

# Daily patient-reported health status assessment improvements with benralizumab for patients with severe, uncontrolled eosinophilic asthma

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**Background:** Patients with severe, uncontrolled asthma experience debilitating symptoms that result in meaningful reductions to health-related quality of life. Benralizumab is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody that reduces exacerbations and improves asthma symptoms for patients with severe, uncontrolled eosinophilic asthma.

**Objective:** The objective of this study was to evaluate improvements in daily asthma-related health status outcomes following treatment with benralizumab.

**Methods:** Pooled results from the SIROCCO (NCT01928771) and CALIMA (NCT01914757) Phase III studies were analyzed. Patients aged 12–75 years with severe, uncontrolled asthma, and blood eosinophil counts (BEC)  $\geq 300$  and  $\geq 150$  cells/ $\mu\text{L}$  were evaluated. Patients received subcutaneous benralizumab 30 mg every 4 weeks (Q4W) or every 8 weeks (Q8W, first three doses Q4W) or placebo and completed a daily diary reporting rescue medication use, night-time awakening requiring rescue medication use, perceived tiredness, and asthma-related activity impairment. Outcome measures were compared across treatment arms from baseline to end of treatment (EOT) using a mixed-effect model for repeated measures analyses.

**Results:** Patients with BEC  $\geq 300$  cells/ $\mu\text{L}$  receiving benralizumab Q8W had greater improvements in all patient-reported outcomes at EOT relative to baseline than patients receiving placebo (all nominal  $P \leq 0.013$ ). Effects were reported as early as 3 days following the initial dose and sustained throughout treatment for daily and night-time rescue medication use and night-time awakenings requiring rescue medication. For patients with BEC  $\geq 300$  and  $\geq 150$  cells/ $\mu\text{L}$ , sustained improvements in activity impairment items (all nominal  $P < 0.05$ ) were achieved with benralizumab Q8W at week 2.

**Conclusion:** Benralizumab produces sustained reductions by as early as 3 days in rescue medication use and activity impairment for patients with severe, uncontrolled eosinophilic asthma.

**Keywords:** asthma, benralizumab, eosinophils, interleukin-5 receptor, monoclonal antibody, patient-reported outcomes

## Introduction

Patients with severe, uncontrolled asthma experience serious health-related quality of life impairments,<sup>1–4</sup> reporting difficulties in performing daily activities and engaging in social interactions, as well as increased tiredness.<sup>2–5</sup> Patients often make adjustments to their daily activities in response to their asthma symptoms, such as pacing themselves during activities or avoiding activities entirely.<sup>2–4</sup> Difficulties with daily activities can be particularly impactful for patients with severe asthma.<sup>6</sup> Symptoms such as shortness of breath, coughing, and night-time awakenings can occur on a daily basis.<sup>2,5,6</sup> This

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can result in a decrease in patients' health-related quality of life that can be challenging for physicians to manage. Treatments to alleviate symptoms, reduce activity impairment, and improve salient aspects of day-to-day life are needed for patients with severe, uncontrolled asthma.

Benralizumab is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody that has received marketing approval in various countries, including the United States and Europe.<sup>7,8</sup> In the United States, benralizumab is indicated for the add-on maintenance treatment of patients with severe asthma, aged  $\geq 12$  years with an eosinophilic phenotype.<sup>7</sup> Benralizumab targets eosinophilic inflammation by inducing direct, rapid, and nearly complete depletion of eosinophils via enhanced antibody-dependent cell-mediated cytotoxicity, an apoptotic process of eosinophil elimination involving natural killer cells.<sup>9,10</sup> Eosinophilic inflammation is present in 50% of patients with asthma and is associated with decreased lung function and increased disease severity, exacerbation frequency, and symptom burden.<sup>11–13</sup> In two Phase III trials, SIROCCO (NCT01928771) and CALIMA (NCT01914757), benralizumab significantly reduced asthma exacerbations and improved lung function and disease symptom control for patients with severe, uncontrolled asthma and blood eosinophil counts (BECs)  $\geq 300$  cells/ $\mu$ L vs placebo in combination with high-dosage inhaled corticosteroids plus long-acting  $\beta_2$ -agonists (ICS/LABA).<sup>14,15</sup> Benralizumab also improved asthma control and health-related quality of life for these patients, as measured by the Asthma Control Questionnaire 6 (ACQ-6) and the Asthma Quality of Life Questionnaire (standardized) for 12 years and older (AQLQ[S]+12).<sup>14,15</sup>

This study evaluated the effect of benralizumab on daily measures of health status, including rescue medication use, asthma-related activity impairment, and patient-perceived tiredness, for patients with severe, uncontrolled asthma with eosinophilic inflammation through a pooled analysis of the SIROCCO and CALIMA studies.

## Methods

### Study design and participants

SIROCCO and CALIMA were randomized, double-blind, parallel-group, placebo-controlled, global Phase III studies.<sup>14,15</sup> The study design comprised an enrollment visit (week -4), 4-week screening/run-in phase, randomization phase (week 0), 48- (SIROCCO) or 56-week (CALIMA) treatment period, and final follow-up visit 8 (SIROCCO) or 4 (CALIMA) weeks following the end-of-treatment (EOT) period.

Enrollment criteria for the studies have been described previously.<sup>14,15</sup> The studies included male and female patients aged 12–75 years with a weight of  $\geq 40$  kg and physician-diagnosed asthma that required treatment with medium- to high-dosage ICS/LABA for  $\geq 12$  months before enrollment. Inclusion criteria included  $\geq 2$  asthma exacerbations within 12 months before enrollment that required systemic corticosteroid therapy or a temporary increase in the usual maintenance dosage of oral corticosteroid. Patients must also have had documented treatment with high-dosage ICS/LABA ( $>500$   $\mu$ g/d fluticasone propionate or equivalent daily dosage) with or without oral corticosteroids and additional asthma controllers for  $\geq 3$  months before enrollment. Additional inclusion criteria included a pre-bronchodilator FEV<sub>1</sub> of  $<80\%$  predicted ( $<90\%$  predicted for patients aged 12–17 years) at screening (week -3), a documented post-bronchodilator reversibility of  $\geq 12\%$  and  $\geq 200$  mL in FEV<sub>1</sub> within 12 months prior to enrollment or demonstrated at screening, and an ACQ-6 score  $\geq 1.5$  at enrollment. Studies were conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice guidelines, and the ethics committee at each participating site.

In both studies, patients were randomized 1:1:1 to receive either subcutaneous benralizumab 30 mg every 4 weeks (Q4W), benralizumab 30 mg Q4W for the first three doses followed by every 8 weeks (Q8W) for the remainder of the treatment period, or placebo Q4W. Patients with baseline BECs  $\geq 300$  and  $<300$  cells/ $\mu$ L were recruited at a ratio of  $\sim 2:1$ , respectively.

## Outcomes

Patients completed an Asthma Daily Diary twice daily at home using a handheld device. Daily patient-reported outcome (PRO) assessments included daytime and night-time symptoms reported previously,<sup>14,15</sup> as well as daytime and night-time rescue medication use; night-time awakenings requiring rescue medication; activity limitations, activity avoidance, need to self-pace during activities; and perceived tiredness. Content of the Asthma Daily Diary was informed by a previously reported patient interview study that indicated these concepts were salient, distinct, and variable.<sup>3</sup> The Asthma Daily Diary was completed in the morning upon awakening and evening before going to bed from the evening of the screening visit to the last morning of the treatment period (SIROCCO, week 48; CALIMA, week 56). Night-time rescue medication use and night-time

awakenings requiring rescue medication were recorded in the morning diary, whereas daytime rescue medication use, activity impairments, and perceived tiredness were captured in the evening diary.

Patient responses to the three activity impairment questions and the perceived tiredness item were captured using a 5-point categorical response scale of 0–4, in which 0 indicated no limitation/none of the time and 4 indicated totally limited/all of the time. Rescue medication use was recorded as the total number of puffs used in each recall period (night-time and daytime). Daily rescue medication use was the sum of the two daily measures. Night-time awakening requiring rescue medication use was assessed with a yes (1)/no (0) response. Baseline for daily measures was the 10-day period before randomization at week 0. Daily assessments were summarized as biweekly means if  $\geq 7$  of 14 daily assessments were available. On days 3 and 7, 3-day and 7-day averages were calculated if  $\geq 2$  and  $\geq 4$  daily assessments were available, respectively. Night-time awakening requiring rescue medication use was calculated as the percentage of nights with awakening requiring rescue medication use during the summary time periods (ie, 3 days, 7 days, and 2 weeks). Outcome measures consisted of changes in biweekly mean item scores from baseline to EOT and changes in mean item scores from baseline to days 1, 3, and 7 of the study. Analyses were performed for patient populations with BECs  $\geq$  and  $< 300$  cells/ $\mu$ L and  $\geq$  and  $< 150$  cells/ $\mu$ L. Data are reported and discussed for the indicated benralizumab Q8W dosage; results for the benralizumab Q4W dosage are presented in tables and figures to allow for evaluation of data consistency with previous studies.

