

DR. SAMEER K MATHUR (Orcid ID : 0000-0001-5978-2594)

Article type : Letter to the Editor

Postbronchodilator Lung Function Improvements with Benralizumab for Patients with Severe Asthma

Target journal: *Allergy*

Short title (currently 49 characters, limit 50): Benralizumab and postbronchodilator lung function

Word count: 1,014 (limit 1,000)

Title character count: 95 characters (limit 100, including spaces)

References: 11 (limit 9)

Figure/tables: 2 (limit 2); figure legends cannot exceed 100 words

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/all.14178](https://doi.org/10.1111/all.14178)

This article is protected by copyright. All rights reserved

To the Editor,

Airway remodeling and loss of lung function are prominent features of asthma.¹ Activated eosinophils release an array of inflammatory cytokines and lipid mediators that play a role in airway remodeling.² Imaging studies using quantitative computed tomography have demonstrated correlations between parameters of airway remodeling and postbronchodilator forced expiratory volume in 1 second (FEV₁) as well as changes over time.^{3,4} Therefore, we sought to determine whether a reduction in eosinophils could affect airway remodeling by examining postbronchodilator FEV₁.

SIROCCO and CALIMA Phase III trials demonstrated that benralizumab, an interleukin (IL)-5 receptor alpha-directed cytolytic monoclonal antibody that depletes eosinophils via enhanced antibody-dependent cell-mediated cytotoxicity,⁵ reduces exacerbations, lessens asthma symptoms, and augments prebronchodilator lung function for patients with severe, eosinophilic asthma.^{6,7} *Post-hoc* analysis of pooled SIROCCO and CALIMA data identified subgroups of patients with long-term oral corticosteroid (OCS) use, nasal polyposis (based on medical history), prebronchodilator forced vital capacity (FVC) <65% predicted at baseline, ≥3 asthma exacerbations in the year prior to enrollment, or age at diagnosis ≥18 years with demonstrated enhanced clinical response to benralizumab.^{8,9}

In this analysis, we examined whether subcutaneous benralizumab 30 mg every 8 weeks (first three doses every 4 weeks) also improved postbronchodilator lung function for these same enhanced responder subgroups, providing further evidence that benralizumab may alter inflammation-induced airway changes. Methods, statistics (including confidence intervals for reported results), and study limitations are provided in the Supplement. All *p*-values are nominal, with *p*<0.05 considered nominally significant. The demographics and baseline clinical characteristics were similar between benralizumab and placebo arms (**Table S1**).⁸

At end of treatment (EOT), postbronchodilator FEV₁ improvements from baseline were greater with benralizumab (n=693) than placebo (n=717) for all patients (least squares [LS] mean difference vs.

placebo 0.09 L, $p=0.0001$) and for each enhanced responder subgroup (**Figures 1 and S1, Tables S2 and S3**). The greatest differences vs. placebo were for patients with nasal polyps (0.33 L, $p<0.0001$), long-term OCS use (0.26 L, $p=0.0001$), and baseline FVC $<65\%$ predicted (0.23 L, $p=0.0001$).

Improvements in postbronchodilator FEV₁ were similar for patients with baseline blood eosinophil counts ≥ 300 and <300 cells/ μL , with numerically greater changes for those with ≥ 300 cells/ μL (**Figure 2, Table S3**). Of patients with baseline blood eosinophil counts <300 cells/ μL , the greatest increases in postbronchodilator FEV₁ with benralizumab vs. placebo were for those with nasal polyps (LS mean difference vs. placebo 0.34 L, $p=0.0031$) and those with ≥ 3 exacerbations in the previous year (LS mean difference vs. placebo 0.14 L, $p=0.0219$).

Greater improvements in postbronchodilator FVC and forced expiratory flow 25–75% predicted (FEF_{25–75}) from baseline to EOT were observed with benralizumab compared with placebo (**Tables S4 and S5**). For all patients, mean postbronchodilator FVC improved by 0.06 L ($p=0.0084$) vs. placebo at EOT. Patients with nasal polyposis again had the greatest improvement (0.30 L, $p<0.0001$) (**Table S4**). Of patients with baseline blood eosinophil counts ≥ 300 or <300 cells/ μL , those with nasal polyps had the greatest improvements from baseline to EOT in postbronchodilator FVC with benralizumab vs. placebo (**Table S4**). Postbronchodilator FEF_{25–75} improved from baseline to EOT with benralizumab vs. placebo for all patients by 0.11 L/s ($p=0.0016$). Treatment effects for patients with baseline OCS use, nasal polyps, or baseline FVC $<65\%$ predicted were more than double those of the unselected, total population (**Table S5**). For patients with blood eosinophil counts ≥ 300 cells/ μL , baseline OCS use was associated with the greatest improvement in postbronchodilator FEF_{25–75}. Patients with baseline nasal polyps had the greatest response of those with blood eosinophil counts <300 cells/ μL .

Bronchodilator responses, measured after up to 8 puffs of albuterol, were similar between patients receiving placebo and benralizumab at EOT relative to baseline, regardless of baseline clinical characteristics, including blood eosinophil counts (**Figure S2 and Table S2**). For the overall population of benralizumab-treated patients, mean reversibility changed from 0.41 L (standard

deviation [SD]=0.36) at baseline to 0.25 L (SD=0.24) at EOT. For placebo, mean reversibility changed from 0.41 L (SD=0.36) to 0.26 L (SD=0.25) at EOT. Thus, the postbronchodilator lung function changes are more likely to result from airway structural changes rather than changes in airway hyperreactivity.

By evaluating postbronchodilator lung function in pooled SIROCCO and CALIMA data, this analysis provides further evidence that benralizumab improves lung function and perhaps modulates airway remodeling pathways related to chronic eosinophil-driven inflammation.^{1,2} The presence of nasal polyposis, maintenance OCS use, and baseline FVC <65% predicted were all associated with enhanced benralizumab response and may provide important clues to the pathogenetic effects of uncontrolled eosinophilic inflammation.²

Blood eosinophil counts are a practical but indirect and imperfect indicator of airway eosinophilia.¹⁰ In our analysis, patients with nasal polyposis and lesser blood eosinophil counts had numerically greater improvements in postbronchodilator FEV₁ compared with patients with nasal polyposis and greater blood eosinophil counts from baseline to EOT with benralizumab vs. placebo. Nasal polyposis is likely a marker for IL-5 and eosinophil-driven inflammation.² Thus, according to the “single airway hypothesis,”¹¹ nasal polyps may be an important surrogate marker for uncontrolled eosinophilic inflammation in the lower airways or other IL-5–dependent pathways for patients with asthma.

