond blood eosinophil counts that use a combination of clinical characteristics (e.g., nasal polyposis), along with blood eosinophil counts.²⁷ Blood eosinophil counts should be measured at several time points to address variability issues that could cause missed diagnoses for patients with eosinophilic inflammation.³² The data from our current analysis demonstrate that benralizumab has clinical efficacy at blood eosinophil counts ≥ 150 cells/ μ L for patients with severe uncontrolled asthma, although greater eosinophil counts were predictive of a greater magnitude of response across asthma outcomes, including exacerbations, lung function, and symptomatology.

In the current analysis, the safety profile for benralizumab was consistent with that previously reported for the SIROCCO and CALIMA studies.^{20,21} In both the SIROCCO and CALIMA studies, the frequency of overall adverse events and serious adverse events reported by benralizumab recipients was similar to that reported by placebo recipients for both the ≥ 150 cells/ μ L and < 150 cells/ μ L blood eosinophil cohorts. Injection-site reactions were infrequent and occurred in similarly small percentages of patients in the benralizumab and placebo cohorts.

Conclusions

Adding benralizumab to a high-dosage ICS-based treatment regimen improved several important measures of asthma control, including asthma exacerbation rate, lung function, and disease-specific quality of life, for patients with severe, uncontrolled asthma with baseline blood eosinophil counts ≥ 150 cells/ μ L. These results suggest that benralizumab reduces the burden of disease and health care costs for this difficult-to-treat population with limited treatment options.

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;43:343–73.
3. Global Initiative for Asthma. Global strategy for asthma management and prevention 2017. Available at: <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/> [Last accessed March 27, 2017].
4. Peters SP, Ferguson G, Deniz Y, et al. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med* 2006;100:1139–51.
5. Fernandes AG, Souza-Machado C, Coelho RC, et al. Risk factors for death in patients with severe asthma. *J Bras Pneumol* 2014;40:364–72.
6. Sadatsafavi M, Lynd L, Marra C, et al. Direct health care costs associated with asthma in British Columbia. *Can Respir J* 2010;17:74–80.
7. Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;9:24.
8. Zhang JY, Wenzel SE. Tissue and BAL based biomarkers in asthma. *Immunol Allergy Clin North Am* 2007;27:623–32.
9. 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.
10. 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.
11. Tan LD, Bratt JM, Godor D, et al. Benralizumab: a unique IL-5 inhibitor for severe asthma. *J Asthma Allergy* 2016;9:71–81.
12. 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;8:125–34.
13. Spector SL, Tan RA. Is a single blood eosinophil count a reliable marker for "eosinophilic asthma?". *J Asthma* 2012;49:807–10.
14. Lopez AF, Vadas MA, Woodcock JM, et al. Interleukin-5, interleukin-3, and granulocyte-macrophage colony-stimulating Factor cross-compete for binding to cell surface receptors on human eosinophils. *J Biol Chem* 1991;266:24741–7.
15. Yamada T, Sun Q, Zeibecoglou K, et al. IL-3, IL-5, granulocyte-macrophage colony-stimulating factor receptor α -subunit, and common β -subunit expression by peripheral leukocytes and blood dendritic cells. *J Allergy Clin Immunol* 1999;101:677–82.
16. Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor α mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol* 2010;125:1344–53.
17. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198–207.

18. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651–9.
19. 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;3:355–66.
20. 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;388:2115–27.
21. 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;388:2128–41.
22. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
23. 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.
24. Juniper EF, Svensson K, Mork AC, et al. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;99:553–8.
25. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017 [Epub ahead of print] doi: 10.1056/NEJMoa1703501.
26. Mukherjee M and Nair P. Blood or sputum eosinophils to guide asthma therapy? *Lancet Respir Med* 2015;3:824–5.
27. Coumou H, Bel EH. Improving the diagnosis of eosinophilic asthma. *Expert Rev Respir Med* 2016;10:1093–103.
28. Westerhof GA, Korevaar DA, Amelink M, et al. Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. *Eur Respir J* 2015;46:688–96.
29. Wagener AH, de Nijs SB, Lutter R, et al. External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. *Thorax* 2015;70:115–20.
30. Hastie AT, Moore WC, Li H, et al. Biomarker surrogates do not accurately predict sputum eosinophils and neutrophils in asthma. *J Allergy Clin Immunol* 2013;132:72–80.
31. Korevaar DA, Westerhof GA, Wang J, et al. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. *Lancet Respir Med* 2015;3:290–300.
32. Mathur SK, Fichtinger PS, Evans MD, et al. Variability of blood eosinophil count as an asthma biomarker. *Ann Allergy Asthma Immunol* 2016;117:551–3.

