ORIGINAL RESEARCH

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/μL 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/μL 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/μL, 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,[1–4] reporting difficulties in performing daily activities and engaging in social interactions, as well as increased tiredness.[2–5] Patients often make adjustments to their daily activities in response to their asthma symptoms, such as pacing themselves during activities or avoiding activities entirely.[2–4] Difficulties with daily activities can be particularly impactful for patients with severe asthma.[6] Symptoms such as shortness of breath, coughing, and night-time awakenings can occur on a daily basis.[2,5,6] 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.[7,8] In the United States, benralizumab is indicated for the add-on maintenance treatment of patients with severe asthma, aged ≥12 years with an eosinophilic phenotype.[7] 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.[9,10] 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.[11–13] 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) ≥300 cells/μL vs placebo in combination with high-dosage inhaled corticosteroids plus long-acting β_2-agonists (ICS/LABA).[14,15] 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).[14,15]

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.[14,15] 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.[14,15] The studies included male and female patients aged 12–75 years with a weight of ≥40 kg and physician-diagnosed asthma that required treatment with medium- to high-dosage ICS/LABA for ≥12 months before enrollment. Inclusion criteria included ≥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 μg/d fluticasone propionate or equivalent daily dosage) with or without oral corticosteroids and additional asthma controllers for ≥3 months before enrollment. Additional inclusion criteria included a pre-bronchodilator FEV_1 of <80% predicted (<90% predicted for patients aged 12–17 years) at screening (week –3), a documented post-bronchodilator reversibility of ≥12% and ≥200 mL in FEV_1 within 12 months prior to enrollment or demonstrated at screening, and an ACQ-6 score ≥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 ≥300 and <300 cells/μL were recruited at a ratio of ~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,[14,15] 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.[3] 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 ≥7 of 14 daily assessments were available. On days 3 and 7, 3-day and 7-day averages were calculated if ≥2 and ≥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 ≥ and < 300 cells/µL and ≥ and < 150 cells/µL. 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 × 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 (≥300 and <300 cells/µL) in analyses for all patients, patients with baseline BECs <300 cells/µL were reweighted using the ratio of the number of patients with baseline BECs ≥300 cells/µL to the number of those who had counts <300 cells/µL. Similar reweighting was performed for patients with BECs <150 cells/µL.

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 ≥300 and ≥150 blood cells/µL, 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.[14,15] 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 ≥300 cells/µL when compared with placebo (all nominal $P≤0.013$) (Table 1). Daily rescue medication use was reduced by 0.71 puffs (95% CI: −1.12 to −0.29, nominal $P≤0.001$) 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 1 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 cells/µL)

PRO assessment	Placebo	Benralizumab 30 mg Q4W	Benralizumab 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 *P* 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 *P* 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 *P* 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 *P* 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 *P* 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 *P* 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 *P* 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 *P* 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 × visit.
Abbreviations: EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting β_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 ≥300 cells/µL)

PRO assessment	Day 1		Day 3[a]		Day 7[a]	
	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 *P* 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 *P* 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 *P* 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 *P* 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 *P* 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 *P* 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 *P* 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 *P* vs placebo	–	0.187	–	0.310	–	0.283

Notes: [a]3-day and 7-day averages were calculated when ≥2 and ≥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 β₂-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 ≥300 cells/µL 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 ≥150 cells/µL)

PRO assessment	Placebo	Benralizumab 30 mg Q4W	Benralizumab 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 *P* 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 *P* 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 *P* vs placebo	–	0.015	0.016
Percentage of nights with awakenings requiring rescue medication use			
Number of patients analyzed	647	464	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 *P* 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 *P* 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 *P* 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 *P* 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 *P* 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 × visit. The estimates were weighted to account for the 2:1 randomization ratio of patients with baseline blood eosinophil counts ≥150 or <150 cells/µL.
Abbreviations: EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting β$_2$-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 ≥300 cells/µL)

PRO assessment	Day 1		Day 3[a]		Day 7[a]	
	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 P 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 P 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 P 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 P 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 P 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 P 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 P 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 P vs placebo	−	0.144	−	0.845	−	0.870

Notes: [a]3-day and 7-day averages were calculated when ≥2 and ≥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 β2-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 ≥150 cells/µL 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/μL)