Patients receiving maintenance OCS also had an enhanced postbronchodilator FEV₁ benralizumab response. Similar to the finding with nasal polyps, this suggested that eosinophilic inflammation or other IL-5–dependent pathways persisted in the airways of some patients while OCS use suppressed peripheral eosinophilia. This may be particularly true for patients with declined lung function, because baseline FVC <65% predicted was one of the three strongest clinical characteristics associated with enhanced benralizumab response. Although these findings should be confirmed with a larger population over a longer observation period, they suggest that some patients with asthma have occult eosinophilic inflammation, which may not be detected with blood eosinophil counts alone as the surrogate marker and may result in loss of lung function.

Accepted Article

In summary, we demonstrated that benralizumab improves postbronchodilator lung function for patients with eosinophilic asthma. Elevated blood eosinophil counts, nasal polyposis, decreased lung function, and long-term OCS use were all potential indicators of an enhanced response. Benralizumab may improve structural changes associated with eosinophil-driven, chronic airway inflammation, which are not always detected with blood eosinophil counts alone.

REFERENCES

1. Prakash YS, Halayko AJ, Gosens R, et al. An official American Thoracic Society research statement: current challenges facing research and therapeutic advances in airway remodeling. *Am J Respir Crit Care Med*. 2017; **195**: e4–e19.
2. Carr TF, Berdnikovs S, Simon HU, Bochner BS, Rosenwasser LJ. Eosinophilic bioactivities in severe asthma. *World Allergy Organ J*. 2016; **9**: 21.
3. Hartley RA, Barker BL, Newby C, et al. Relationship between lung function and quantitative computed tomographic parameters of airway remodeling, air trapping, and emphysema in patients with asthma and chronic obstructive pulmonary disease: a single-center study. *J Allergy Clin Immunol*. 2016; **137**: 1413–1422.
4. Witt CA, Sheshadri A, Carlstrom L, et al. Longitudinal changes in airway remodeling and air trapping in severe asthma. *Acad Radiol*. 2014; **21**: 986–993.
5. Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol*. 2010; **125**: 1344–1353.
6. 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 β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016; **388**: 2115–2127.

- Accepted Article
7. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016; **388**: 2128–2141.
 8. Bleecker ER, Wechsler ME, FitzGerald JM, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *Eur Respir J*. 2018; **52**: 1800936.
 9. FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med*. 2018; **6**: 51–64.
 10. Fowler SJ, Tavernier G, Niven R. High blood eosinophil counts predict sputum eosinophilia in patients with severe asthma. *J Allergy Clin Immunol*. 2015; **135**: 822–824.
 11. Grossman J. One airway, one disease. *Chest*. 1997; **111**: 11S–16S.

FIGURE LEGENDS

Figure 1. Postbronchodilator FEV₁ Improvements with Benralizumab for Subgroups (Full Analysis Set)

≥300 cells/μL, blood eosinophil counts ≥300 cells/μL; BD, bronchodilator; Dx, age at diagnosis; EX, exacerbations; FEV₁, forced expiratory volume in 1 second; FVC <65%, prebronchodilator forced vital capacity <65% predicted; LS, least squares; OCS, oral corticosteroids; Q8W, every 8 weeks; Y, years.

Estimates calculated via a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, OCS use at time of randomization (except for OCS use subgroup), visit, and visit × treatment.

*Nominal $p \leq 0.0001$ benralizumab vs. placebo.

**Nominal $p = 0.0008$ benralizumab vs. placebo.

Figure 2. Postbronchodilator FEV₁ Differences Between Benralizumab and Placebo at EOT for Patients with Blood Eosinophil Counts ≥300 and <300 cells/μL (Full Analysis Set)

≥18Y, age at diagnosis ≥18 years; <65%, prebronchodilator forced vital capacity <65% predicted; EOT, end of treatment; EX, exacerbations; FEV₁, forced expiratory volume in 1 second; LS, least squares; NP, nasal polyps; OCS, oral corticosteroids.

n values are the total numbers of patients with EOT data.

*Nominal $p < 0.001$ benralizumab vs. placebo.

**Nominal $p < 0.0001$ benralizumab vs. placebo.

***Nominal $p < 0.05$ benralizumab vs. placebo.

****Nominal $p < 0.01$ benralizumab vs. placebo.

Authors:

Sameer K. Mathur¹, Brian D. Modena², Hanneke Coumou³, Peter Barker⁴,
James L. Kreindler⁵, James G. Zangrilli⁶

¹Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; ²Department of Medicine, National Jewish Health, Denver, CO, USA; ³Department of Pulmonary Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; ⁴Research and Development, AstraZeneca, Gaithersburg, MD, USA; ⁵Respiratory Biologics, AstraZeneca, Wilmington, DE, USA; ⁶Global Medical Affairs, Respiratory Biologics, AstraZeneca, Gaithersburg, MD, USA

Corresponding author:

Sameer K. Mathur, MD, PhD
Division of Allergy, Pulmonary and Critical Care
Department of Medicine
University of Wisconsin School of Medicine and Public Health
H4/618 Clinical Sciences Center
600 Highland Avenue
Madison, WI 53792, USA
Telephone: +1-608-262-2804
E-mail: skmathur@wisc.edu

CONFLICT OF INTEREST

Sameer K. Mathur is a consultant for and received honorarium from AstraZeneca and received research funds for his institution from Novartis. Brian D. Modena has received consulting fees from AstraZeneca. Hanneke Coumou has nothing to declare. Peter Barker, James L. Kreindler, and James G. Zangrilli are employees of AstraZeneca.

