# Influence of Key Clinical Baseline Characteristics on Benralizumab Response for Patients with Severe, Uncontrolled Asthma and Moderate Blood Eosinophilia

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## Abstract

**Rationale:** Various clinical characteristics are significantly associated with enhanced benralizumab response for patients with severe, uncontrolled asthma and blood eosinophil counts (BEC) ≥300 cells/μL (*Eur Respir J* 2018;52:1800936). We evaluated these factors' influence on benralizumab response for patients with BEC 150–299 cells/μL.

**Methods:** This *post-hoc* analysis of pooled data from Phase III SIROCCO (*Lancet* 2016;388:2115–27) and CALIMA (*Lancet* 2016;388:2128–41) trials evaluated baseline factors of oral corticosteroid (OCS) use, history of nasal polyposis (NP), prebronchodilator forced vital capacity (FVC) <65% predicted, ≥3 exacerbations during the year before enrollment, and asthma diagnosis at ≥18 years of age. Pooled benralizumab Q4W and Q8W data were compared with placebo.

**Results:** Baseline factors of ≥3 prior exacerbations, OCS use, and history of NP were associated with enhanced exacerbation rate reduction (rate ratio [95% confidence interval {CI}], n=benralizumab/placebo): 0.57 (0.34, 0.97), n=58/35; 0.49 (0.24, 1.04), n=21/14; and 0.34 (0.11, 1.02), n=22/12, respectively, compared with the total subpopulation: 0.59 (0.40, 0.88), n=190/88. Baseline factors of ≥3 prior exacerbations, OCS use, FVC <65% predicted, and asthma diagnosis at ≥18 years of age were associated with enhanced improvement in prebronchodilator forced expiratory volume in 1 second (difference vs. placebo [L] [95% CI], n=benralizumab/placebo): 0.116 (–0.016, 0.249), n=58/35; 0.130 (–0.078, 0.337), n=21/14; 0.214 (0.048, 0.380), n=30/27; and 0.142 (0.048, 0.235), n=139/54, respectively, compared with the total subpopulation: 0.101 (0.016, 0.186), n=190/88.

**Conclusions:** Exacerbation history, OCS use, history of NP, FVC, and age at asthma diagnosis are associated with enhanced benralizumab efficacy for patients with severe, uncontrolled asthma and moderate eosinophilia.

## Rationale

- Baseline clinical factors and blood eosinophil counts (BEC) can help guide clinical decisions on the use of benralizumab in patients with severe, uncontrolled asthma[1,2]
- In an analysis of pooled data from the global Phase III SIROCCO (NCT01928771) and CALIMA (NCT01914757) trials, oral corticosteroid (OCS) use, nasal polyposis (NP), prebronchodilator forced vital capacity (FVC) <65% of predicted, more frequent exacerbations (≥3 in the previous year), and age at diagnosis of ≥18 years were predictors of enhanced response to benralizumab Q8W treatment for reducing exacerbations and increasing lung function in the overall patient population and those with BEC ≥300 cells/μL[1]
- For patients with BEC <300 cells/μL, OCS use, NP, and prebronchodilator FVC <65% of predicted were associated with greater benralizumab Q8W responsiveness for reducing exacerbations, whereas NP was the most important factor for influencing responsiveness for increasing lung function[1]
- The BORA extension study enrolled patients who had completed the 48-week SIROCCO or the 56-week CALIMA trial and provided a 2-year integrated efficacy and safety analysis supporting the use of benralizumab for long-term maintenance of exacerbation frequency reductions and lung function improvements[3,4]

## Aim

- The aim of this *post-hoc* analysis was to evaluate the influence of baseline clinical factors on benralizumab response through 2 years of treatment by blood eosinophil subgroup (150–299 cells/μL and ≥300 cells/μL) for patients who participated in the SIROCCO/CALIMA studies and BORA.

## Methods

### Study Design and Participants

- SIROCCO (N=1,204) and CALIMA (N=1,306) were randomized, double-blind, parallel-group, placebo-controlled Phase III studies with a treatment period of 48 (SIROCCO) or 56 (CALIMA) weeks
- Patients were randomized 1:1:1 to receive subcutaneous benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses Q4W), or placebo Q4W
- Patients with BEC ≥300 cells/μL and <300 cells/μL were randomized in a ratio of 2:1, respectively
- In this 2-year integrated analysis, patients aged ≥12 years treated with high-dosage inhaled corticosteroids/long-acting $\beta_2$-agonists (ICS/LABA) (defined as fluticasone ≥500 μg/day or equivalent total daily dosage) and benralizumab Q4W or Q8W who were originally in SIROCCO or CALIMA and moved into BORA were evaluated. Placebo-treated patients in SIROCCO and CALIMA were randomized to benralizumab Q4W or Q8W when they entered BORA and are excluded from the 2-year integrated analysis.
- Baseline patient factors previously identified as predictors of enhanced responses to benralizumab[1,2] were selected for evaluation in this study
- Analyses were performed for OCS use at baseline (yes/no); presence of NP (yes/no); prebronchodilator FVC categories of <65% and ≥65% of predicted; exacerbations in the 12 months before enrollment categories of 2 and ≥3; and age at diagnosis categories of <18 and ≥18 years. Subgroups analyzed within these categories were BEC ≥300 cells/μL and 150–299 cells/μL).