## Statistical analysis

Analyses were based on the full analysis set according to the intention-to-treat principle for the pooled SIROCCO and CALIMA studies. This set included all randomized patients who received any study treatment and continued participation in the study, regardless of protocol adherence. Analyses were performed with SAS version 9.2 and above (SAS Institute Inc, Cary, NC, USA).

Each PRO measure was compared across treatment arms from baseline to EOT for patients in the pooled data set using a mixed-effect model for repeated measures analysis, with adjustments for treatment, study code, baseline value, region, oral corticosteroids use, visit, and treatment  $\times$  visit. For days 1, 3, and 7 analyses, comparisons across treatment arms used analysis of covariance, with adjustments for treatment, study code, baseline value, oral corticosteroid use, and geographic

region. Least squares (LS) means, treatment differences in LS means, 95% confidence intervals, and *P*-values were calculated. Because these analyses were not part of the formal testing strategy, all *P*-values were nominal. To account for the 2:1 stratification for baseline BECs ( $\geq 300$  and  $< 300$  cells/ $\mu$ L) in analyses for all patients, patients with baseline BECs  $< 300$  cells/ $\mu$ L were reweighted using the ratio of the number of patients with baseline BECs  $\geq 300$  cells/ $\mu$ L to the number of those who had counts  $< 300$  cells/ $\mu$ L. Similar reweighting was performed for patients with BECs  $< 150$  cells/ $\mu$ L.

## Ethics approval

Before any patient was enrolled, an independent ethics committee or institutional review board at each study center approved the clinical study protocol, and the national regulatory authority either approved the clinical study protocol or received a notification according to local regulations. All patients provided written informed consent at enrollment.

## Results

A total of 1,537 (515 placebo, 516 benralizumab Q4W, 506 benralizumab Q8W) and 1,941 (648 placebo, 647 benralizumab Q4W, 646 benralizumab Q8W) patients with BECs  $\geq 300$  and  $\geq 150$  blood cells/ $\mu$ L, respectively, receiving high-dosage ICS/LABA were evaluated from the SIROCCO and CALIMA studies. Demographics and clinical characteristics were similar between the placebo and benralizumab Q8W groups.<sup>14,15</sup> Only the indicated Q8W dosage of benralizumab is discussed here, with Q4W results provided in the Tables 1–5 and Figures 1–4 for completeness, as they were part of the SIROCCO and CALIMA studies.

Improvements from baseline to EOT were observed for all daily PROs for patients receiving benralizumab Q8W and with BECs  $\geq 300$  cells/ $\mu$ L when compared with placebo (all nominal  $P \leq 0.013$ ) (Table 1). Daily rescue medication use was reduced by 0.71 puffs (95% CI:  $-1.12$  to  $-0.29$ , nominal  $P \leq 0.001$ ) with benralizumab Q8W vs placebo. Overall, daily rescue medication use for patients receiving benralizumab Q8W decreased by a mean of 2.93, from 4.4 puffs at baseline to 1.47 puffs at EOT. Changes in daytime and night-time rescue medication use for benralizumab Q8W vs placebo contributed similarly to overall daily use (Table 1). Reductions in daily and night-time rescue medication use began as early as 3 days with benralizumab Q8W, and decreased daytime rescue medication use was observed at 1 week (Table 2). These reductions in rescue medication use were sustained until EOT (Figure 1A–C). Patients in

**Table I** Patient-reported outcome assessment changes from baseline to EOT for patients receiving benralizumab vs placebo and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts  $\geq 300$  cells/ $\mu$ L)

| PRO assessment                                                       | Placebo   | Benralizumab<br>30 mg Q4W | Benralizumab<br>30 mg Q8W |
|----------------------------------------------------------------------|-----------|---------------------------|---------------------------|
| Daily rescue medication use, puffs                                   |           |                           |                           |
| Number of patients analyzed                                          | 514       | 514                       | 500                       |
| Baseline, mean (SD)                                                  | 5.1 (7.0) | 4.6 (5.6)                 | 4.4 (4.1)                 |
| LS mean change from baseline                                         | -2.23     | -2.45                     | -2.93                     |
| Difference vs placebo (95% CI)                                       | -         | -0.22 (-0.63 to 0.19)     | -0.71 (-1.12 to -0.29)    |
| Nominal <i>P</i> vs placebo                                          | -         | 0.287                     | <0.001                    |
| Night-time rescue medication use, puffs per night                    |           |                           |                           |
| Number of patients analyzed                                          | 514       | 515                       | 501                       |
| Baseline, mean (SD)                                                  | 2.1 (3.3) | 1.9 (2.6)                 | 1.9 (2.0)                 |
| LS mean change from baseline                                         | -0.92     | -1.00                     | -1.28                     |
| Difference vs placebo (95% CI)                                       | -         | -0.08 (-0.27 to 0.11)     | -0.36 (-0.56 to -0.17)    |
| Nominal <i>P</i> vs placebo                                          | -         | 0.405                     | <0.001                    |
| Daytime rescue medication use, puffs per day                         |           |                           |                           |
| Number of patients analyzed                                          | 514       | 515                       | 501                       |
| Baseline, mean (SD)                                                  | 3.0 (3.9) | 2.7 (3.1)                 | 2.6 (2.3)                 |
| LS mean change from baseline                                         | -1.28     | -1.44                     | -1.67                     |
| Difference vs placebo (95% CI)                                       | -         | -0.16 (-0.39 to 0.07)     | -0.40 (-0.63 to -0.16)    |
| Nominal <i>P</i> vs placebo                                          | -         | 0.180                     | <0.001                    |
| Percentage of nights with awakenings requiring rescue medication use |           |                           |                           |
| Number of patients analyzed                                          | 514       | 515                       | 501                       |
| Baseline, mean (SD)                                                  | 50% (40%) | 40% (40%)                 | 50% (40%)                 |
| LS mean change from baseline                                         | -34%      | -35%                      | -38%                      |
| Difference vs placebo (95% CI)                                       | -         | -1% (-4% to 2%)           | -4% (-7% to -1%)          |
| Nominal <i>P</i> vs placebo                                          | -         | 0.620                     | 0.013                     |
| Activity limitation                                                  |           |                           |                           |
| Number of patients analyzed                                          | 514       | 515                       | 501                       |
| Baseline, mean (SD)                                                  | 1.8 (0.7) | 1.7 (0.7)                 | 1.8 (0.7)                 |
| LS mean change from baseline                                         | -0.66     | -0.77                     | -0.83                     |
| Difference vs placebo (95% CI)                                       | -         | -0.11 (-0.20 to -0.01)    | -0.16 (-0.26 to -0.07)    |
| Nominal <i>P</i> vs placebo                                          | -         | 0.025                     | <0.001                    |
| Activity avoidance                                                   |           |                           |                           |
| Number of patients analyzed                                          | 514       | 515                       | 501                       |
| Baseline, mean (SD)                                                  | 1.8 (0.8) | 1.8 (0.8)                 | 1.8 (0.8)                 |
| LS mean change from baseline                                         | -0.68     | -0.78                     | -0.85                     |
| Difference vs placebo (95% CI)                                       | -         | -0.10 (-0.19 to 0.00)     | -0.16 (-0.26 to -0.06)    |
| Nominal <i>P</i> vs placebo                                          | -         | 0.060                     | 0.001                     |
| Need to pace oneself                                                 |           |                           |                           |
| Number of patients analyzed                                          | 514       | 515                       | 501                       |
| Baseline, mean (SD)                                                  | 1.9 (0.8) | 1.9 (0.8)                 | 1.9 (0.8)                 |
| LS mean change from baseline                                         | -0.68     | -0.81                     | -0.87                     |
| Difference vs placebo (95% CI)                                       | -         | -0.13 (-0.23 to -0.03)    | -0.19 (-0.30 to -0.09)    |
| Nominal <i>P</i> vs placebo                                          | -         | 0.013                     | <0.001                    |
| Perceived tiredness                                                  |           |                           |                           |
| Number of patients analyzed                                          | 514       | 515                       | 501                       |
| Baseline, mean (SD)                                                  | 1.9 (0.7) | 1.9 (0.7)                 | 1.9 (0.8)                 |
| LS mean change from baseline                                         | -0.67     | -0.74                     | -0.82                     |
| Difference vs placebo (95% CI)                                       | -         | -0.07 (-0.17 to 0.03)     | -0.14 (-0.25 to -0.04)    |
| Nominal <i>P</i> vs placebo                                          | -         | 0.159                     | 0.005                     |

**Notes:** 14-day summary score changes from baseline to EOT. Estimates calculated using a mixed-effect model for repeated measures analysis, with adjustment for treatment, study code, baseline value, region, oral corticosteroid use, visit, and treatment  $\times$  visit.