DATA-SHARING STATEMENT

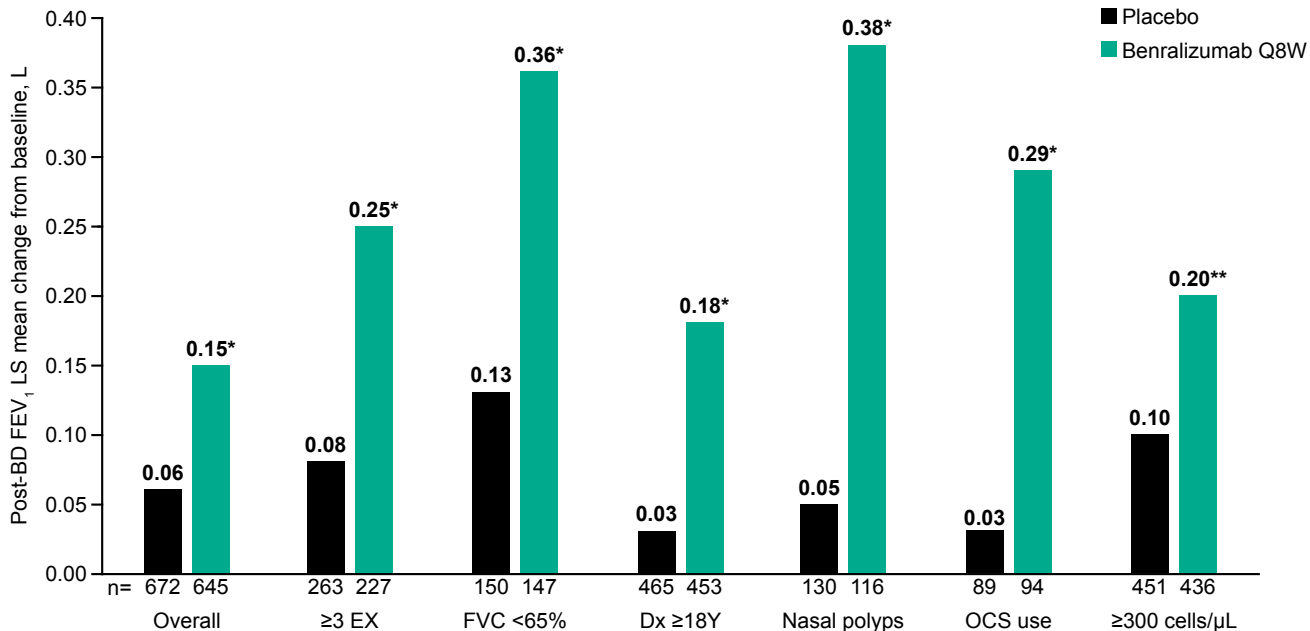
Data underlying the findings described in this manuscript may be requested in accordance with AstraZeneca's data-sharing policy described at <https://astrazenecagroup-dt.pharmam.com/DT/Home>.

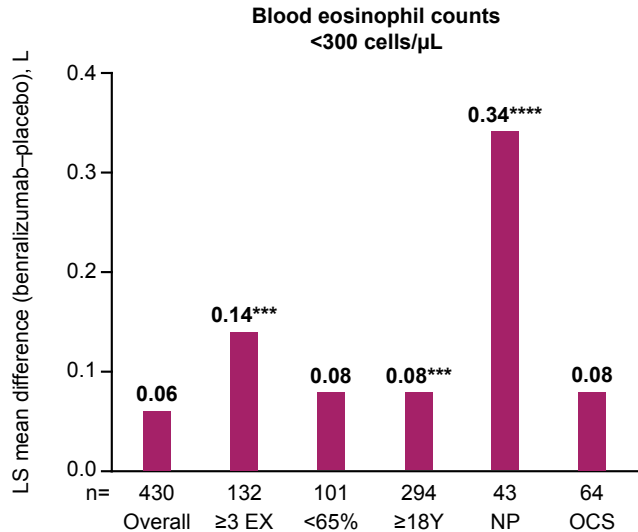
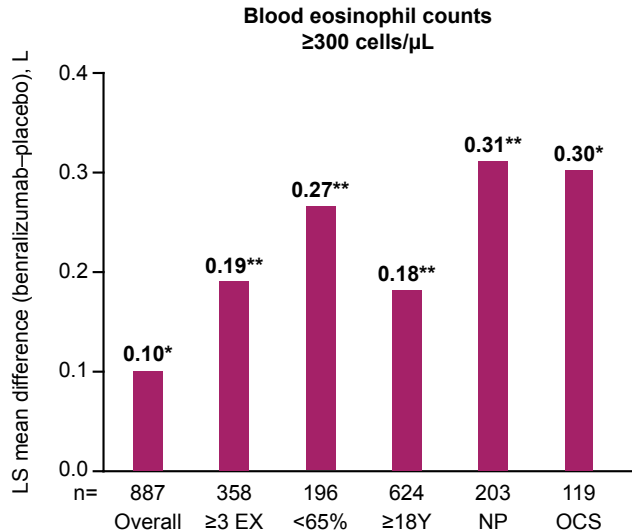
AUTHOR CONTRIBUTIONS

All authors conceived and designed the study. Peter Barker, James L. Kreindler, and James G. Zangrilli acquired the data. All authors analyzed and interpreted the data. All authors participated in the development and review of the manuscript and gave approval to submit for publication.

ACKNOWLEDGMENTS

Funding for this study was provided by AstraZeneca. 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 JK Associates, Inc. (Conshohocken, PA, USA), and Michael A. Nissen, ELS, of AstraZeneca (Gaithersburg, MD, USA). Writing support was funded by AstraZeneca.





Supporting information

Postbronchodilator Lung Function Improvements with Benralizumab for Patients with Severe Asthma

Sameer K. Mathur, Brian D. Modena, Hanneke Coumou, Peter Barker, James L. Kreindler, James G. Zangrilli

METHODS

Description of Patients and Study Designs

In this *post-hoc* analysis, we examined pooled data from SIROCCO and CALIMA, which were randomized, double-blind, placebo-controlled Phase III clinical trials.^{1,2} Both study designs included an enrollment visit, a 4-week run-in phase, randomization, a treatment period (48 weeks for SIROCCO; 56 weeks for CALIMA), and a final follow-up visit (8 weeks for SIROCCO; 4 weeks for CALIMA). Enrollment criteria included male and female patients aged 12–75 years who had ≥ 2 asthma exacerbations within the past 12 months (requiring a prescription of, or temporary increase in, maintenance oral corticosteroid [OCS] dosage) despite treatment with medium- to high-dosage inhaled corticosteroids/long-acting β_2 -agonists. Exclusion criteria included any major lung disease other than asthma (e.g., chronic obstructive pulmonary disease) and smoking history (≥ 10 pack-years). 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. Although benralizumab 30 mg every 4 weeks was studied in both trials, results presented here are for the FDA-approved dosage of 30 mg every 8 weeks (first three doses every 4 weeks) only. 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.