Figure

Figure 1. Change from baseline in prebronchodilator FEV₁ for patients receiving high-dosage ICS/LABA with baseline eosinophil counts (A, B) ≥ 150 cells/ μ L and (C, D) < 150 cells/ μ L for the SIROCCO (A, C) and CALIMA (B, D) studies (adults).

FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonists; Q8W, every 8 weeks (first three doses every 4 weeks).

* $P < 0.05$ for benralizumab Q8W versus placebo treatment comparison.

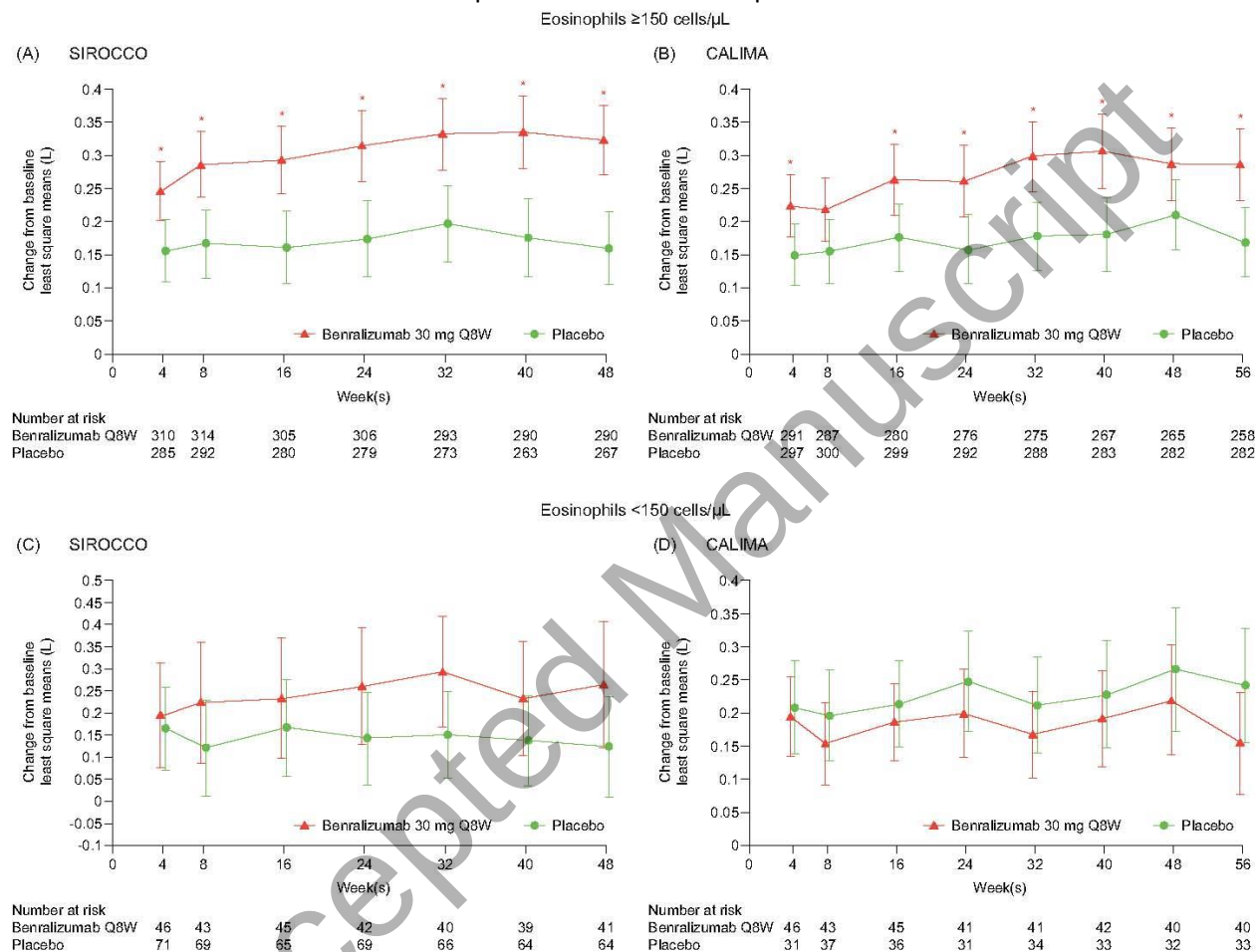


Table 1. Demographics and baseline clinical characteristics (adults).

	SIROCCO (N=753)				CALIMA (N=703)			
	High-dosage ICS/LABA + baseline blood eosinophils ≥ 150 cells/ μ L (n=631)		High-dosage ICS/LABA + baseline blood eosinophils <150 cells/ μ L (n=122)		High-dosage ICS/LABA + baseline blood eosinophils ≥ 150 cells/ μ L (n=615)		High-dosage ICS/LABA + baseline blood eosinophils <150 cells/ μ L (n=88)	
	Benralizumab		Benralizumab		Benralizumab		Benralizumab	
	Placebo	30 mg Q8W	Placebo	30 mg Q8W	Placebo	30 mg Q8W	Placebo	30 mg Q8W
	(n=306)	(n=325)	(n=74)	(n=48)	(n=315)	(n=300)	(n=40)	(n=48)
Age (years), mean (SD)	50.8 (12.6)	49.6 (12.7)	51.6 (12.0)	48.3 (12.6)	50.6 (12.9)	51.0 (11.8)	53.3 (13.5)	52.3 (13.5)
Sex, n (%)								
Male	96 (31)	114 (35)	25 (34)	19 (40)	125 (40)	119 (40)	15 (37.5)	14 (29)