**Abbreviations:** EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$ -agonists; LS, least squares; PRO, patient-reported outcome; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W).

**Table 2** Patient-reported outcome assessments on days 1, 3, and 7 for patients receiving benralizumab Q8W vs placebo and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts  $\geq 300$  cells/ $\mu$ L)

| PRO assessment                                                       | Day 1   |                       | Day 3 <sup>a</sup> |                        | Day 7 <sup>a</sup> |                        |
|----------------------------------------------------------------------|---------|-----------------------|--------------------|------------------------|--------------------|------------------------|
|                                                                      | Placebo | Benralizumab Q8W      | Placebo            | Benralizumab Q8W       | Placebo            | Benralizumab Q8W       |
| Daily rescue medication use, puffs                                   |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 489     | 478                   | 498                | 486                    | 505                | 490                    |
| LS mean change from baseline                                         | -0.01   | -0.11                 | -0.50              | -0.89                  | -0.78              | -1.19                  |
| Difference vs placebo (95% CI)                                       | -       | -0.10 (-0.47 to 0.28) | -                  | -0.39 (-0.66 to -0.12) | -                  | -0.41 (-0.68 to -0.14) |
| Nominal <i>P</i> vs placebo                                          | -       | 0.608                 | -                  | 0.005                  | -                  | 0.003                  |
| Night-time rescue medication use, puffs per night                    |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 491                   | 505                | 493                    | 508                | 495                    |
| LS mean change from baseline                                         | -0.28   | -0.45                 | -0.29              | -0.54                  | -0.38              | -0.58                  |
| Difference vs placebo (95% CI)                                       | -       | -0.17 (-0.34 to 0.00) | -                  | -0.24 (-0.38 to -0.11) | -                  | -0.20 (-0.33 to -0.07) |
| Nominal <i>P</i> vs placebo                                          | -       | 0.053                 | -                  | <0.001                 | -                  | 0.004                  |
| Daytime rescue medication use, puffs per day                         |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 496     | 487                   | 502                | 495                    | 508                | 498                    |
| LS mean change from baseline                                         | 0.24    | 0.34                  | -0.23              | -0.34                  | -0.40              | -0.62                  |
| Difference vs placebo (95% CI)                                       | -       | 0.11 (-0.17 to 0.39)  | -                  | -0.12 (-0.29 to 0.05)  | -                  | -0.22 (-0.38 to -0.06) |
| Nominal <i>P</i> vs placebo                                          | -       | 0.453                 | -                  | 0.173                  | -                  | 0.006                  |
| Percentage of nights with awakenings requiring rescue medication use |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 491                   | 505                | 493                    | 508                | 495                    |
| LS mean change from baseline                                         | -7%     | -9%                   | -9%                | -13%                   | -12%               | -15%                   |
| Difference vs placebo (95% CI)                                       | -       | -2% (-7% to 2%)       | -                  | -4% (-7% to -1%)       | -                  | -3% (-6% to 0%)        |
| Nominal <i>P</i> vs placebo                                          | -       | 0.367                 | -                  | 0.018                  | -                  | 0.037                  |
| Activity limitation                                                  |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 491                   | 505                | 493                    | 508                | 495                    |
| LS mean change from baseline                                         | -0.06   | -0.03                 | -0.14              | -0.18                  | -0.21              | -0.25                  |
| Difference vs placebo (95% CI)                                       | -       | 0.03 (-0.04 to 0.10)  | -                  | -0.04 (-0.09 to 0.02)  | -                  | -0.04 (-0.09 to 0.02)  |
| Nominal <i>P</i> vs placebo                                          | -       | 0.410                 | -                  | 0.217                  | -                  | 0.166                  |
| Activity avoidance                                                   |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 491                   | 505                | 493                    | 508                | 495                    |
| LS mean change from baseline                                         | -0.13   | -0.05                 | -0.19              | -0.19                  | -0.25              | -0.28                  |
| Difference vs placebo (95% CI)                                       | -       | 0.08 (0.01 to 0.15)   | -                  | -0.00 (-0.06 to 0.06)  | -                  | -0.03 (-0.08 to 0.03)  |
| Nominal <i>P</i> vs placebo                                          | -       | 0.027                 | -                  | 0.914                  | -                  | 0.375                  |
| Need to pace oneself                                                 |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 491                   | 505                | 493                    | 508                | 495                    |
| LS mean change from baseline                                         | -0.11   | -0.06                 | -0.19              | -0.22                  | -0.24              | -0.29                  |
| Difference vs placebo (95% CI)                                       | -       | 0.05 (-0.03 to 0.12)  | -                  | -0.03 (-0.10 to 0.03)  | -                  | -0.05 (-0.11 to 0.01)  |
| Nominal <i>P</i> vs placebo                                          | -       | 0.192                 | -                  | 0.267                  | -                  | 0.123                  |
| Perceived tiredness                                                  |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 491                   | 505                | 493                    | 508                | 495                    |
| LS mean change from baseline                                         | -0.06   | -0.01                 | -0.15              | -0.18                  | -0.23              | -0.26                  |
| Difference vs placebo (95% CI)                                       | -       | 0.05 (-0.02 to 0.12)  | -                  | -0.03 (-0.09 to 0.03)  | -                  | -0.03 (-0.09 to 0.03)  |
| Nominal <i>P</i> vs placebo                                          | -       | 0.187                 | -                  | 0.310                  | -                  | 0.283                  |

**Notes:** <sup>a</sup>3-day and 7-day averages were calculated when  $\geq 2$  and  $\geq 4$  daily assessments were available, respectively. Estimates calculated using an analysis of covariance, with adjustment for treatment, study code, baseline value, region, and oral corticosteroid use.

**Abbreviations:** ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$ -agonists; LS, least squares; PRO, patient-reported outcome; Q8W, every 8 weeks (first three doses every 4 weeks).

the benralizumab Q8W and placebo groups with BECs  $\geq 300$  cells/ $\mu$ L experienced night-time awakenings requiring rescue medication use on 50% of nights during the baseline period, which was reduced to 12% and 16%, respectively, at EOT (Table 1).

Patients receiving benralizumab Q8W showed improvement from baseline to EOT in the three activity impairment items and perceived tiredness compared with those receiving placebo (Table 1). The reduction in activity impairments in favor of benralizumab Q8W was observed as soon as week 2

**Table 3** Patient-reported outcome assessment changes from baseline to EOT for patients receiving benralizumab vs placebo and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts  $\geq 150$  cells/ $\mu$ L)