Measured Outcomes of this Analysis

Changes in postbronchodilator forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), forced expiratory flow 25–75% predicted, and airway reversibility were all measured from baseline to end of treatment and compared between treatment groups. Maximal postbronchodilator FEV₁ was assessed both at baseline and during the treatment period after the administration of four, six, and eight puffs of albuterol (360, 540, and 720 mg, respectively).³ We performed a subgroup analysis based on known predictors of enhanced benralizumab response,^{4,5} including ≥ 3 exacerbations in the prior year, prebronchodilator FVC $< 65\%$ predicted, adult-onset asthma, nasal polyposis, and long-term OCS use, and further stratified by blood eosinophil counts (≥ 300 vs. < 300 cells/ μ L). Postbronchodilator lung function was evaluated after four puffs of albuterol.

Statistical Analysis

According to an intention-to-treat principle, all randomized patients who received study treatment, regardless of protocol adherence and continued participation, were included in the analysis. Similar study designs allowed for results to be easily pooled. Analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). Endpoints were analyzed via a mixed-effects model for repeated measures analysis, with adjustments for study code, treatment, baseline values, region, OCS use at time of randomization (except for long-term OCS use subgroup), visit, and visit $\times$ treatment. Least squares (LS) means, treatment differences in LS means, 95% confidence intervals, and *p*-values were calculated. All *p*-values were nominal.

STUDY LIMITATIONS

There are several important limitations to this study. Although the potential of benralizumab for improving lung structure is suggested by our findings, we did not confirm this. It is difficult to determine such changes because of intrinsic complications associated with airway remodeling studies, including lack of biomarkers and universally accepted noninvasive measuring techniques.⁶ Therefore, mechanistic studies of benralizumab on airway remodeling are warranted. One such approach used computational modeling prediction and clinical validation to demonstrate a decrease in smooth muscle burden with benralizumab.⁷ Another limitation was that the pooled analyses were not part of the general testing strategy. In relation, all comparator results of benralizumab vs. placebo use nominal *p*-values, and no formal statistical significance can be inferred. In addition, this study had a relatively short observation period for considering issues related to airway remodeling. Finally, there were comparatively low numbers of patients evaluated for some subgroups, particularly those with blood eosinophil counts < 300 cells/ μ L, making generalizability to large populations difficult.

Table S1. Patient Demographics and Baseline Clinical Characteristics (Full Analysis Set)

	Placebo (n=777)	Benralizumab Q8W (n=762)
Eosinophil count [cells/ μ L], median (range) ^{†,‡}	375 (0–4,494)	380 (0–3,100)
Prebronchodilator FEV ₁ [L], mean (SD) ^{†,‡}	1.71 (0.61)	1.70 (0.60)
Prebronchodilator FEV ₁ [% predicted normal], median (range) ^{‡,§}	58.3 (12.5–110.0)	57.6 (16.8–89.0)
Prebronchodilator FVC [% predicted normal], median (range) ^{†,§}	75.6 (19.2–122.4)	76.1 (33.4–143.1)
Reversibility [%], median (range) ^{†,‡}	20 (–26–814)	21 (–13–171)
Postbronchodilator FEV ₁ [% predicted normal], median (range) ^{‡,§}	71.5 (22.6–133.8)	71.7 (22.3–162.3)
Postbronchodilator FVC [% predicted normal], median (range) ^{‡,§}	75.6 (19.2–122.4)	76.1 (33.4–143.1)
Postbronchodilator FEV ₁ /FVC [%], median (range) ^{‡,§}	65.7 (13.5)	65.3 (13.6)
Number of exacerbations in previous 12 months, median (range) [†]	2.0 (2.0–20.0)	2.0 (1.0–15.0)
Age at asthma diagnosis [years], median (range)	31.6 (0.0–72.4)	32.0 (0.0–72.0)
OCS use, n (%) [†]	109 (14)	110 (14)
Nasal polyps, n (%) [†]	146 (19)	135 (18)

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; OCS, oral corticosteroids; Q8W, every 8 weeks; SD, standard deviation.

Additional patient demographics and baseline clinical characteristics information has been reported.³

[†]Previously reported.³ [‡]Data not available for all randomized patients. [§]Percentage predicted normal is expressed as a percentage of the normal value for a person of the same sex, age, and height.

Table S2. Postbronchodilator FEV₁, FVC, and Reversibility at EOT Based on Baseline Clinical Characteristics Associated with Benralizumab Response (Full Analysis Set, Pooled)