PRO assessment	Blood eosinophil counts <300 cells/μL			Blood eosinophil counts <150 cells/μL		
	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 (−1.04 to 0.19)	−0.19 (−0.80 to −0.42)	–	0.17 (−0.74 to 1.08)	−0.21 (−1.11 to 0.69)
Nominal P 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 (−0.44 to 0.13)	0.00 (−0.28 to 0.28)	–	0.07 (−0.37 to 0.51)	−0.16 (−0.59 to 0.27)
Nominal P 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 (−0.72 to 0.01)	−0.14 (−0.50 to 0.22)	–	−0.01 (−0.52 to 0.49)	−0.11 (−0.60 to 0.39)
Nominal P 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% (−5% to 5%)	−1% (−6% to 4%)	–	4% (−4% to 12%)	−2% (−10% to 6%)
Nominal P 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 (−0.31 to −0.04)	−0.18 (−0.31 to −0.05)	–	−0.02 (−0.20 to 0.15)	−0.26 (−0.44 to −0.08)
Nominal P 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 (−0.32 to −0.04)	−0.19 (−0.33 to −0.05)	–	0.03 (−0.19 to 0.25)	−0.20 (−0.42 to 0.02)
Nominal P 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 (−0.33 to −0.04)	−0.20 (−0.34 to −0.05)	–	0.01 (−0.19 to 0.20)	−0.26 (−0.46 to −0.07)
Nominal P vs placebo	–	0.011	0.008	–	0.944	0.008

(Continued)

Table 5 (*Continued*)

PRO assessment	Blood eosinophil counts <300 cells/µL			Blood eosinophil counts <150 cells/µL		
	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 (−0.21 to 0.08)	−0.11 (−0.25 to 0.03)	–	0.11 (−0.12 to 0.33)	−0.19 (−0.41 to 0.03)
Nominal *P* 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 × visit.
Abbreviations: EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting β$_2$-agonists; LS, least squares; PRO, patient-reported outcome; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W).
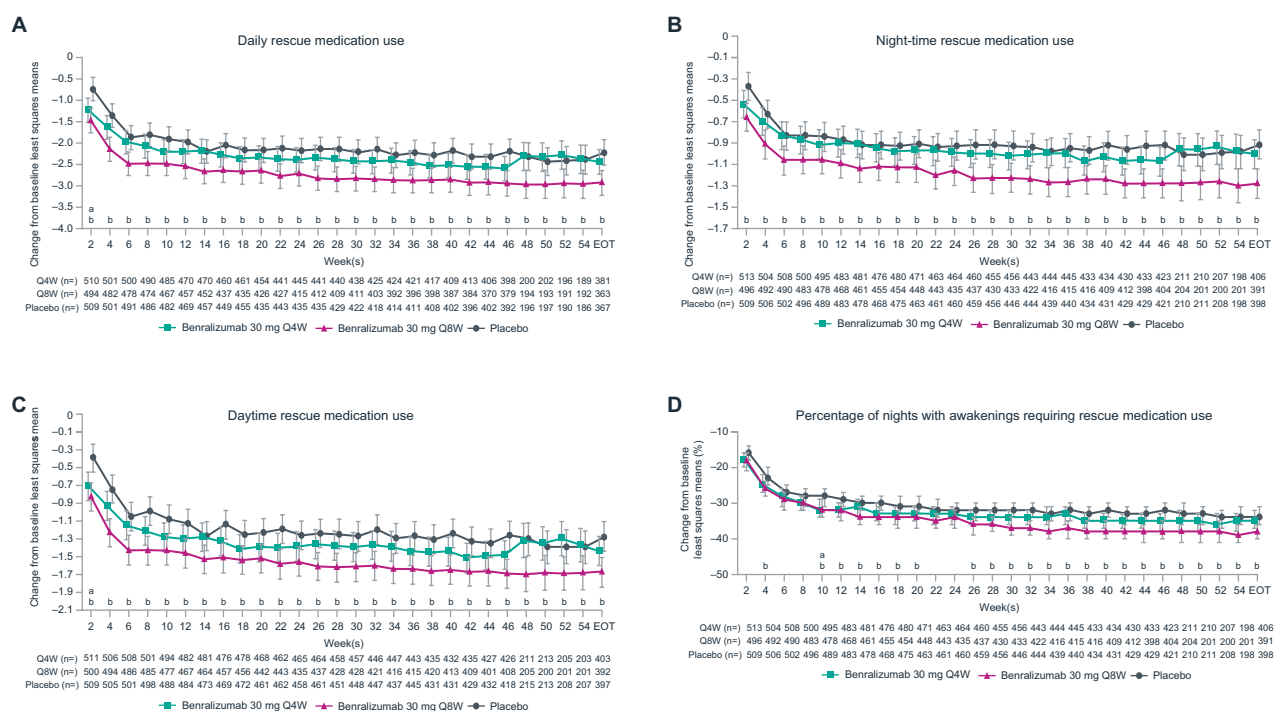