| PRO assessment                                                       | Placebo   | Benralizumab<br>30 mg Q4W | Benralizumab<br>30 mg Q8W |
|----------------------------------------------------------------------|-----------|---------------------------|---------------------------|
| Daily rescue medication use, puffs                                   |           |                           |                           |
| Number of patients analyzed                                          | 647       | 645                       | 637                       |
| Baseline, mean (SD)                                                  | 2.9 (3.7) | 2.7 (3.0)                 | 2.7 (2.4)                 |
| LS mean change from baseline                                         | -2.13     | -2.48                     | -2.58                     |
| Difference vs placebo (95% CI)                                       | -         | -0.35 (-0.73 to 0.02)     | -0.45 (-0.82 to -0.07)    |
| Nominal <i>P</i> vs placebo                                          | -         | 0.063                     | 0.019                     |
| Night-time rescue medication use, puffs per night                    |           |                           |                           |
| Number of patients analyzed                                          | 647       | 646                       | 639                       |
| Baseline, mean (SD)                                                  | 2.0 (3.1) | 2.0 (2.5)                 | 1.9 (2.0)                 |
| LS mean change from baseline                                         | -0.92     | -1.03                     | -1.08                     |
| Difference vs placebo (95% CI)                                       | -         | -0.11 (-0.28 to 0.06)     | -0.16 (-0.33 to 0.02)     |
| Nominal <i>P</i> vs placebo                                          | -         | 0.211                     | 0.075                     |
| Daytime rescue medication use, puffs per day                         |           |                           |                           |
| Number of patients analyzed                                          | 647       | 646                       | 642                       |
| Baseline, mean (SD)                                                  | 2.9 (3.7) | 2.7 (3.0)                 | 2.7 (2.4)                 |
| LS mean change from baseline                                         | -1.17     | -1.45                     | -1.44                     |
| Difference vs placebo (95% CI)                                       | -         | -0.27 (-0.50 to -0.05)    | -0.27 (-0.49 to -0.05)    |
| Nominal <i>P</i> vs placebo                                          | -         | 0.015                     | 0.016                     |
| Percentage of nights with awakenings requiring rescue medication use |           |                           |                           |
| Number of patients analyzed                                          | 647       | 644                       | 639                       |
| Baseline, mean (SD)                                                  | 50% (40%) | 50% (40%)                 | 50% (40%)                 |
| LS mean change from baseline                                         | -34%      | -35%                      | -36%                      |
| Difference vs placebo (95% CI)                                       | -         | -1% (-4% to 2%)           | -2% (-5% to 1%)           |
| Nominal <i>P</i> vs placebo                                          | -         | 0.391                     | 0.116                     |
| Activity limitation                                                  |           |                           |                           |
| Number of patients analyzed                                          | 647       | 646                       | 639                       |
| Baseline, mean (SD)                                                  | 1.7 (0.7) | 1.7 (0.7)                 | 1.8 (0.7)                 |
| LS mean change from baseline                                         | -0.59     | -0.75                     | -0.73                     |
| Difference vs placebo (95% CI)                                       | -         | -0.17 (-0.25 to -0.08)    | -0.14 (-0.23 to -0.06)    |
| Nominal <i>P</i> vs placebo                                          | -         | <0.001                    | <0.001                    |
| Activity avoidance                                                   |           |                           |                           |
| Number of patients analyzed                                          | 647       | 646                       | 639                       |
| Baseline, mean (SD)                                                  | 1.8 (0.8) | 1.8 (0.8)                 | 1.8 (0.8)                 |
| LS mean change from baseline                                         | -0.60     | -0.77                     | -0.75                     |
| Difference vs placebo (95% CI)                                       | -         | -0.17 (-0.26 to -0.08)    | -0.15 (-0.24 to -0.06)    |
| Nominal <i>P</i> vs placebo                                          | -         | <0.001                    | <0.001                    |
| Need to pace oneself                                                 |           |                           |                           |
| Number of patients analyzed                                          | 647       | 646                       | 639                       |
| Baseline, mean (SD)                                                  | 1.9 (0.8) | 1.9 (0.8)                 | 1.9 (0.8)                 |
| LS mean change from baseline                                         | -0.59     | -0.79                     | -0.76                     |
| Difference vs placebo (95% CI)                                       | -         | -0.20 (-0.29 to -0.11)    | -0.17 (-0.26 to -0.08)    |
| Nominal <i>P</i> vs placebo                                          | -         | <0.001                    | <0.001                    |
| Perceived tiredness                                                  |           |                           |                           |
| Number of patients analyzed                                          | 647       | 646                       | 639                       |
| Baseline, mean (SD)                                                  | 1.9 (0.7) | 1.9 (0.7)                 | 1.9 (0.8)                 |
| LS mean change from baseline                                         | -0.61     | -0.72                     | -0.71                     |
| Difference vs placebo (95% CI)                                       | -         | -0.11 (-0.20 to -0.02)    | -0.10 (-0.19 to -0.01)    |
| Nominal <i>P</i> vs placebo                                          | -         | 0.015                     | 0.026                     |

**Notes:** 14-day summary score change from baseline to EOT. Estimates calculated using a mixed-effect model for repeated measures analysis, with adjustment for treatment, study code, baseline value, region, oral corticosteroid use, visit, and treatment  $\times$  visit. The estimates were weighted to account for the 2:1 randomization ratio of patients with baseline blood eosinophil counts  $\geq 150$  or  $<150$  cells/ $\mu$ L.

**Abbreviations:** EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$ -agonists; LS, least squares; PRO, patient-reported outcome; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W).



**Table 4** Patient-reported outcome assessments on days 1, 3, and 7 for patients receiving benralizumab Q4W vs placebo and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts  $\geq 300$  cells/ $\mu$ L)

| PRO assessment                                                       | Day 1   |                       | Day 3 <sup>a</sup> |                        | Day 7 <sup>a</sup> |                        |
|----------------------------------------------------------------------|---------|-----------------------|--------------------|------------------------|--------------------|------------------------|
|                                                                      | Placebo | Benralizumab Q4W      | Placebo            | Benralizumab Q4W       | Placebo            | Benralizumab Q4W       |
| Daily rescue medication use, puffs                                   |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 489     | 491                   | 498                | 507                    | 505                | 508                    |
| LS mean change from baseline                                         | −0.01   | −0.17                 | −0.50              | −0.94                  | −0.78              | −1.17                  |
| Difference vs placebo (95% CI)                                       | –       | −0.16 (−0.53 to 0.21) | –                  | −0.44 (−0.70 to −0.17) | –                  | −0.39 (−0.65 to −0.12) |
| Nominal <i>P</i> vs placebo                                          | –       | 0.384                 | –                  | 0.001                  | –                  | 0.005                  |
| Night-time rescue medication use, puffs per night                    |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 506                   | 505                | 513                    | 508                | 511                    |
| LS mean change from baseline                                         | −0.28   | −0.39                 | −0.29              | −0.47                  | −0.38              | −0.51                  |
| Difference vs placebo (95% CI)                                       | –       | −0.11 (−0.28 to 0.06) | –                  | −0.18 (−0.31 to −0.04) | –                  | −0.13 (−0.26 to −0.00) |
| Nominal <i>P</i> vs placebo                                          | –       | 0.198                 | –                  | 0.010                  | –                  | 0.048                  |
| Daytime rescue medication use, puffs per day                         |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 496     | 499                   | 502                | 511                    | 508                | 509                    |
| LS mean change from baseline                                         | 0.24    | 0.23                  | −0.23              | −0.44                  | −0.40              | −0.64                  |
| Difference vs placebo (95% CI)                                       | –       | −0.01 (−0.29 to 0.27) | –                  | −0.22 (−0.39 to −0.05) | –                  | −0.24 (−0.39 to −0.08) |
| Nominal <i>P</i> vs placebo                                          | –       | 0.963                 | –                  | 0.012                  | –                  | 0.003                  |
| Percentage of nights with awakenings requiring rescue medication use |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 506                   | 505                | 513                    | 508                | 511                    |
| LS mean change from baseline                                         | −7%     | −9%                   | −9%                | −12%                   | −12%               | −14%                   |
| Difference vs placebo (95% CI)                                       | –       | −2% (−7% to 2%)       | –                  | −3% (−6% to 0%)        | –                  | −2% (−5% to 1%)        |
| Nominal <i>P</i> vs placebo                                          | –       | 0.343                 | –                  | 0.076                  | –                  | 0.135                  |
| Activity limitation                                                  |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 506                   | 505                | 513                    | 508                | 511                    |
| LS mean change from baseline                                         | −0.06   | −0.06                 | −0.14              | −0.17                  | −0.21              | −0.24                  |
| Difference vs placebo (95% CI)                                       | –       | 0.00 (−0.07 to 0.08)  | –                  | −0.02 (−0.08 to 0.03)  | –                  | −0.03 (−0.08 to 0.03)  |
| Nominal <i>P</i> vs placebo                                          | –       | 0.907                 | –                  | 0.417                  | –                  | 0.332                  |
| Activity avoidance                                                   |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 506                   | 505                | 513                    | 508                | 511                    |
| LS mean change from baseline                                         | −0.13   | −0.10                 | −0.19              | −0.21                  | −0.25              | −0.28                  |
| Difference vs placebo (95% CI)                                       | –       | 0.03 (−0.04 to 0.10)  | –                  | −0.02 (−0.08 to 0.04)  | –                  | −0.02 (−0.08 to 0.03)  |
| Nominal <i>P</i> vs placebo                                          | –       | 0.395                 | –                  | 0.575                  | –                  | 0.400                  |
| Need to pace oneself                                                 |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 506                   | 505                | 513                    | 508                | 511                    |
| LS mean change from baseline                                         | −0.11   | −0.08                 | −0.19              | −0.22                  | −0.24              | −0.27                  |
| Difference vs placebo (95% CI)                                       | –       | 0.03 (−0.04 to 0.11)  | –                  | −0.03 (−0.09 to 0.03)  | –                  | −0.03 (−0.09 to 0.03)  |
| Nominal <i>P</i> vs placebo                                          | –       | 0.406                 | –                  | 0.358                  | –                  | 0.328                  |
| Perceived tiredness                                                  |         |                       |                    |                        |                    |                        |
| Number of patients analyzed                                          | 500     | 506                   | 505                | 513                    | 508                | 511                    |
| LS mean change from baseline                                         | −0.06   | −0.00                 | −0.15              | −0.14                  | −0.23              | −0.23                  |
| Difference vs placebo (95% CI)                                       | –       | 0.05 (−0.02 to 0.13)  | –                  | 0.01 (−0.05 to 0.06)   | –                  | −0.00 (−0.06 to 0.05)  |
| Nominal <i>P</i> vs placebo                                          | –       | 0.144                 | –                  | 0.845                  | –                  | 0.870                  |

**Notes:** <sup>a</sup>3-day and 7-day averages were calculated when  $\geq 2$  and  $\geq 4$  daily assessments were available, respectively. Estimates calculated using an analysis of covariance, with adjustment for treatment, study code, baseline value, region, and oral corticosteroid use.