Female	210 (69)	211 (65)	49 (66)	29 (60)	190 (60)	181 (60)	25 (62.5)	34 (71)
Race, n (%)								
White	221 (72)	239 (74)	59 (80)	30 (62.5)	273 (87)	255 (85)	34 (85)	42 (88)
Black/African American	12 (4)	11 (3)	3 (4)	2 (4)	11 (3)	12 (4)	0	0
Asian	41 (13)	40 (12)	8 (11)	9 (19)	31 (10)	32 (11)	6 (15)	6 (13)
Other ^a	32 (10)	35 (11)	4 (5)	7 (15)	0	1 (<1)	0	0

Ethnic group, n								
(%)	61 (20)	62 (19)	12 (16)	10 (21)	64 (20)	68 (23)	6 (15)	6 (13)
Hispanic or Latino	245 (80)	263 (81)	62 (84)	38 (79)	251 (80)	232 (77)	34 (85)	42 (88)
Not Hispanic or Latino								
BMI [kg/m ²], mean (SD) ^b	29.0 (6.8)	28.4 (5.9)	30.8 (7.5)	29.2 (5.2)	29.6 (6.4)	29.1 (6.1)	28.5 (7.6)	29.1 (7.5)
Eosinophil count [cells/μL], median (range) ^b	435 (150–2,690)	400 (150–3,100)	100 (0–149)	100 (0–140)	410 (150–4,494)	440 (150–2,600)	100 (0–148)	85 (0–143)
FEV ₁ prebronchodilator [L], mean (SD) ^b	1.600 (0.553)	1.665 (0.576)	1.664 (0.606)	1.590 (0.518)	1.759 (0.614)	1.720 (0.623)	1.474 (0.535)	1.710 (0.614)
FEV ₁ prebronchodilator [% predicted normal], mean (SD) ^{b,c}	55.1% (14.3)	55.6% (14.3)	56.9% (15.4)	54.3% (15.1)	57.7% (14.1)	56.3% (14.3)	50.4% (15.5)	58.6% (14.1)
FEV ₁ [L] /FVC [L] prebronchodilator [%], mean (SD) ^b	61 (13)	60 (12)	60 (12)	62 (14)	60 (12)	59 (13)	57 (14)	61 (16)