	Placebo	Total Benralizumab Q8W	Blood eosinophil counts ≥300 cells/μL		Blood eosinophil counts <300 cells/μL	
			Placebo	Benralizumab Q8W	Placebo	Benralizumab Q8W
Postbronchodilator FEV ₁ (L)						
Overall						
Baseline, mean (SD), n	2.11 (0.77), 750	2.11 (0.75), 737	2.15 (0.77), 501	2.12 (0.76), 489	2.04 (0.75), 249	2.09 (0.71), 248
EOT, mean (SD), n	2.17 (0.82), 695	2.28 (0.80), 666	2.25 (0.82), 462	2.34 (0.81), 451	2.03 (0.80), 233	2.15 (0.76), 215
≥3 exacerbations						
Baseline, mean (SD), n	2.04 (0.73), 293	2.00 (0.71), 274	2.04 (0.74), 211	2.02 (0.74), 193	2.04 (0.73), 82	1.97 (0.66), 81
EOT, mean (SD), n	2.12 (0.81), 267	2.28 (0.80), 233	2.19 (0.82), 195	2.35 (0.81), 171	1.95 (0.74), 72	2.09 (0.75), 62
FVC <65% predicted						
Baseline, mean (SD), n	1.63 (0.64), 180	1.63 (0.61), 177	1.66 (0.65), 109	1.63 (0.60), 119	1.58 (0.63), 71	1.62 (0.64), 58
EOT, mean (SD), n	1.76 (0.76), 153	2.00 (0.83), 152	1.84 (0.74), 91	2.08 (0.85), 110	1.63 (0.78), 62	1.79 (0.76), 42
Age at diagnosis ≥18 years						
Baseline, mean (SD), n	2.01 (0.70), 516	2.02 (0.70), 510	2.05 (0.71), 343	2.03 (0.72), 344	1.94 (0.67), 173	2.01 (0.67), 166
EOT, mean (SD), n	2.06 (0.74), 484	2.22 (0.78), 469	2.13 (0.74), 322	2.30 (0.80), 322	1.91 (0.71), 162	2.06 (0.70), 147
Nasal polyps						
Baseline, mean (SD), n	2.14 (0.64), 143	2.05 (0.77), 129	2.14 (0.66), 115	2.05 (0.79), 109	2.16 (0.59), 28	2.10 (0.71), 20
EOT, mean (SD), n	2.19 (0.69), 132	2.49 (0.84), 121	2.23 (0.72), 104	2.52 (0.85), 105	2.03 (0.52), 28	2.31 (0.80), 16
OCS use						
Baseline, mean (SD), n	1.90 (0.66), 108	1.89 (0.64), 105	1.92 (0.68), 64	1.81 (0.63), 73	1.86 (0.63), 44	2.08 (0.65), 32
EOT, mean (SD), n	1.90 (0.74), 90	2.25 (0.69), 98	1.99 (0.78), 55	2.31 (0.72), 69	1.76 (0.66), 35	2.12 (0.60), 29
Postbronchodilator FVC (L)						
Overall						
Baseline, mean (SD), n	3.23 (1.01), 750	3.28 (0.97), 737	3.27 (1.02), 501	3.30 (0.98), 489	3.14 (1.00), 249	3.22 (0.94), 248
EOT, mean (SD), n	3.31 (1.05), 695	3.43 (1.02), 666	3.38 (1.05), 462	3.49 (1.03), 451	3.17 (1.05), 233	3.30 (0.99), 215
≥3 exacerbations						
Baseline, mean (SD), n	3.15 (0.96), 293	3.17 (0.94), 274	3.19 (0.98), 211	3.21 (0.98), 193	3.05 (0.93), 82	3.08 (0.84), 81
EOT, mean (SD), n	3.25 (1.05), 267	3.43 (1.02), 233	3.33 (1.06), 195	3.48 (1.05), 171	3.04 (1.01), 72	3.28 (0.90), 62
FVC <65% predicted						
Baseline, mean (SD), n	2.51 (0.78), 180	2.57 (0.75), 177	2.53 (0.80), 109	2.60 (0.76), 119	2.48 (0.74), 71	2.51 (0.74), 58
EOT, mean (SD), n	2.70 (0.90), 153	2.91 (0.98), 152	2.76 (0.91), 91	3.00 (1.02), 110	2.61 (0.88), 62	2.67 (0.83), 42
Age at diagnosis ≥18 years						
Baseline, mean (SD), n	3.14 (0.98), 516	3.20 (0.95), 510	3.18 (0.98), 343	3.23 (0.98), 344	3.05 (0.98), 173	3.15 (0.90), 166
EOT, mean (SD), n	3.23 (1.03), 484	3.37 (1.03), 469	3.30 (1.01), 322	3.45 (1.06), 322	3.10 (1.07), 162	3.21 (0.95), 147

Nasal polyps							
Baseline, mean (SD), n	3.43 (0.89), 143	3.46 (1.00), 129	3.41 (0.88), 115	3.47 (0.98), 109	3.54 (0.95), 28	3.39 (1.12), 20	
EOT, mean (SD), n	3.48 (0.98), 132	3.84 (1.08), 121	3.48 (1.01), 104	3.87 (1.08), 105	3.45 (0.89), 28	3.68 (1.08), 16	
OCS use							
Baseline, mean (SD), n	3.09 (0.96), 108	3.12 (0.92), 105	3.22 (1.01), 64	3.08 (0.92), 73	2.90 (0.85), 44	3.20 (0.93), 32	
EOT, mean (SD), n	3.17 (1.07), 90	3.39 (0.93), 98	3.34 (1.11), 55	3.45 (0.96), 69	2.90 (0.97), 35	3.26 (0.84), 29	
Reversibility (L)							
Overall							
Baseline, mean (SD), n	0.41 (0.36), 739	0.41 (0.36), 732	0.41 (0.35), 494	0.42 (0.37), 489	0.39 (0.37), 245	0.39 (0.23), 243	
EOT, mean (SD), n	0.26 (0.25), 691	0.25 (0.24), 665	0.28 (0.26), 461	0.26 (0.24), 450	0.23 (0.20), 230	0.24 (0.22), 215	
≥3 exacerbations							
Baseline, mean (SD), n	0.39 (0.36), 287	0.40 (0.34), 274	0.38 (0.34), 206	0.41 (0.35), 193	0.41 (0.40), 81	0.37 (0.32), 81	
EOT, mean (SD), n	0.27 (0.26), 264	0.26 (0.23), 233	0.29 (0.27), 194	0.26 (0.23), 171	0.23 (0.22), 70	0.25 (0.23), 62	
FVC <65% predicted							
Baseline, mean (SD), n	0.40 (0.40), 179	0.41 (0.34), 177	0.41 (0.39), 108	0.41 (0.35), 119	0.39 (0.41), 71	0.42 (0.32), 58	
EOT, mean (SD), n	0.25 (0.23), 151	0.26 (0.25), 151	0.28 (0.23), 91	0.27 (0.27), 109	0.22 (0.24), 60	0.22 (0.20), 42	
Age at diagnosis ≥18 years							
Baseline, mean (SD), n	0.38 (0.33), 510	0.39 (0.34), 506	0.38 (0.31), 339	0.39 (0.34), 344	0.37 (0.38), 171	0.38 (0.33), 162	
EOT, mean (SD), n	0.25 (0.22), 482	0.26 (0.24), 469	0.26 (0.23), 322	0.26 (0.24), 322	0.23 (0.20), 160	0.24 (0.24), 147	
Nasal polyps							
Baseline, mean (SD), n	0.42 (0.33), 142	0.38 (0.34), 129	0.42 (0.33), 114	0.38 (0.35), 109	0.41 (0.33), 28	0.41 (0.35), 20	
EOT, mean (SD), n	0.28 (0.20), 131	0.31 (0.29), 121	0.29 (0.20), 104	0.31 (0.29), 105	0.26 (0.21), 27	0.29 (0.27), 16	
OCS use							
Baseline, mean (SD), n	0.38 (0.35), 106	0.33 (0.28), 105	0.39 (0.36), 63	0.32 (0.26), 73	0.37 (0.35), 43	0.36 (0.31), 32	
EOT, mean (SD), n	0.25 (0.22), 89	0.27 (0.20), 98	0.29 (0.24), 55	0.29 (0.21), 69	0.20 (0.17), 34	0.21 (0.14), 29	

EOT, end of treatment; 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; SD, standard deviation.