**Abbreviations:** ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$ -agonists; LS, least squares; PRO, patient-reported outcome; Q4W, every 4 weeks.

(Figure 2A–C), whereas continued separation in favor of benralizumab Q8W for perceived tiredness was not achieved until week 26 (Figure 2D).

Patients with BECs  $\geq 150$  cells/ $\mu$ L showed greater improvement in all daily PROs compared with placebo,

except for night-time rescue medication use and night-time awakenings requiring rescue medication use, at EOT with benralizumab Q8W (all nominal  $P < 0.05$ ; Table 3). Consistently greater reductions vs placebo in activity limitation, activity avoidance, and need for self-pacing began after

**Table 5** Patient-reported outcome assessment changes from baseline to EOT for patients receiving benralizumab vs placebo and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts <300 or <150 cells/ $\mu$ L)

| PRO assessment                                                       | Blood eosinophil counts <300 cells/ $\mu$ L |                           |                           | Blood eosinophil counts <150 cells/ $\mu$ L |                          |                           |
|----------------------------------------------------------------------|---------------------------------------------|---------------------------|---------------------------|---------------------------------------------|--------------------------|---------------------------|
|                                                                      | Placebo                                     | Benralizumab 30 mg Q4W    | Benralizumab 30 mg Q8W    | Placebo                                     | Benralizumab 30 mg Q4W   | Benralizumab 30 mg Q8W    |
| Daily rescue medication use, puffs                                   |                                             |                           |                           |                                             |                          |                           |
| Number of patients analyzed                                          | 261                                         | 238                       | 251                       | 121                                         | 99                       | 103                       |
| Baseline, mean (SD)                                                  | 4.8 (5.6)                                   | 4.9 (4.9)                 | 5.1 (5.7)                 | 5.3 (6.4)                                   | 4.5 (4.4)                | 4.4 (6.6)                 |
| LS mean change from baseline                                         | -1.92                                       | -2.35                     | -2.12                     | -1.83                                       | -1.66                    | -2.04                     |
| Difference vs placebo (95% CI)                                       | -                                           | -0.43<br>(-1.04 to 0.19)  | -0.19<br>(-0.80 to -0.42) | -                                           | 0.17<br>(-0.74 to 1.08)  | -0.21<br>(-1.11 to 0.69)  |
| Nominal <i>P</i> vs placebo                                          | -                                           | 0.174                     | 0.532                     | -                                           | 0.716                    | 0.644                     |
| Night-time rescue medication use, puffs per night                    |                                             |                           |                           |                                             |                          |                           |
| Number of patients analyzed                                          | 261                                         | 238                       | 253                       | 121                                         | 99                       | 104                       |
| Baseline, mean (SD)                                                  | 2.0 (2.5)                                   | 2.0 (2.3)                 | 2.1 (2.8)                 | 2.2 (3.0)                                   | 1.8 (2.0)                | 1.9 (3.2)                 |
| LS mean change from baseline                                         | -0.84                                       | -0.99                     | -0.84                     | -0.72                                       | -0.65                    | -0.87                     |
| Difference vs placebo (95% CI)                                       | -                                           | -0.15<br>(-0.44 to 0.13)  | 0.00<br>(-0.28 to 0.28)   | -                                           | 0.07<br>(-0.37 to 0.51)  | -0.16<br>(-0.59 to 0.27)  |
| Nominal <i>P</i> vs placebo                                          | -                                           | 0.295                     | 0.998                     | -                                           | 0.748                    | 0.471                     |
| Daytime rescue medication use, puffs per day                         |                                             |                           |                           |                                             |                          |                           |
| Number of patients analyzed                                          | 261                                         | 240                       | 254                       | 121                                         | 101                      | 105                       |
| Baseline, mean (SD)                                                  | 2.8 (3.2)                                   | 2.8 (2.7)                 | 3.0 (3.1)                 | 3.1 (3.5)                                   | 2.7 (2.6)                | 2.5 (3.5)                 |
| LS mean change from baseline                                         | -1.04                                       | -1.409                    | -1.18                     | -1.06                                       | -1.08                    | -1.17                     |
| Difference vs placebo (95% CI)                                       | -                                           | -0.36<br>(-0.72 to 0.01)  | -0.14<br>(-0.50 to 0.22)  | -                                           | -0.01<br>(-0.52 to 0.49) | -0.11<br>(-0.60 to 0.39)  |
| Nominal <i>P</i> vs placebo                                          | -                                           | 0.056                     | 0.446                     | -                                           | 0.954                    | 0.676                     |
| Percentage of nights with awakenings requiring rescue medication use |                                             |                           |                           |                                             |                          |                           |
| Number of patients analyzed                                          | 261                                         | 238                       | 253                       | 121                                         | 99                       | 104                       |
| Baseline, mean (SD)                                                  | 50% (40%)                                   | 50% (40%)                 | 50% (40%)                 | 50% (40%)                                   | 50% (40%)                | 4% (4%)                   |
| LS mean change from baseline                                         | -33%                                        | -34%                      | -34%                      | -30%                                        | -26%                     | -32%                      |
| Difference vs placebo (95% CI)                                       | -                                           | 0%<br>(-5% to 5%)         | -1%<br>(-6% to 4%)        | -                                           | 4%<br>(-4% to 12%)       | -2%<br>(-10% to 6%)       |
| Nominal <i>P</i> vs placebo                                          | -                                           | 0.932                     | 0.771                     | -                                           | 0.324                    | 0.603                     |
| Activity limitation                                                  |                                             |                           |                           |                                             |                          |                           |
| Number of patients analyzed                                          | 261                                         | 238                       | 253                       | 121                                         | 99                       | 104                       |
| Baseline, mean (SD)                                                  | 1.7 (0.7)                                   | 1.8 (0.8)                 | 1.9 (0.8)                 | 1.8 (0.7)                                   | 1.9 (0.9)                | 1.8 (0.8)                 |
| LS mean change from baseline                                         | -0.42                                       | -0.59                     | -0.60                     | -0.38                                       | -0.40                    | -0.64                     |
| Difference vs placebo (95% CI)                                       | -                                           | -0.17<br>(-0.31 to -0.04) | -0.18<br>(-0.31 to -0.05) | -                                           | -0.02<br>(-0.20 to 0.15) | -0.26<br>(-0.44 to -0.08) |
| Nominal <i>P</i> vs placebo                                          | -                                           | 0.011                     | 0.008                     | -                                           | 0.792                    | 0.004                     |
| Activity avoidance                                                   |                                             |                           |                           |                                             |                          |                           |
| Number of patients analyzed                                          | 261                                         | 238                       | 253                       | 121                                         | 99                       | 104                       |
| Baseline, mean (SD)                                                  | 1.8 (0.8)                                   | 1.9 (0.9)                 | 1.9 (0.8)                 | 1.9 (0.8)                                   | 1.9 (0.9)                | 1.9 (0.9)                 |
| LS mean change from baseline                                         | -0.43                                       | -0.61                     | -0.62                     | -0.42                                       | -0.39                    | -0.62                     |
| Difference vs placebo (95% CI)                                       | -                                           | -0.18<br>(-0.32 to -0.04) | -0.19<br>(-0.33 to -0.05) | -                                           | 0.03<br>(-0.19 to 0.25)  | -0.20<br>(-0.42 to 0.02)  |
| Nominal <i>P</i> vs placebo                                          | -                                           | 0.014                     | 0.009                     | -                                           | 0.789                    | 0.069                     |
| Need to pace oneself                                                 |                                             |                           |                           |                                             |                          |                           |
| Number of patients analyzed                                          | 261                                         | 238                       | 253                       | 121                                         | 99                       | 104                       |
| Baseline, mean (SD)                                                  | 1.9 (0.8)                                   | 2.0 (0.9)                 | 2.0 (0.8)                 | 2.0 (0.9)                                   | 2.0 (0.9)                | 2.0 (0.9)                 |
| LS mean change from baseline                                         | -0.42                                       | -0.61                     | -0.62                     | -0.41                                       | -0.41                    | -0.68                     |
| Difference vs placebo (95% CI)                                       | -                                           | -0.19<br>(-0.33 to -0.04) | -0.20<br>(-0.34 to -0.05) | -                                           | 0.01<br>(-0.19 to 0.20)  | -0.26<br>(-0.46 to -0.07) |
| Nominal <i>P</i> vs placebo                                          | -                                           | 0.011                     | 0.008                     | -                                           | 0.944                    | 0.008                     |

(Continued)