Reversibility [%], median (range) ^b	22% (−8 to 154)	21% (−12 to 157)	17% (−7 to 112)	24% (−2 to 114)	19.5% (−18 to 133)	20% (−13 to 170.5)	17% (−2 to 814)	17% (−10 to 130)
ACQ-6 score, mean (SD) ^d	2.90 (0.96)	2.82 (0.88)	2.85 (0.90)	2.72 (0.88)	2.71 (0.92)	2.81 (0.93)	2.92 (0.86)	2.89 (1.05)
Time since asthma diagnosis [years], median (range)	14.2 (1.1– 65.2)	14.8 (1.1–66.9)	21.1 (1.6–72.4)	14.1 (1.2–58.8)	18.3 (1.3– 69.9)	16.7 (1.2–64.6)	12.6 (1.2– 64.9)	18.5 (1.1–57.3)
Number of exacerbations in previous 12 months, mean (SD)	3.1 (1.9)	2.9 (1.55)	2.7 (1.6)	2.4 (0.8)	2.7 (1.5)	2.7 (1.2)	2.5 (1.3)	3.1 (2.4)
Number of exacerbations in previous 12 months resulting in ED visit, mean (SD)	0.3 (0.8)	0.3 (0.9)	0.3 (0.7)	0.2 (0.7)	0.3 (1.3)	0.2 (0.6)	0.1 (0.4)	0.2 (0.5)
Number of exacerbations in previous 12 months resulting in hospitalization, mean (SD)	0.4 (0.8)	0.4 (0.85)	0.5 (0.8)	0.4 (0.8)	0.3 (0.7)	0.3 (0.6)	0.2 (0.6)	0.2 (0.5)

Total asthma symptom score, mean (SD) ^b	2.72 (1.10)	2.71 (1.11)	2.66 (0.91)	2.65 (1.13)	2.67 (1.03)	2.79 (1.04)	2.92 (1.09)	2.81 (1.13)
AQLQ(S)+12 score, mean (SD) ^{b,e}	3.89 (1.01)	3.90 (0.97)	3.79 (1.01)	4.01 (1.11)	3.96 (1.03)	3.86 (1.02)	3.89 (0.89)	3.79 (0.95)
Diagnosis of allergic rhinitis, n (%)	168 (55)	175 (54)	36 (49)	31 (65)	177 (56)	154 (51)	18 (45)	20 (42)
Nasal polyps, n (%)	69 (23)	70 (22)	8 (11)	3 (6)	62 (20)	58 (19)	5 (13)	3 (6)
Maintenance OCS use, n (%)	51 (17)	62 (19)	17 (23)	6 (13)	36 (11)	29 (10)	4 (10)	9 (19)

ACQ-6, Asthma Control Questionnaire 6; AQLQ(S)+12, Standardized Asthma Quality of Life Questionnaire for 12 years and older; BMI, body mass index; ED, emergency department; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; OCS, oral corticosteroids; Q8W, every 8 weeks (first three doses every 4 weeks); SD, standard deviation.

^aNative Hawaiian or other Pacific Islander, American Indian or Alaska Native, and Other. ^bData not available for all randomized patients. ^cPercent predicted normal is FEV₁ expressed as a percentage of the normal value for a person of the same sex, age, and height. ^dThe ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β -agonist use on a 0–6 scale (low numbers represent better control). ^eThe AQLQ(S)+12 is a 32-item questionnaire to

assess asthma-related quality of life scored on a 1–7 scale (high numbers indicate better quality of life).

Table 2. Annual exacerbation rates for patients with baseline blood eosinophil counts ≥ 150 and < 150 cells/ μL treated with benralizumab plus high-dosage ICS/LABA (adults).