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 mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, OCS use at time of randomization (except for OCS use subgroup), visit, and visit $\times$ treatment.

Table S3. Postbronchodilator FEV₁ (L) Change (EOT–Baseline) Based on Baseline Clinical Characteristics Associated with Benralizumab Response (Full Analysis Set, Pooled)

	Total Benralizumab Q8W (n=693)		Blood eosinophil counts ≥300 cells/μL Benralizumab Q8W (n=462)		Blood eosinophil counts <300 cells/μL Benralizumab Q8W (n=231)	
	Placebo (n=717)		Placebo (n=484)		Placebo (n=233)	
Overall						
Number of patients with EOT data	672	645	451	436	221	209
LS mean change	0.06	0.15	0.10	0.20	−0.02	0.04
LS mean difference vs. placebo	–	0.09	–	0.10	–	0.06
(95% CI)		(0.04 to 0.14)		(0.04 to 0.16)		(−0.00 to 0.12)
Nominal <i>p</i> vs. placebo	–	0.0001	–	0.0008	–	0.0666
≥3 exacerbations						
Number of patients in analysis	279	250	204	177	75	73
Number of patients with EOT data	263	227	192	166	71	61
LS mean change	0.08	0.25	0.14	0.32	−0.07	0.07
LS mean difference vs. placebo	–	0.17	–	0.19	–	0.14
(95% CI)		(0.09 to 0.25)		(0.09 to 0.29)		(0.02 to 0.27)
Nominal <i>p</i> vs. placebo	–	<0.0001	–	0.0003	–	0.0219
FVC <65% predicted						
Number of patients in analysis	164	162	100	112	64	50
Number of patients with EOT data	150	147	91	105	59	42
LS mean change	0.13	0.36	0.20	0.46	0.05	0.13
LS mean difference vs. placebo	–	0.23	–	0.27	–	0.08
(95% CI)		(0.11 to 0.34)		(0.11 to 0.42)		(−0.07 to 0.23)
Nominal <i>p</i> vs. placebo	–	0.0001	–	0.0007	–	0.3022
Age at diagnosis ≥18 years						
Number of patients in analysis	492	481	331	327	161	154
Number of patients with EOT data	465	453	313	311	152	142
LS mean change	0.03	0.18	0.07	0.25	−0.04	0.04
LS mean difference vs. placebo	–	0.15	–	0.18	–	0.08
(95% CI)		(0.10 to 0.21)		(0.11 to 0.25)		(0.00 to 0.15)
Nominal <i>p</i> vs. placebo	–	<0.0001	–	<0.0001	–	0.0379
Nasal polyps						
Number of patients in analysis	139	121	111	102	28	19
Number of patients with EOT data	130	116	103	100	27	16
LS mean change	0.05	0.38	0.10	0.41	−0.15	0.19
LS mean difference vs. placebo	–	0.33	–	0.31	–	0.34
(95% CI)		(0.20 to 0.46)		(0.16 to 0.46)		(0.12 to 0.57)

Nominal <i>p</i> vs. placebo	–	<0.0001	–	<0.0001	–	0.0031
OCS use						
Number of patients in analysis	96	101	58	70	38	31
Number of patients with EOT data	89	94	54	65	35	29
LS mean change	0.03	0.29	0.10	0.40	–0.07	0.01
LS mean difference vs. placebo	–	0.26	–	0.30	–	0.08
(95% CI)		(0.13 to 0.39)		(0.13 to 0.47)		(–0.08 to 0.24)
Nominal <i>p</i> vs. placebo	–	0.0001	–	0.0008	–	0.3406

CI, confidence interval; EOT, end of treatment; 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; Q8W, every 8 weeks.

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 mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, OCS use at time of randomization (except for OCS use subgroup), visit, and visit $\times$ treatment.

Table S4. Postbronchodilator FVC (L) Change (EOT–Baseline) Based on Baseline Clinical Characteristics Associated with Benralizumab Response (Full Analysis Set, Pooled)

	Total Benralizumab		Blood eosinophil counts ≥ 300 cells/ μ L		Blood eosinophil counts < 300 cells/ μ L	
	Placebo (n=717)	Q8W (n=693)	Placebo (n=484)	Q8W (n=462)	Placebo (n=233)	Q8W (n=231)
Overall						
Number of patients with EOT data	672	645	451	436	221	209
LS mean change	0.07	0.13	0.09	0.18	0.03	0.04
LS mean difference vs. placebo	–	0.06	–	0.09	–	0.02
(95% CI)		(0.02 to 0.11)		(0.03 to 0.15)		(–0.06 to 0.09)
Nominal <i>p</i> vs. placebo	–	0.0084	–	0.0056	–	0.6319
≥ 3 exacerbations						
Number of patients in analysis	279	250	204	177	75	73
Number of patients with EOT data	263	227	192	166	71	61
LS mean change	0.08	0.21	0.11	0.26	–0.01	0.07
LS mean difference vs. placebo	–	0.13	–	0.15	–	0.09
(95% CI)		(0.05 to 0.21)		(0.05 to 0.25)		(–0.04 to 0.22)
Nominal <i>p</i> vs. placebo	–	0.0019	–	0.0035	–	0.1860
FVC $< 65\%$ predicted						
Number of patients in analysis	164	162	100	112	64	50
Number of patients with EOT data	150	147	91	105	59	42
LS mean change	0.17	0.34	0.21	0.42	0.13	0.18
LS mean difference vs. placebo	–	0.17	–	0.21	–	0.05
(95% CI)		(0.04 to 0.30)		(0.04 to 0.38)		(–0.12 to 0.22)
Nominal <i>p</i> vs. placebo	–	0.0082	–	0.0141	–	0.5394
Age at diagnosis ≥ 18 years						
Number of patients in analysis	492	481	331	327	161	154
Number of patients with EOT data	465	453	313	311	152	142
LS mean change	0.06	0.16	0.08	0.22	0.02	0.04
LS mean difference vs. placebo	–	0.10	–	0.13	–	0.02
(95% CI)		(0.04 to 0.16)		(0.06 to 0.21)		(–0.07 to 0.11)
Nominal <i>p</i> vs. placebo	–	0.0012	–	0.0005	–	0.6362
Nasal polyps						
Number of patients in analysis	139	121	111	102	28	19
Number of patients with EOT data	130	116	103	100	27	16
LS mean change	0.04	0.34	0.07	0.38	–0.02	0.14
LS mean difference vs. placebo	–	0.30	–	0.31	–	0.16
(95% CI)		(0.17 to 0.43)		(0.16 to 0.46)		(–0.10 to 0.41)