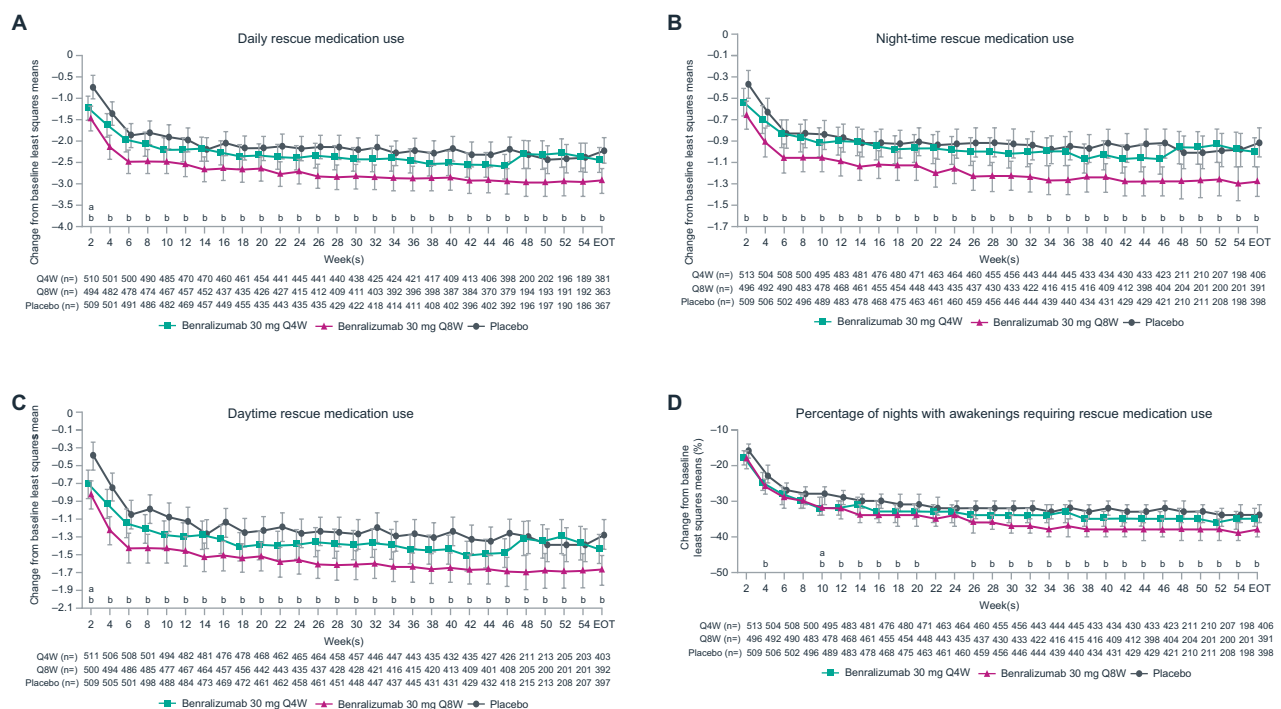


Table 5 (Continued)

| PRO assessment                 | Blood eosinophil counts <300 cells/ $\mu$ L |                          |                          | Blood eosinophil counts <150 cells/ $\mu$ L |                         |                          |
|--------------------------------|---------------------------------------------|--------------------------|--------------------------|---------------------------------------------|-------------------------|--------------------------|
|                                | Placebo                                     | Benralizumab 30 mg Q4W   | Benralizumab 30 mg Q8W   | Placebo                                     | Benralizumab 30 mg Q4W  | Benralizumab 30 mg Q8W   |
| Perceived tiredness            |                                             |                          |                          |                                             |                         |                          |
| Number of patients analyzed    | 261                                         | 238                      | 253                      | 121                                         | 99                      | 104                      |
| Baseline, mean (SD)            | 1.9 (0.8)                                   | 2.0 (0.8)                | 2.0 (0.8)                | 2.0 (0.8)                                   | 2.1 (0.9)               | 2.0 (0.8)                |
| LS mean change from baseline   | −0.51                                       | −0.58                    | −0.62                    | −0.50                                       | −0.40                   | −0.69                    |
| Difference vs placebo (95% CI) | —                                           | −0.06<br>(−0.21 to 0.08) | −0.11<br>(−0.25 to 0.03) | —                                           | 0.11<br>(−0.12 to 0.33) | −0.19<br>(−0.41 to 0.03) |
| Nominal <i>P</i> vs placebo    | —                                           | 0.379                    | 0.129                    | —                                           | 0.349                   | 0.086                    |

**Notes:** 14-day summary score change from baseline to EOT. Estimates calculated using a mixed-effect model for repeated measures analysis, with adjustment for treatment, study code, baseline value, region, oral corticosteroids use, visit, and treatment  $\times$  visit.

**Abbreviations:** EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$ -agonists; LS, least squares; PRO, patient-reported outcome; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W).



**Figure 1** Reduction in rescue medication use with benralizumab and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts  $\geq 300$  cells/ $\mu$ L).

**Notes:** \*Nominal  $P < 0.05$  benralizumab Q4W vs placebo. <sup>b</sup>Nominal  $P < 0.05$  benralizumab Q8W vs placebo. Error bars represent 95% CI. Estimates calculated using a mixed-effect model for repeated measures analysis, with adjustments for treatment, study code, baseline value, region, oral corticosteroid use, visit, and treatment  $\times$  visit.

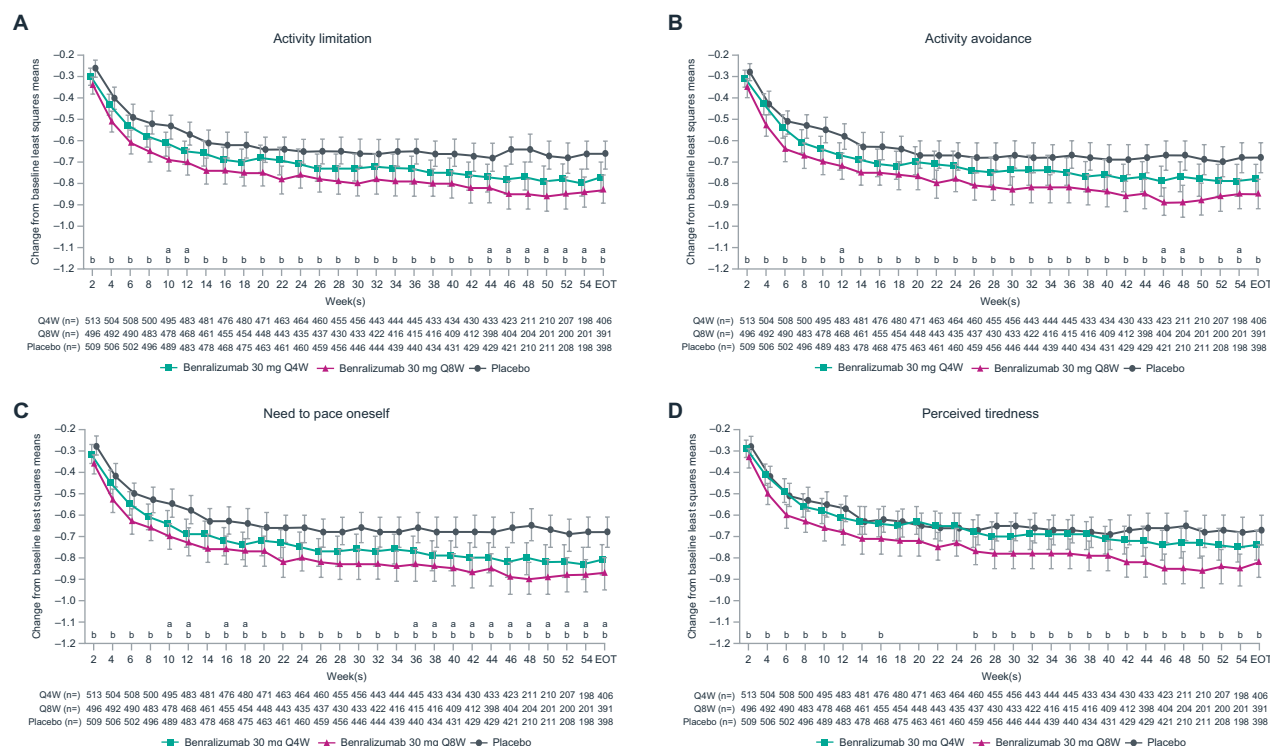
**Abbreviations:** EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$ -agonists; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W).

2 weeks with benralizumab Q8W (all nominal  $P < 0.05$ ; Figure 4A–C). Changes in daily PROs from baseline to EOT for patients with BECs  $< 300$  or  $< 150$  cells/ $\mu$ L were greater in the benralizumab Q8W group compared with placebo (Table 5). However, these differences were less than those observed for groups with BECs  $\geq 300$  or  $\geq 150$  cells/ $\mu$ L.