### Outcomes

- The primary efficacy endpoint was annual asthma exacerbation rate (AER)
- Secondary endpoints included change from baseline at end of treatment in prebronchodilator forced expiratory volume in 1 second ($FEV_1$)

### Statistical Analysis of Endpoints

- Exacerbation rates were evaluated using a negative binomial model with covariate adjustments for treatment and study. The rate ratio of benralizumab vs. placebo, corresponding 95% confidence intervals (CI), and two-sided *p*-values 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.
- Prebronchodilator $FEV_1$ was determined using a mixed-effects model for repeated measures analysis with covariant adjustment. Least squares (LS) means, treatment differences in LS means, 95% CIs, and *p*-values were calculated.
- Benralizumab Q4W and Q8W treatment groups had similar efficacy on exacerbation rate reduction and improvement in $FEV_1$ and were pooled in this analysis. The full analysis set (FAS) included patients who completed SIROCCO/CALIMA and received at least one dose of benralizumab in BORA.
- Because these analyses were not part of the formal testing strategy, all *p*-values were nominal
- Statistical calculations were performed using SAS versions 9.2, 9.3, and 9.4

## Results

### Demographics and Baseline Clinical Characteristics

Patients with blood eosinophil counts ≥300 cells/μL and 150–299 cells/μL had similar baseline characteristics, including most of the clinical factors evaluated for influencing benralizumab efficacy: OCS use, prebronchodilator FVC <65% of predicted, ≥3 exacerbations in the previous year, and age at diagnosis of ≥18 years. A higher proportion of patients in the ≥300 cells/μL subgroup had a history of NP (**Table 1**).

**Table 1. Patient Demographics and Baseline Clinical Characteristics of 2-Year Integrated Analysis Patients (FAS, Pooled[a])**

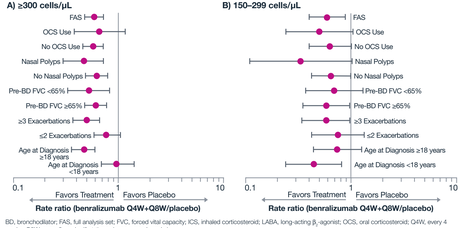
| | Overall (N=1576) | BEC ≥300 cells/μL (n=979) | BEC 150–299 cells/μL (n=278) |
|---|---|---|---|
| Age [years], mean (SD) | 48.9 (14.7) | 48.2 (14.5) | 50.7 (14.5) |
| Sex, n (%) | | | |
| Male | 603 (38) | 385 (39) | 105 (38) |
| Female | 973 (62) | 594 (61) | 173 (62) |
| Race, n (%) | | | |
| White | 1,207 (77) | 736 (75) | 234 (84) |
| Black or African-American | 35 (2) | 22 (2) | 8 (3) |
| Asian | 275 (17) | 165 (17) | 34 (12) |
| Other[b] | 59 (4) | 56 (6) | 2 (1) |
| BMI [kg/m$^2$], mean (SD) | 28.6 (6.6) | 28.5 (6.7) | 29.3 (6.5) |
| BEC [cells/μL], median (range) | 350 (0–4150) | 470 (0–4150) | 200 (10–880) |
| Prebronchodilator $FEV_1$ [L], mean (SD) | 1.7 (0.6) | 1.7 (0.6) | 1.7 (0.6) |
| Prebronchodilator $FEV_1$ [% predicted normal], mean (SD) | 57.9 (14.6) | 57.7 (14.2) | 58.0 (14.7) |
| Prebronchodilator $FEV_1$/FVC, mean (SD) | 61.0 (12.6) | 61.0 (12.3) | 60.3 (12.3) |
| Reversibility [%], mean (SD) | 25.4 (36.5) | 24.7 (23.1) | 26.8 (52.1) |
| Prebronchodilator FVC [% predicted normal], mean (SD) | 77.0 (15.6) | 76.8 (15.5) | 77.6 (16.3) |
| Time since asthma diagnosis [years], median (range) | 15.2 (1.1–72.4) | 14.8 (1.1–69.9) | 15.0 (1.1–62.5) |
| Age at asthma diagnosis [years], mean (SD) | 30.1 (18.8) | 30.0 (18.5) | 31.7 (20.2) |
| Number of exacerbations in the last 12 months, mean (SD) | 2.8 (1.6) | 2.8 (1.7) | 2.6 (1.3) |
| Total asthma symptom score, mean (SD) | 2.7 (1.1) | 2.7 (1.0) | 2.7 (1.1) |
| ACQ-6 score, mean (SD) | 2.7 (0.9) | 2.7 (0.9) | 2.7 (0.9) |
| AQLQ(S)+12 score, mean (SD) | 4.0 (1.0) | 3.9 (1.0) | 4.0 (1.0) |
| Nasal polyps, n (%) | 258 (16) | 199 (20) | 34 (12) |
| Atopic, n (%) | 999 (63) | 632 (65) | 174 (63) |
| OCS use, n (%) | 195 (12) | 123 (13) | 35 (13) |