Nominal <i>p</i> vs. placebo	–	<0.0001	–	<0.0001	–	0.2264
OCS use						
Number of patients in analysis	96	101	58	70	38	31
Number of patients with EOT data	89	94	54	65	35	29
LS mean change	0.08	0.20	0.14	0.28	0.02	–0.01
LS mean difference vs. placebo	–	0.12	–	0.14	–	–0.02
(95% CI)		(–0.02 to 0.26)		(–0.04 to 0.32)		(–0.21 to 0.16)
Nominal <i>p</i> vs. placebo	–	0.0878	–	0.1295	–	0.8202

CI, confidence interval; EOT, end of treatment; FVC, forced vital capacity; ICS, inhaled corticosteroids; ITT, intention-to-treat; LABA, long-acting β_2 -agonists; LS, least squares; OCS, oral corticosteroids; Q8W, every 8 weeks.

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 mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, OCS use at time of randomization (except for OCS use subgroup), visit, and visit $\times$ treatment.

Table S5. Postbronchodilator FEF₂₅₋₇₅ Change (L/s) (EOT–Baseline) Based on Baseline Clinical Characteristics Associated with Benralizumab Response (Full Analysis Set, Pooled)

	Total Benralizumab Q8W (n=693)		Blood eosinophil counts ≥300 cells/μL Benralizumab Q8W (n=462)		Blood eosinophil counts <300 cells/μL Benralizumab Q8W (n=231)	
	Placebo (n=717)		Placebo (n=484)		Placebo (n=233)	
Overall						
Number of patients with EOT data	672	645	451	436	221	209
LS mean change	0.07	0.18	0.13	0.25	−0.04	0.03
LS mean difference vs. placebo	–	0.11	–	0.12	–	0.07
(95% CI)		(0.04 to 0.17)		(0.04 to 0.21)		(−0.02 to 0.17)
Nominal <i>p</i> vs. placebo	–	0.0016	–	0.0051	–	0.1268
≥3 exacerbations						
Number of patients in analysis	279	250	204	177	75	73
Number of patients with EOT data	263	227	192	166	71	61
LS mean change	0.11	0.27	0.18	0.35	−0.10	0.07
LS mean difference vs. placebo	–	0.16	–	0.17	–	0.17
(95% CI)		(0.05 to 0.28)		(0.04 to 0.31)		(−0.02 to 0.36)
Nominal <i>p</i> vs. placebo	–	0.0043	–	0.0128	–	0.0745
FVC <65% predicted						
Number of patients in analysis	164	162	100	112	64	50
Number of patients with EOT data	150	147	91	105	59	42
LS mean change	0.11	0.42	0.19	0.57	0.01	0.05
LS mean difference vs. placebo	–	0.30	–	0.38	–	0.04
(95% CI)		(0.14 to 0.46)		(0.17 to 0.59)		(−0.19 to 0.26)
Nominal <i>p</i> vs. placebo	–	0.0002	–	0.0004	–	0.7457
Age at diagnosis ≥18 years						
Number of patients in analysis	492	481	331	327	161	154
Number of patients with EOT data	465	453	313	311	152	142
LS mean change	0.02	0.22	0.07	0.30	−0.07	0.03
LS mean difference vs. placebo	–	0.19	–	0.23	–	0.10
(95% CI)		(0.12 to 0.27)		(0.13 to 0.33)		(−0.01 to 0.21)
Nominal <i>p</i> vs. placebo	–	<0.0001	–	<0.0001	–	0.0632
Nasal polyps						
Number of patients in analysis	139	121	111	102	28	19
Number of patients with EOT data	130	116	103	100	27	16
LS mean change	0.05	0.35	0.11	0.38	−0.18	0.19
LS mean difference vs. placebo	–	0.30	–	0.26	–	0.37
(95% CI)		(0.13 to 0.46)		(0.07 to 0.46)		(0.07 to 0.66)