	High-dosage ICS/LABA with baseline blood eosinophils ≥ 150 cells/ μL ^a				High-dosage ICS/LABA with baseline blood eosinophils < 150 cells/ μL ^a			
	SIROCCO (n=631)		CALIMA (n=615)		SIROCCO (n=122)		CALIMA (n=88)	
	Placebo (n=306)	Benralizumab 30 mg Q8W (n=325)	Placebo (n=315)	Benralizumab 30 mg Q8W(n=300)	Placebo (n=74)	Benralizumab 30 mg Q8W (n=48)	Placebo (n=40)	Benralizumab 30 mg Q8W (n=48)
All exacerbations								
Number of patients analyzed	306	325	315	300	74	48	40	48
Rate estimate (95% CI)	1.50 (1.27 to 1.76)	0.87 (0.72 to 1.05)	1.10 (0.94 to 1.28)	0.70 (0.58 to 0.85)	1.34 (1.00 to 1.79)	1.01 (0.66 to 1.55)	1.55 (1.06 to 2.28)	1.01 (0.69 to 1.48)
Absolute difference estimate (95% CI)	—	−0.63 (−0.91 to −0.35)	—	−0.40 (−0.61 to −0.19)	—	−0.33 (−0.91 to 0.25)	—	−0.54 (−1.23 to 0.14)
Rate ratio vs.	—	0.58	—	0.64	—	0.76	—	0.65

placebo (95% CI, <i>p</i> -value)		(0.46 to 0.74, <0.001)		(0.50 to 0.81, <0.001)		(0.45 to 1.27, 0.287)		(0.39 to 1.09, 0.105)
Exacerbations associated with emergency department visits or hospitalizations								
Number of patients analyzed	306	325	315	300	74	48	40	48
Rate estimate (95% CI)	0.23 (0.16 to 0.32)	0.12 (0.08 to 0.18)	NC	NC	0.16 (0.09 to 0.30)	0.31 (0.15 to 0.64)	NC	NC
Absolute difference estimate (95% CI)	—	−0.10 (−0.19 to (−0.02)	—	NC	—	0.15 (−0.10 to 0.40)	—	NC
Rate ratio vs. placebo (95% CI, <i>p</i> -value)	—	0.54 (0.32 to 0.90, 0.018)	—	NC	—	1.92 (0.72 to 5.14, 0.192)	—	NC

CI, confidence interval; ICS, inhaled corticosteroids; ITT, intention-to-treat; LABA, long-acting β_2 -agonists; NC, not calculable; Q8W, every 8 weeks (first three doses every 4 weeks).

Data are from the ITT population from the high-dosage ICS plus LABA treatment cohort from the SIROCCO and CALIMA studies. ^aEstimates were calculated by using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomization, and prior exacerbations. The estimates were weighted to account for the 2:1 randomization ratio of patients with baseline blood eosinophil counts $\geq 300/\mu\text{L}$ or $< 300/\mu\text{L}$.

Table 3. Change in key secondary endpoints with benralizumab plus high-dosage ICS/LABA treatment for patients with blood eosinophil counts ≥ 150 or < 150 cells/ μL (adults).

High-dosage ICS/LABA with baseline blood eosinophils					High-dosage ICS/LABA with baseline blood eosinophils			
≥150 cells/μL					<150 cells/μL			
SIROCCO (n=631)		CALIMA (n=615)		SIROCCO (n=122)		CALIMA (n=88)		
Placebo	Benralizuma	Placebo	Benralizumab	Placebo	Benralizumab	Placebo	Benralizuma	
(n=306)	b 30 mg	(n=315)	30 mg	(n=74)	30 mg Q8W	(n=40)	b 30 mg	
	Q8W		Q8W(n=300)		(n=48)		Q8W (n=48)	
	(n=325)							
FEV ₁ [L] ^a								
Number of	300	323	308	298	72	46	37	46
patients								
analyzed								
LS mean	0.160 (267)	0.323 (290)	0.169 (282)	0.286 (258)	0.125 (64)	0.265 (41)	0.164 (33)	0.033 (40)
(number of								
patients at								
EOT)								
LS mean	—	0.163 (0.087	—	0.116 (0.041 to	—	0.140 (−0.045	—	−0.131
difference vs.		to 0.239,		0.191, 0.002)		to 0.325,		(−0.306 to
placebo (95%		<0.001)				0.136)		0.045,
CI, <i>p</i> -value)								0.142)
Total asthma symptom score ^a								
Number of	306	320	314	298	73	47	40	48
patients								
analyzed								
LS mean	−0.95 (213)	−1.18 (221)	−1.08 (242)	−1.24 (227)	−0.80 (50)	−1.20 (34)	−0.84 (29)	−0.79 (37)
(number of								