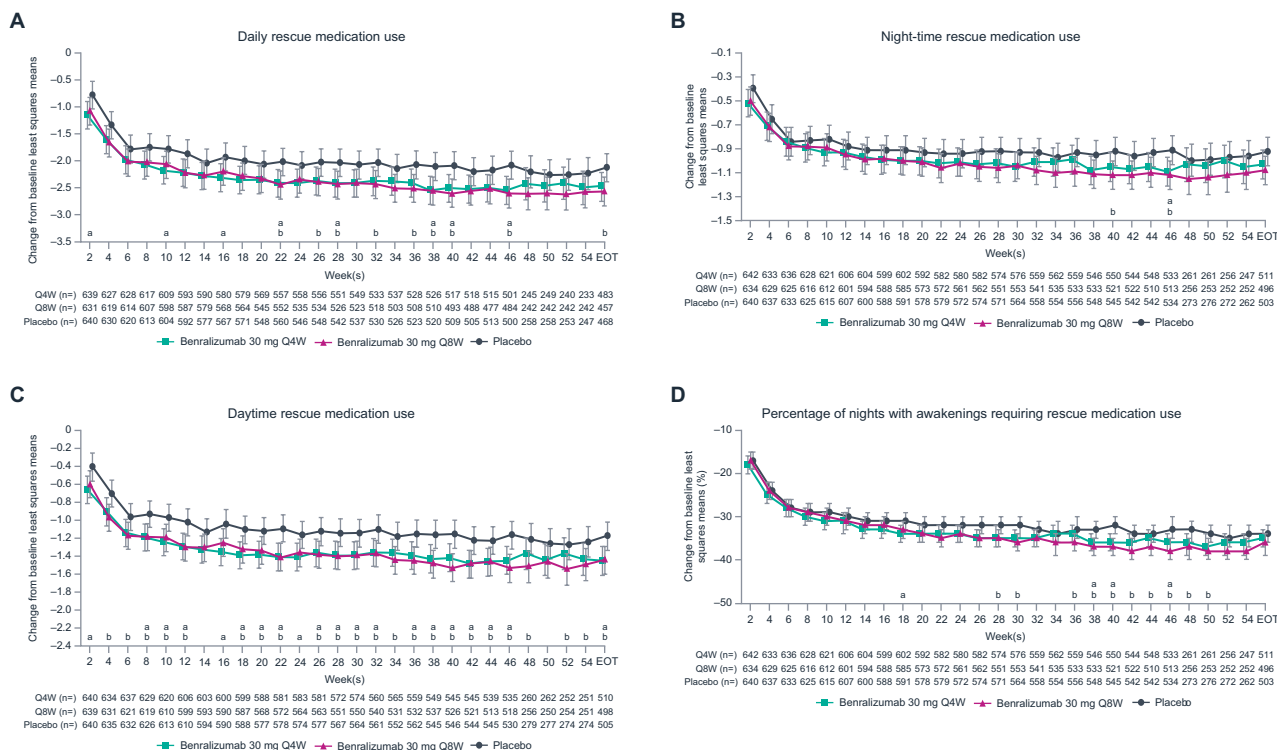
## Discussion

Patients with severe, uncontrolled asthma experience debilitating symptoms that result in meaningful reductions

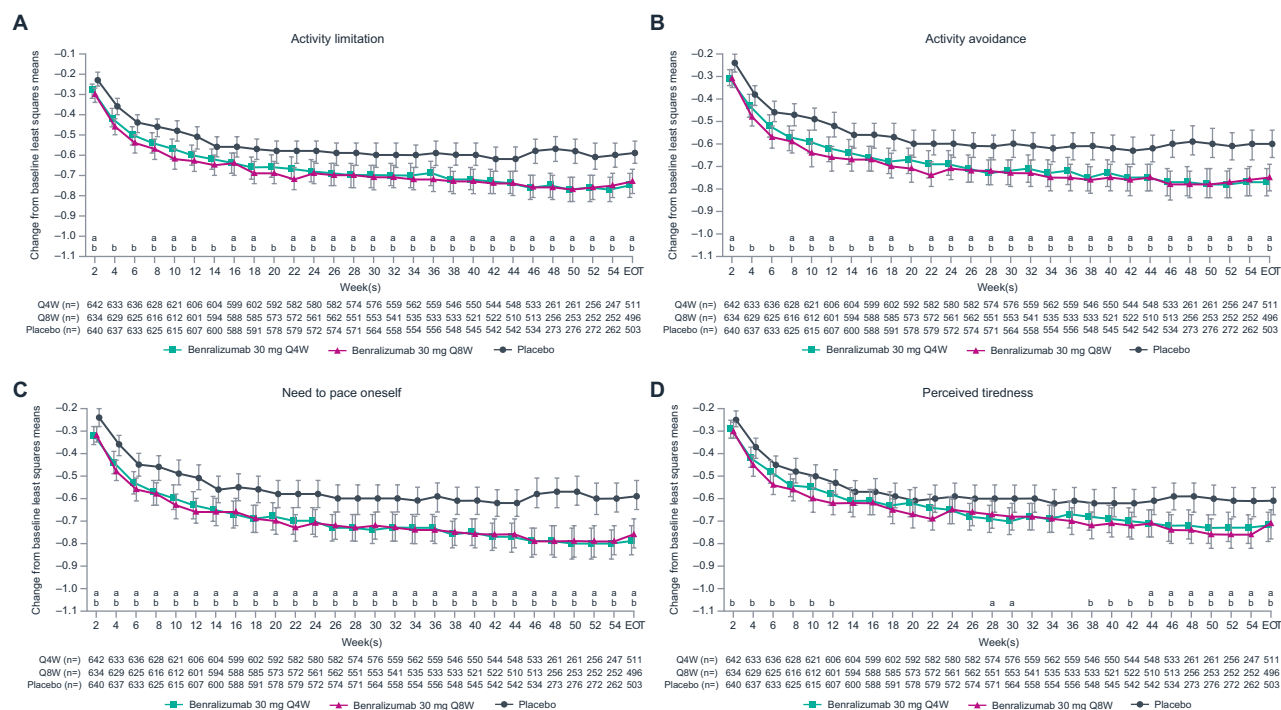
to health-related quality of life. Asthma symptoms compromise a patient's ability to perform day-to-day activities and sleep without interruption, and this can manifest as increased feelings of tiredness, anxiety, and depression.<sup>3</sup> Patients often have to pace themselves during activities or avoid activities as a response to symptoms or as a way to pre-emptively avoid symptom worsening.<sup>3</sup> Treatments that provide symptom relief for patients with severe, uncontrolled asthma need to demonstrate benefits for patients' well-being and ability to perform daily activities. In this study, we demonstrate that



**Figure 2** Improvement in patient-reported outcomes with benralizumab and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts  $\geq 300$  cells/ $\mu$ L)  
**Notes:** \*Nominal  $P < 0.05$  benralizumab Q4W vs placebo. \*Nominal  $P < 0.05$  benralizumab Q8W vs placebo. Error bars represent 95% CI. Estimates calculated using a mixed-effect model for repeated measures analysis, with adjustments for treatment, study code, baseline value, region, oral corticosteroid use, visit, and treatment  $\times$  visit.  
**Abbreviations:** EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$ -agonists; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W).



**Figure 3** Reduction in rescue medication use with benralizumab and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts  $\geq 150$  cells/ $\mu$ L).  
**Notes:** \*Nominal  $P < 0.05$  benralizumab Q4W vs placebo. \*Nominal  $P < 0.05$  benralizumab Q8W vs placebo. Error bars represent 95% CI. Estimates calculated using a mixed-effect model for repeated measures analysis, with adjustments for treatment, study code, baseline value, region, oral corticosteroid use, visit, and treatment  $\times$  visit.  
**Abbreviations:** EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$ -agonists; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W).



**Figure 4** Improvement in patient-reported outcomes with benralizumab and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts  $\geq 150$  cells/ $\mu$ L).

**Notes:** <sup>a</sup>Nominal  $P < 0.05$  benralizumab Q4W vs placebo. <sup>b</sup>Nominal  $P < 0.05$  benralizumab Q8W vs placebo. Error bars represent 95% CI. Estimates calculated using a mixed effect model for repeated measures analysis, with adjustments for treatment, study code, baseline value, region, oral corticosteroid use, visit, and treatment  $\times$  visit.

**Abbreviations:** EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting  $\beta_2$ -agonists; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W).

benralizumab Q8W in combination with high-dosage ICS/LABA can reduce rescue medication use by as early as 3 days and decrease activity impairments for patients with severe, uncontrolled asthma and BECs  $\geq 300$  cells/ $\mu$ L compared with placebo. Reductions in daily and night-time medication use were observed as early as day 3 following treatment with benralizumab Q8W vs placebo. Patient-reported activity limitations, activity avoidance, and need for self-pacing were consistently decreased after 2 weeks.