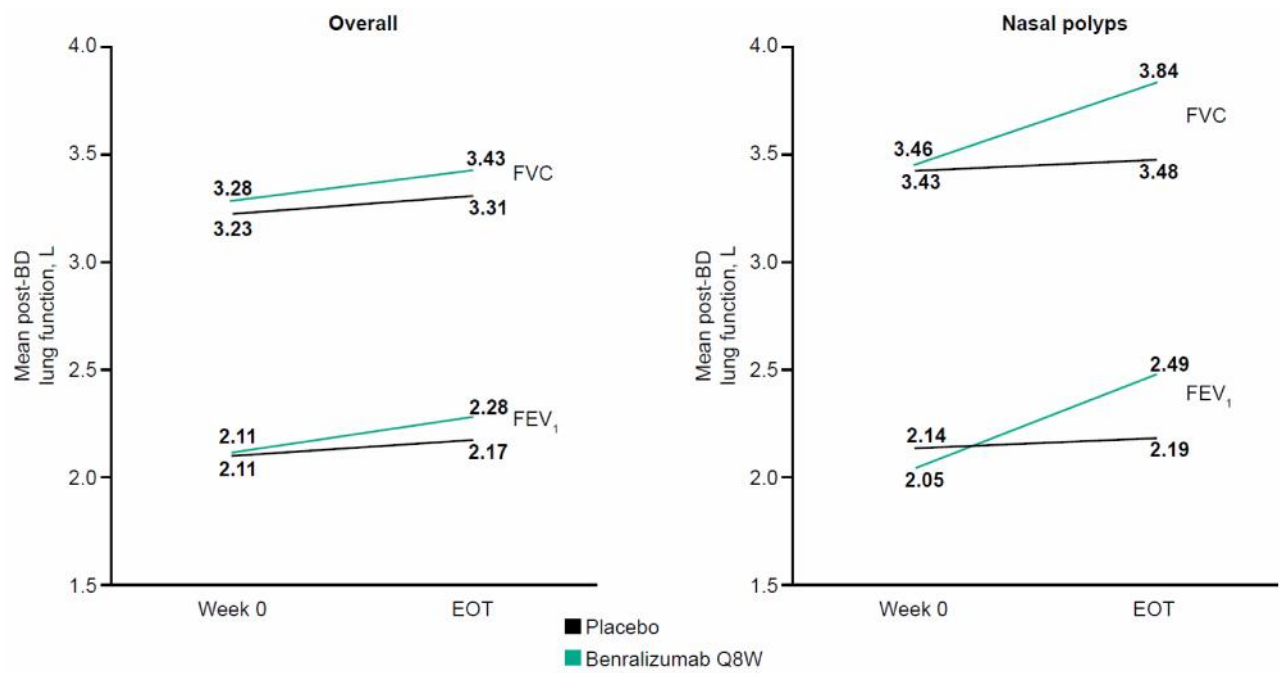
Nominal <i>p</i> vs. placebo	–	0.0004	–	0.0068	–	0.0154
OCS use						
Number of patients in analysis	96	101	58	70	38	31
Number of patients with EOT data	89	94	54	65	35	29
LS mean change	–0.01	0.33	0.06	0.46	–0.12	0.02
LS mean difference vs. placebo	–	0.34	–	0.40	–	0.14
(95% CI)		(0.17 to 0.52)		(0.17 to 0.64)		(–0.08 to 0.35)
Nominal <i>p</i> vs. placebo	–	0.0001	–	0.0009	–	0.2151

CI, confidence interval; EOT, end of treatment; FEF_{25–75}, forced expiratory flow 25–75% predicted; FVC, forced vital capacity; ICS, inhaled corticosteroids; ITT, intention-to-treat; LABA, long-acting β_2 -agonists; LS, least squares; OCS, oral corticosteroids; Q8W, every 8 weeks.

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).

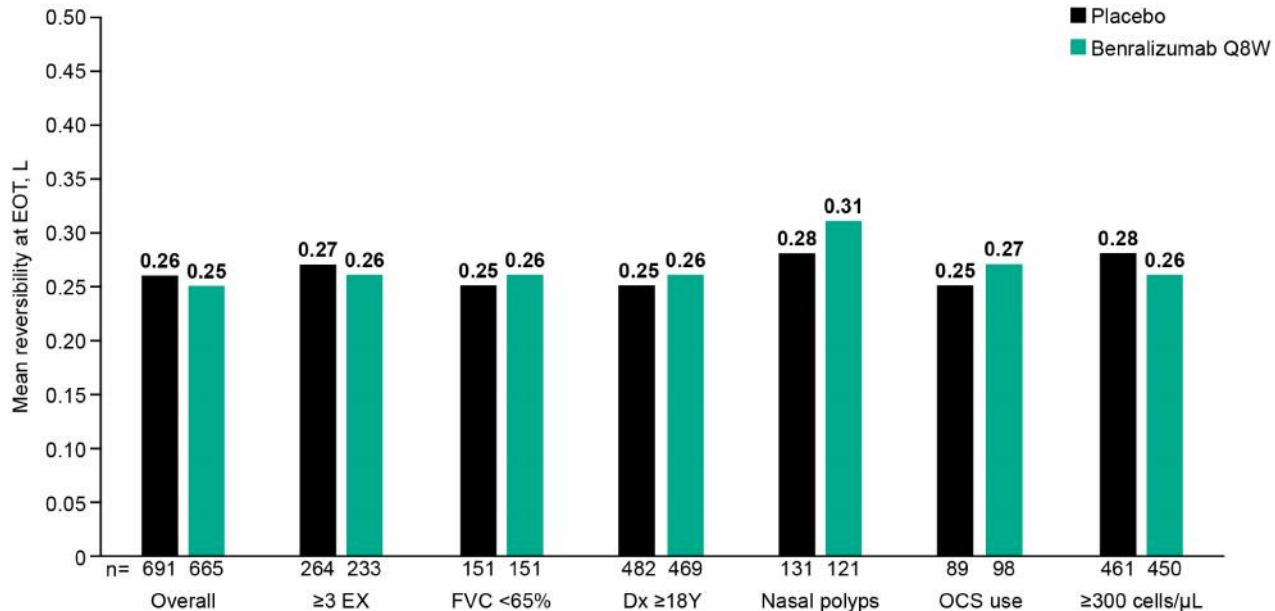
Estimates calculated via a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, OCS use at time of randomization (except for OCS use subgroup), visit, and visit $\times$ treatment.

Figure S1. Postbronchodilator FEV₁ and FVC Improvements with Benralizumab (Full Analysis Set)



BD, bronchodilator; EOT, end of treatment; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; Q8W, every 8 weeks.

Figure S2. Bronchodilator Responses for Patients Receiving Benralizumab or Placebo (Full Analysis Set)



≥300 cells/μL, blood eosinophil counts ≥300 cells/μL; Dx, age at diagnosis; EOT, end of treatment; EX, exacerbations; FVC <65%, prebronchodilator forced vital capacity <65% predicted; OCS, oral corticosteroids; Q8W, every 8 weeks; Y, years.

REFERENCES

1. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016; **388**: 2115–2127.
2. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016; **388**: 2128–2141.
3. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol*. 2007; **119**:405–413.
4. Bleecker ER, Wechsler ME, FitzGerald JM, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *Eur Respir J*. 2018; **52**: 1800936.
5. FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med*. 2018; **6**: 51–64.
6. Prakash YS, Halayko AJ, Gosens R, et al. An official American Thoracic Society research statement: current challenges facing research and therapeutic advances in airway remodeling. *Am J Respir Crit Care Med*. 2017; **195**: e4–e19.
7. Chachi L, Diver S, Kaul H, et al. Computational modelling prediction and clinical validation of impact of benralizumab on airway smooth muscle mass in asthma. *Eur Respir J*. 2019; **54**: 1900930.