patients at								
EOT)								
LS mean	—	−0.23 (−0.41	—	−0.16 (−0.33 to	—	−0.40 (−0.78	—	0.04 (−0.37
difference vs.		to −0.06,		0.01, 0.073)		to −0.03,		to 0.45,
placebo (95%		0.009)				0.035)		0.842)
CI, <i>p</i> -value)								

CI, confidence interval; EOT, end of treatment; FEV₁, forced expiratory volume in 1 second; 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).

Data are from the ITT population from the high-dosage ICS plus LABA treatment cohorts of the SIROCCO and CALIMA studies. Prebronchodilator FEV₁ and total asthma symptom score change are from baseline to EOT (SIROCCO: Week 48; CALIMA: Week 56). ^aEstimates were calculated by using a mixed-effects model for repeated measures analysis with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit $\times$ treatment. The estimates were weighted to account for the 2:1 randomization ratio of patients with baseline blood eosinophil counts $\geq 300/\mu\text{L}$ or $< 300/\mu\text{L}$.

Table 4. Change in AQLQ(S)+12 and ACQ-6 with benralizumab plus high-dosage ICS/LABA treatment for patients with blood eosinophil counts ≥ 150 or < 150 cells/ μ L (adults).

	High-dosage ICS/LABA with baseline blood eosinophils ≥ 150 cells/ μ L				High-dosage ICS/LABA with baseline blood eosinophils < 150 cells/ μ L			
	SIROCCO (n=631)		CALIMA (n=615)		SIROCCO (n=122)		CALIMA (n=88)	
	Placebo (n=306)	Benralizumab 30 mg Q8W (n=325)	Placebo (n=315)	Benralizumab 30 mg Q8W(n=300)	Placebo (n=74)	Benralizumab 30 mg Q8W (n=48)	Placebo (n=40)	Benralizumab 30 mg Q8W (n=48)
AQLQ(S)+12^a								
Number of patients analyzed	294	307	305	292	70	46	39	46
LS mean (number of patients at EOT)	1.18 (204)	1.37 (226)	1.19 (245)	1.39 (221)	0.77 (53)	1.24 (34)	0.98 (29)	0.97 (34)
LS mean difference vs. placebo (95% CI, <i>p</i> -value)	—	0.19 (0.01 to 0.37, 0.036)	—	0.20 (0.02 to 0.38, 0.029)	—	0.46 (−0.01 to 0.94, 0.056)	—	−0.01 (−0.48 to 0.47, 0.972)
ACQ-6^a								
Number of patients analyzed	305	321	314	300	73	47	40	48
LS mean (number of patients at EOT)	−1.13 (209)	−1.27 (233)	−1.08 (252)	−1.30 (226)	−0.62 (52)	−1.32 (35)	−0.84 (30)	−0.91 (35)

Table 5. Adverse events, injection-site reactions, and hypersensitivity during on study period
(adults)