Figure 1 Reduction in rescue medication use with benralizumab and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts ≥300 cells/µL).
Notes: [a]Nominal *P*<0.05 benralizumab Q4W vs placebo. [b]Nominal *P*<0.05 benralizumab Q8W vs placebo. Error bars represent 95% CI. Estimates calculated using a mixed-effect model for repeated measures analysis, with adjustments for treatment, study code, baseline value, region, oral corticosteroid use, visit, and treatment × visit.
Abbreviations: EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting β$_2$-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/µL were greater in the benralizumab Q8W group compared with placebo (Table 5). However, these differences were less than those observed for groups with BECs ≥300 or ≥150 cells/µL.

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.[3] 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.[3] 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
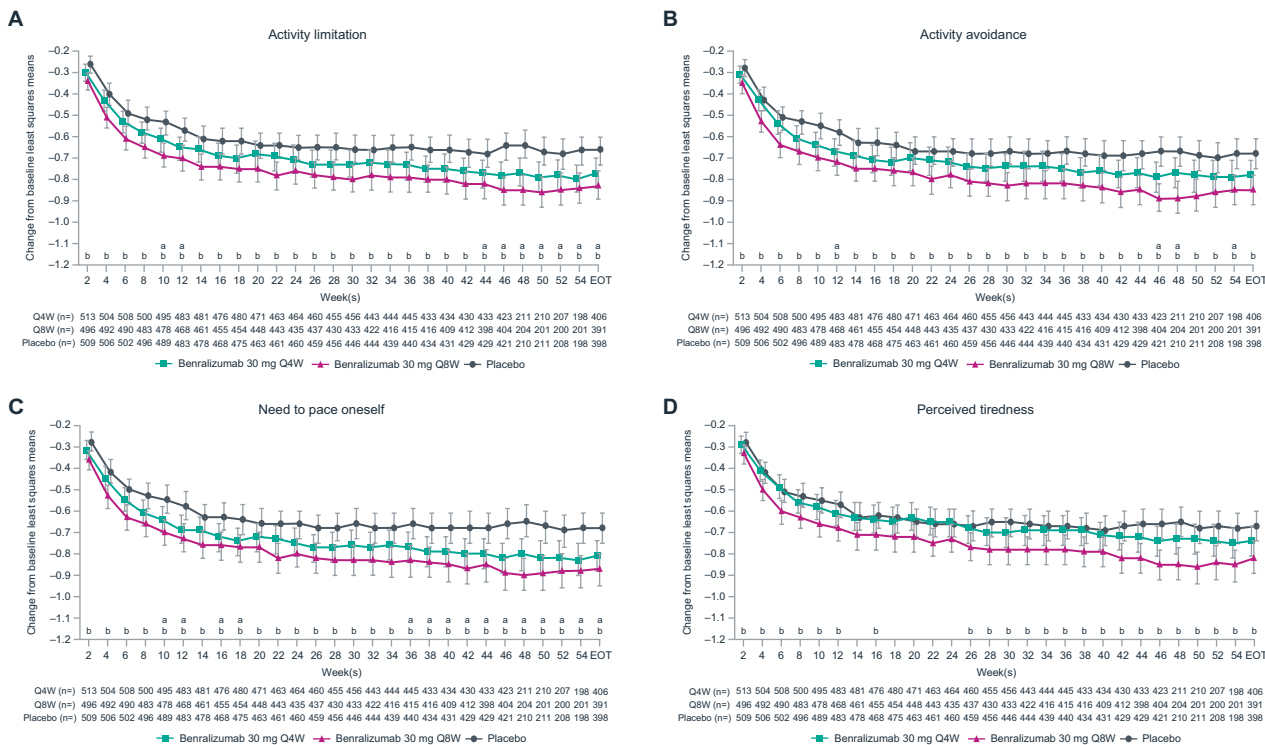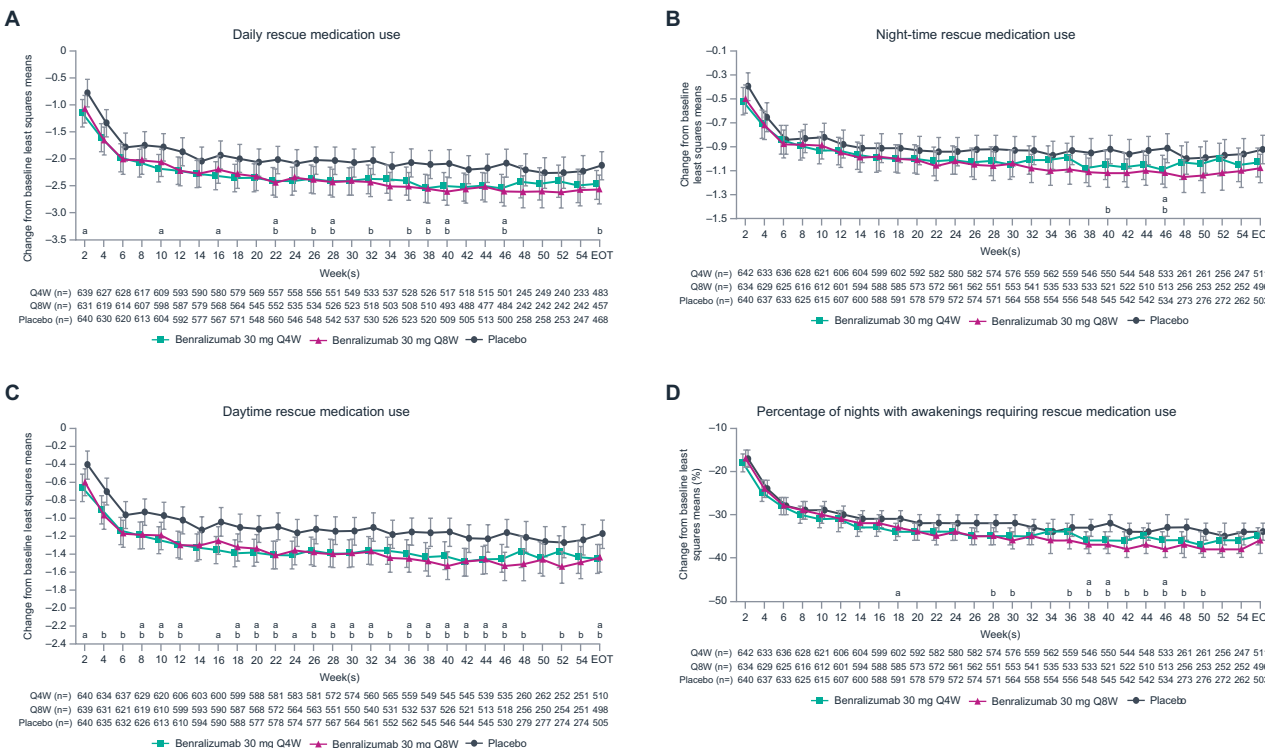
Figure 2 Improvement in patient-reported outcomes with benralizumab and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts ≥300 cells/μL)
Notes: [a]Nominal *P*<0.05 benralizumab Q4W vs placebo. [b]Nominal *P*<0.05 benralizumab Q8W vs placebo. Error bars represent 95% CI. Estimates 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 × visit.
Abbreviations: EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting β$_2$-agonists; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W).
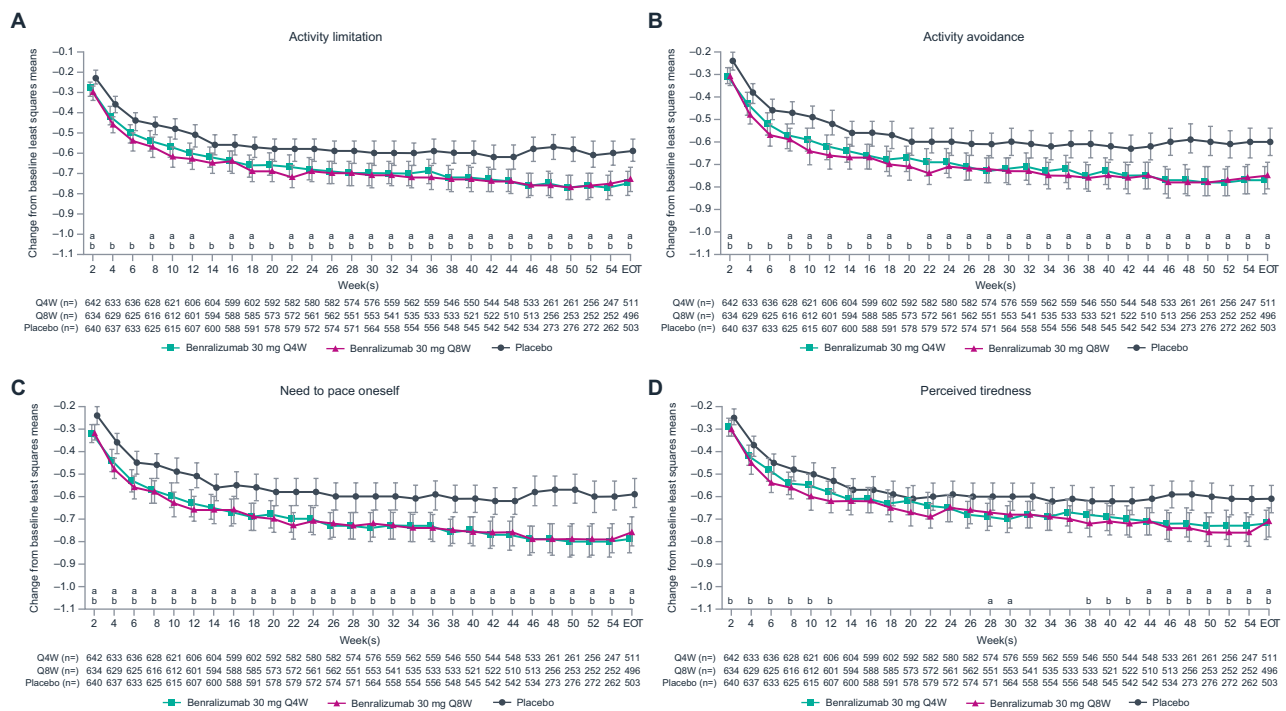