ACQ-6, Asthma Control Questionnaire 6; AQLQ(S)+12, Asthma Quality of Life Questionnaire (standardized) for 12 years and older; BMI, body mass index; FAS, full analysis set; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting $\beta_2$-agonists; OCS, oral corticosteroids; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W); SD, standard deviation.
[a]Pooled population of patients from the SIROCCO and CALIMA studies who received placebo or benralizumab Q4W or Q8W with high-dosage ICS/LABA and who continued into BORA and received at least one dose of benralizumab. Data not available for all randomized patients.
[b]Native Hawaiian or other Pacific Islander, American Indian, or Alaska Native, and Other.

### Baseline Factor Influence on Benralizumab-Mediated AER Reduction by BEC Subgroup

- A greater reduction in AER was observed for the pooled population of patients with BEC ≥300 cells/μL receiving benralizumab Q4W or Q8W and with any baseline clinical factor evaluated compared with the efficacy in the overall full analysis set (FAS), with the exception of OCS use (**Figure 1**)
- For patients with BEC 150–299 cells/μL, OCS use, NP, and more frequent exacerbations had the greatest influence on improvement of AER with benralizumab Q4W and Q8W combined

**Figure 1. Influence of Baseline Factors on Annual Exacerbation Rate Improvements with Benralizumab and High-Dosage ICS/LABA in Year 1 (FAS, Pooled[a])**

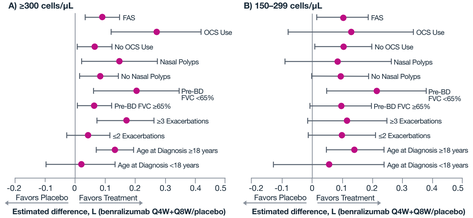



BD, bronchodilator; FAS, full analysis set; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting $\beta_2$-agonist; OCS, oral corticosteroid; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses every 4 weeks).
[a]Data are from the pooled modified intention-to-treat population from the high-dosage ICS/LABA treatment cohorts in SIROCCO and CALIMA (benralizumab Q4W plus Q8W combined). Estimates were calculated by using a negative binomial model with adjustment for study code and treatment group.

### Baseline Factor Influence on Benralizumab-Mediated Lung Function Improvements by BEC Subgroup

- Baseline clinical factors of OCS use, NP, prebronchodilator FVC <65% of predicted, ≥3 prior exacerbations, and age at asthma diagnosis of ≥18 years were all associated with greater lung function improvements with benralizumab Q4W or Q8W in the population of patients with BEC ≥300 cells/μL and those with BEC 150–299 cells/μL, with the exception of NP history in the BEC 150–299 cells/μL subgroup (**Figure 2**)

**Figure 2. Influence of Baseline Factors on Prebronchodilator $FEV_1$ (L) Change (EOT–Baseline) Improvements with Benralizumab and High-Dosage ICS/LABA in Year 1 (FAS, Pooled[a])**

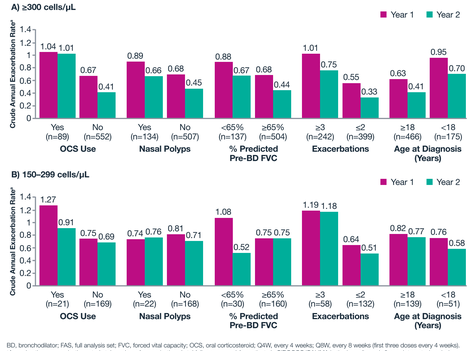



BD, bronchodilator; FAS, full analysis set; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; OCS, oral corticosteroid; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses every 4 weeks).
[a]Data are from the pooled modified intention-to-treat population from the high-dosage ICS/LABA treatment cohorts in SIROCCO and CALIMA (benralizumab Q4W plus Q8W combined). Estimates were calculated by using a negative binomial model with adjustment for study code, treatment group, baseline $FEV_1$, and visit.