	SIROCCO (N=753)				CALIMA (N=703)			
	High-dosage ICS/LABA + baseline blood eosinophils ≥ 150 cells/ μ L (n=631)		High-dosage ICS/LABA + baseline blood eosinophils <150 cells/ μ L (n=122)		High-dosage ICS/LABA + baseline blood eosinophils ≥ 150 cells/ μ L (n=615)		High-dosage ICS/LABA + baseline blood eosinophils <150 cells/ μ L (n=88)	
	Benralizumab		Benralizumab		Benralizumab		Benralizumab	
	Placebo	30 mg Q8W	Placebo	30 mg Q8W	Placebo	30 mg Q8W	Placebo	30 mg Q8W
	(n=306)	(n=325)	(n=74)	(n=48)	(n=315)	(n=300)	(n=40)	(n=48)
Any AE, n (%)	238 (78)	233 (72)	62 (84)	37 (77)	248 (79)	237 (79)	33 (83)	37 (77)
Any SAE, n (%)	44 (14)	43 (13)	13 (18)	10 (21)	44 (14)	33 (11)	9 (23)	3 (6)

AEs in $\geq 5\%$ of
patients, n (%)^a

Asthma worsening	64 (21)	39 (12)	17 (23)	7 (15)	51 (16)	35 (12)	5 (13)	3 (6)
Nasopharyngitis	42 (14)	37 (11)	6 (8)	5 (10)	73 (23)	57 (20)	10 (25)	14 (29)
Upper respiratory tract infection	29 (10)	26 (8)	6 (8)	5 (10)	25 (8)	24 (8)	3 (8)	7 (15)
Bronchitis	25 (8)	13 (4)	4 (5)	2 (4)	42 (13)	26 (9)	4 (10)	8 (17)
Sinusitis	21 (7)	19 (6)	6 (8)	4 (8)	34 (11)	16 (6)	2 (5)	1 (2)
Influenza	20 (7)	17 (5)	3 (4)	1 (2)	15 (5)	7 (2)	1 (3)	1 (2)
Headache	17 (6)	33 (10)	1 (1)	2 (4)	28 (9)	22 (8)	1 (3)	4 (8)
Rhinitis	10 (3)	7 (2)	3 (4)	3 (6)	14 (4)	13 (5)	1 (3)	2 (4)
Back pain	10 (3)	8 (3)	4 (5)	0	11 (4)	8 (3)	3 (8)	2 (4)
Arthralgia	8 (3)	17 (5)	4 (5)	1 (2)	9 (3)	8 (3)	0	3 (6)
Hypertension	8 (3)	10 (3)	3 (4)	0	15 (5)	12 (4)	5 (13)	5 (10)
Pharyngitis	7 (2)	16 (5)	4 (5)	4 (8)	6 (2)	6 (2)	1 (3)	2 (4)
Dizziness	6 (2)	2 (1)	1 (1)	0	2 (1)	3 (1)	1 (3)	4 (8)
Urticaria	6 (2)	8 (3)	1 (1)	0	7 (2)	4 (1)	2 (5)	3 (6)
Rhinitis allergic	5 (2)	12 (4)	1 (1)	0	14 (4)	10 (3)	3 (8)	1 (2)
Gastroenteritis	4 (1)	8 (3)	2 (3)	3 (6)	8 (3)	3 (1)	1 (3)	1 (2)
Ligament sprain	4 (1)	3 (1)	1 (1)	1 (2)	2 (1)	3 (1)	0	3 (6)
Cystitis	3 (1)	0	0	3 (6)	5 (2)	3 (1)	NA	NA
Musculoskeletal pain	3 (1)	6 (2)	NA	NA	3 (1)	3 (1)	2 (5)	1 (2)
	2 (1)	2 (1)	1 (4)	0	1 (<1)	2 (1)	1 (3)	3 (6)
	1 (<1)	2 (1)	NA	NA	3 (1)	1 (<1)	2 (5)	0

Injection site reactions, n (%)	5 (2)	7 (2)	0	2 (4)	6 (2)	6 (2)	1 (3)	2 (4)
Hypersensitivity adverse events	7 (2)	10 (3)	4 (5)	1 (2)	13 (4)	9 (3)	2 (5)	3 (6)

AE, adverse event; NA, not available; Q8W, every 8 weeks (first three doses every 4 weeks);

SAE, serious adverse event. ^aMedical Dictionary for Regulatory Activities version 18.1.

Accepted Manuscript