Figure 3 Reduction in rescue medication use with benralizumab and high-dosage ICS/LABA (full analysis set, pooled, blood eosinophil counts ≥150 cells/μL).
Notes: [a]Nominal *P*<0.05 benralizumab Q4W vs placebo. [b]Nominal *P*<0.05 benralizumab Q8W vs placebo. Error bars represent 95% CI. Estimates calculated using a mixed-effect model for repeated measures analysis, with adjustments for treatment, study code, baseline value, region, oral corticosteroid use, visit, and treatment × visit.
Abbreviations: EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting β$_2$-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 ≥150 cells/µL).
Notes: [a]Nominal $P<0.05$ benralizumab Q4W vs placebo. [b]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 × visit.
Abbreviations: EOT, end of treatment; ICS, inhaled corticosteroids; LABA, long-acting β_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 ≥300 cells/µL 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.[14,15] In both SIROCCO and CALIMA, significant improvements in prebronchodilator FEV$_1$ occurred after 4 weeks of treatment with benralizumab Q8W relative to placebo for patients with BECs ≥300 cells/ µL.[14,15] 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.[14,15] 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.[14,15]

For patients with BECs ≥150 cells/µL, 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 ≥150 cells/µL.[16,17] Changes in daily PROs for patients with BECs <150 or <300 cells/µL receiving benralizumab Q8W were directionally consistent with those observed for patients with BECs ≥150 or ≥300 cells/µL. 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.[18–20] 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.[21] 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.[22,23] Improvements were observed as early as 12 and 16 weeks with mepolizumab and reslizumab, respectively.[22,23]

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.[24–26] 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.[25] 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.[26]

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)

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.

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