Results from this study are consistent with reported efficacy results for patients with severe, uncontrolled asthma with eosinophilic inflammation receiving benralizumab Q8W and high-dosage ICS/LABA.<sup>14,15</sup> In both SIROCCO and CALIMA, significant improvements in prebronchodilator FEV<sub>1</sub> occurred after 4 weeks of treatment with benralizumab Q8W relative to placebo for patients with BECs  $\geq 300$  cells/ $\mu$ L.<sup>14,15</sup> Overall assessments of patient-reported symptoms and/or health-related quality of life using total asthma symptom score, ACQ-6, and AQLQ[S]+12 also indicated benefits with benralizumab Q8W vs placebo at EOT.<sup>14,15</sup> Consistent improvements in total asthma symptom score with benralizumab Q8W vs placebo were observed by week 36 (nominal  $P < 0.5$ ) in SIROCCO and CALIMA, while ACQ-6, and AQLQ(S)+12 were not reported.<sup>14,15</sup>

For patients with BECs  $\geq 150$  cells/ $\mu$ L, all daily PROs, except for night-time rescue medication use and awakenings requiring rescue medication use, improved by EOT with benralizumab Q8W. Decreases in activity avoidance and need for self-pacing were reported after 4 weeks. These findings are consistent with previous findings indicating that benralizumab Q8W reduces exacerbations and improves lung function and asthma symptoms for patients with BECs  $\geq 150$  cells/ $\mu$ L.<sup>16,17</sup> Changes in daily PROs for patients with BECs  $< 150$  or  $< 300$  cells/ $\mu$ L receiving benralizumab Q8W were directionally consistent with those observed for patients with BECs  $\geq 150$  or  $\geq 300$  cells/ $\mu$ L. These findings suggest that BECs may not be an absolute predictor for benralizumab responsiveness. Although BECs are a practical and reliable surrogate measure for eosinophilic airway inflammation, the measure may lack specificity at low BECs.<sup>18–20</sup> For patients with low BECs, additional baseline factors may be needed to identify patients who may respond to benralizumab.

To the best of our knowledge, this is the first report evaluating the quantitative effect of an asthma biologic on daily PROs for patients with asthma at early treatment time points. The use of daily measures has many advantages, including reduced recall bias and improved precision, thus enabling assessment at earlier time points. The use of daily PROs for

evaluating health status is supported by observations that changes in overall health-related quality of life measures, ACQ-6 and AQLQ(S)+12, strongly correlate with changes from baseline to EOT in daily activity impairment and perceived tiredness and moderately correlate with changes in rescue medication use and night-time awakenings.<sup>21</sup> Validated daily PRO measurements that reflect early and sustained responses to benralizumab will be important in obtaining a more complete efficacy profile of benralizumab, and potentially other drugs, early in treatment.

Previously, the humanized anti-interleukin-5 monoclonal antibodies mepolizumab and reslizumab were evaluated for improvements in health-related quality of life measures for patients with severe asthma with eosinophilic inflammation.<sup>22,23</sup> Improvements were observed as early as 12 and 16 weeks with mepolizumab and reslizumab, respectively.<sup>22,23</sup>

This study has some limitations. First, this post hoc analysis was not designed to compare daily PRO changes between different BEC groups or the two benralizumab treatment cohorts. Second, improvements for patients in the placebo group may be explained by their participation in a clinical trial. Patients in clinical trials receive more intensive treatment and are closely monitored. Also, being in a clinical trial may, from a psychological aspect, positively influence a patient's perceived tiredness and activity impairment. Several studies have demonstrated that patients respond positively to a placebo agent or sham procedure in a clinical trial based on perceived benefit.<sup>24–26</sup> In a study of bronchial thermoplasty treatment for severe asthma, 64% of patients undergoing a sham procedure reported improvements in health-related quality of life.<sup>25</sup> Wechsler et al demonstrated that although significant objective improvements were achieved for patients with asthma receiving albuterol vs placebo, subjective improvements of 45%–50% were reported by patients receiving either albuterol or placebo.<sup>26</sup>

## Conclusion

Benralizumab Q8W reduces rescue medication use by as early as 3 days and decreases activity impairment and perceived tiredness, as reported by patients with severe, uncontrolled asthma with eosinophilic inflammation.

## Data availability

Registry URL and database number:

SIROCCO trial: NCT01928771 (URL: <https://clinicaltrials.gov/ct2/show/NCT01928771>)

CALIMA trial: NCT01914757 (URL: <https://clinicaltrials.gov/ct2/show/NCT01914757>)

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## Author contributions

Sean O'Quinn, Xiao Xu, and Ian Hirsch were involved in the conception and design, data acquisition, analysis, and interpretation for the study. All authors participated in the preparation of the manuscript and gave final approval of the version of the manuscript for publication. All authors agreed to be accountable for all aspects of the work.

## Disclosure

Sean O'Quinn, Xiao Xu, and Ian Hirsch are employees of AstraZeneca.

## References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention. Available from: <http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed April 5, 2018.
2. Svedsater H, Roberts J, Patel C, Macey J, Hilton E, Bradshaw L. Life impact and treatment preferences of individuals with asthma and chronic obstructive pulmonary disease: results from qualitative interviews and focus groups. *Adv Ther*. 2017;34(6):1466–1481.
3. McLaurin KK, Pokorsywiniski R, O'Quinn S, Xu X, Hareendran A. Conceptualization of symptoms and symptom impacts among adults with inadequately controlled moderate-severe asthma. *Am J Respir Crit Care Med*. 2012;185:A1086.
4. Chipps BE, Haselkorn T, Paknis B, et al. More than a decade follow-up in patients with severe or difficult-to-treat asthma: The epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) II. *J Allergy Clin Immunol*. 2018;141(5):1590–1597.
5. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax*. 1992;47(2):76–83.
6. Nelsen LM, Kimel M, Murray LT, et al. Qualitative evaluation of the St George's respiratory questionnaire in patients with severe asthma. *Respir Med*. 2017;126:32–38.
7. Fasenra™ (benralizumab) prescribing information. Available from: [https://www.azpicentral.com/fasenra/fasenra\\_pi.pdf#page=1](https://www.azpicentral.com/fasenra/fasenra_pi.pdf#page=1). Accessed January 10, 2018.
8. Fasenra™ (benralizumab) summary of product characteristics. Available from: [http://ec.europa.eu/health/documents/community-register/2018/20180108139598/anx\\_139598\\_en.pdf](http://ec.europa.eu/health/documents/community-register/2018/20180108139598/anx_139598_en.pdf). Accessed March 13, 2018.
9. 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(6):1344–1353.

10. Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med*. 2016;111:21–29.
11. Pavord ID. Eosinophilic phenotypes of airway disease. *Ann Am Thorac Soc*. 2013;10 Suppl:S143–S149.
12. 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.
13. 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(1):e005748.
14. 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  $\beta_2$ -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *The Lancet*. 2016;388(10056):2115–2127.
15. 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. *The Lancet*. 2016;388(10056):2128–2141.
16. 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(1):51–64.
17. Goldman M, Hirsch I, Zangrilli JG, Newbold P, Xu X. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies. *Curr Med Res Opin*. 2017;33(9):1605–1613.
18. Fowler SJ, Tavernier G, Niven R. High blood eosinophil counts predict sputum eosinophilia in patients with severe asthma. *J Allergy Clin Immunol*. 2015;135(3):822–824.
19. Hastie AT, Moore WC, Li H, et al. Biomarker surrogates do not accurately predict sputum eosinophil and neutrophil percentages in asthmatic subjects. *J Allergy Clin Immunol*. 2013;132(1):72–80.
20. Wagener AH, de Nijs SB, Lutter R, et al. External validation of blood eosinophils, FE<sub>NO</sub> and serum periostin as surrogates for sputum eosinophils in asthma. *Thorax*. 2015;70(2):115–120.
21. Xu X, O'Quinn S, Hirsch I, Gopalan G. Asthma symptom improvements with benralizumab are associated with improvements in activity functions and health-related quality of life for patients with severe, uncontrolled asthma: results of pooled phase III benralizumab studies. *Am J Respir Crit Care Med*. 2017:A4682.
22. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med*. 2017;5(5):390–400.
23. 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(5):355–366.
24. Dutilleul S, Kaptchuk TJ, Wechsler ME. The placebo effect in asthma. *Curr Allergy Asthma Rep*. 2014;14(8):456.
25. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med*. 2010;181(2):116–124.
26. Wechsler ME, Kelley JM, Boyd IO, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *N Engl J Med*. 2011;365(2):119–126.

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