### Sustained Efficacy Through 2 Years of Benralizumab Q4W or Q8W Treatment

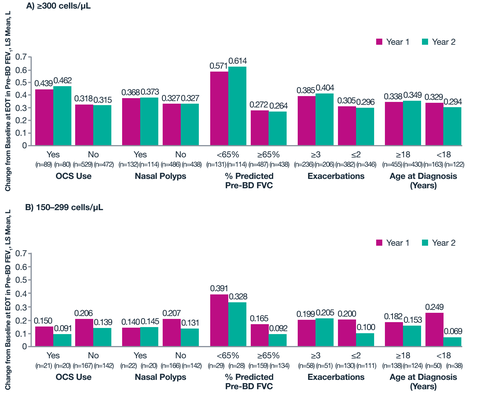
- Efficacy of benralizumab Q4W or Q8W on AER (**Figure 3**) and lung function (**Figure 4**) was generally sustained through 2 years of treatment for both BEC subgroups

**Figure 3. Influence of Baseline Factors on Annual Exacerbation Rate Through 2 Years (FAS, Pooled[a])**




BD, bronchodilator; FAS, full analysis set; FVC, forced vital capacity; OCS, oral corticosteroid; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses every 4 weeks).
[a]Annual asthma exacerbation rate (total number of exacerbations/total follow-up years) for patients in SIROCCO/CALIMA in the benralizumab 2-year integrated analysis (FAS, pooled Q4W/Q8W on-treatment period) through Year 1 (Week 0–48 in SIROCCO and Week 0–56 in CALIMA) and through Year 2 (Week 56–112 in the BORA extension study). Eosinophil subgroup represents counts at baseline of SIROCCO/CALIMA.

**Figure 4. Influence of Baseline Factors on Prebronchodilator $FEV_1$ (L) Change (EOT–Baseline) Through 2 Years (FAS, Pooled[a])**




BD, bronchodilator; EOT, end of treatment; FAS, full analysis set; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; LS, least squares; OCS, oral corticosteroid.
[a]LS mean change from SIROCCO/CALIMA baseline to Year 1 EOT (Week 48 in SIROCCO and Week 56 in CALIMA) and from SIROCCO/CALIMA baseline to Year 2 EOT (Week 56 in BORA) for patients in the benralizumab 2-year integrated analysis.

## Conclusions

- We have previously demonstrated that OCS use, NP, prebronchodilator FVC <65% of predicted, more frequent exacerbations, and age at diagnosis were associated with enhanced benralizumab efficacy for patients with severe, uncontrolled asthma in the pooled analysis of SIROCCO and CALIMA[1]
- In the present analysis, we confirmed that these baseline characteristics were predictors of enhanced response to benralizumab for reducing exacerbations and increasing lung function for the subset of patients with BEC ≥300 cells/μL who had enrolled in the BORA extension study
- The identified predictors were also associated with enhanced response on exacerbation rate reduction and improvement in lung function in patients with baseline BEC 150–299 cells/μL who continued in the BORA study
- Efficacy of benralizumab was sustained during the 2-year treatment period for both eosinophil subgroups, extending previous findings supporting the long-term benefit of benralizumab for patients with severe, uncontrolled asthma and BEC ≥150 cells/μL[5]

### References

**1.** Bleecker ER, et al. *Eur Respir J*. 2018;52:1800936. **2.** FitzGerald JM, et al. *Lancet Respir Med*. 2016;4:51–64. **3.** FitzGerald JM, et al. *J Asthma Allergy*. 2019;12:401–13. **4.** Busse WW, et al. *Lancet Respir Med*. 2019;7:46–59. **5.** Goldman M, et al. *Curr Med Res Opin*. 2017;33:1605–13.

### Acknowledgments and Disclosures

This analysis was funded by AstraZeneca.
**Peter Barker**, **James L. Kreindler**, and **Paul Newbold** are employees of AstraZeneca.
Editorial support was provided by Kay Square Scientific and **Michael A. Nissen**, ELS, of AstraZeneca.
This support was funded by AstraZeneca.

Presented at the American Academy of Allergy, Asthma & Immunology (AAAAI) Congress March 13–16, 2020, Philadelphia, PA United States