

Seasonal variability of exacerbations of severe, uncontrolled eosinophilic asthma and clinical benefits of benralizumab

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ABSTRACT

Background: Benralizumab is a humanized, afucosylated, monoclonal antibody that targets interleukin-5 receptor alpha and induces direct, rapid, and nearly complete depletion of eosinophils via enhanced antibody-dependent cell-mediated cytotoxicity. In the United States, benralizumab is indicated for add-on maintenance treatment of patients ≥ 12 years old with severe asthma and an eosinophilic phenotype.

Objective: This study evaluated the effect of benralizumab treatment on seasonal asthma exacerbation rates for patients with severe, uncontrolled asthma.

Methods: This was a post hoc analysis of pooled data from the phase III SIROCCO (ClinicalTrials.gov identifier: NCT01928771) and CALIMA (NCT01914757) trials. The primary analysis population was patients ages 12–75 years treated with high-dosage inhaled corticosteroids and long-acting beta-2 agonists who had baseline blood eosinophil counts of ≥ 300 cells/ μ L. Patients received benralizumab 30 mg subcutaneously every 4 weeks or every 8 weeks (the first three doses every 4 weeks) or placebo every 4 weeks. Crude exacerbation rates (asthma exacerbations per patient-year) were determined for each month and season. Marginal asthma exacerbation rates and exacerbation rate ratios were estimated by season or month by using a negative binomial model that included covariates for study code, treatment, region, use of maintenance oral corticosteroids, and number of exacerbations in the previous year. Hemispheric seasons were accounted for by normalizing the study site locations.

Results: Observed crude exacerbation rates were higher in the fall and winter than in the spring and summer for all the patients. For the patients who received placebo, benralizumab every 4 weeks, and benralizumab every 8 weeks, crude exacerbation rates were the following: fall, 1.52, 0.86, and 0.81, respectively; winter, 1.44, 0.91, and 0.82, respectively; spring, 1.11, 0.66, and 0.52, respectively; and summer, 1.02, 0.55, and 0.51, respectively. Rate reductions in seasonal marginal annual exacerbation rates were 37–50% versus placebo at each season ($p < 0.001$).

Conclusion: Benralizumab significantly and consistently reduced asthma exacerbations across all seasons versus placebo for patients with severe, uncontrolled eosinophilic asthma.

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Asthma exacerbations are influenced by a number of factors, including age, body mass index, sex, eosinophil count, and seasonal changes.^{1–3} Because of differences in asthma triggers, patients with atopic and

nonatopic asthma can experience different seasonal exacerbation patterns.⁴ For school-age children, exacerbation peaks are seen in the fall^{1,3,5} and spring.^{3,6} Adults are more likely to experience peaks in the winter,^{1,3,4} but peaks in the fall have also been reported.³

Benralizumab (Fasenra™, AstraZeneca, Cambridge, UK), a humanized, afucosylated, interleukin-5 receptor- α directed monoclonal antibody that induces rapid and nearly complete depletion of eosinophils via enhanced antibody-dependent cell-mediated cytotoxicity,⁷ is, in the United States, indicated for add-on maintenance treatment of patients ≥ 12 years old with severe asthma and with an eosinophilic phenotype.⁸ The recommended dosage is 30 mg, administered by subcutaneous injection once every 4 weeks (Q4W) for three doses, and then once every 8 weeks (Q8W) there-

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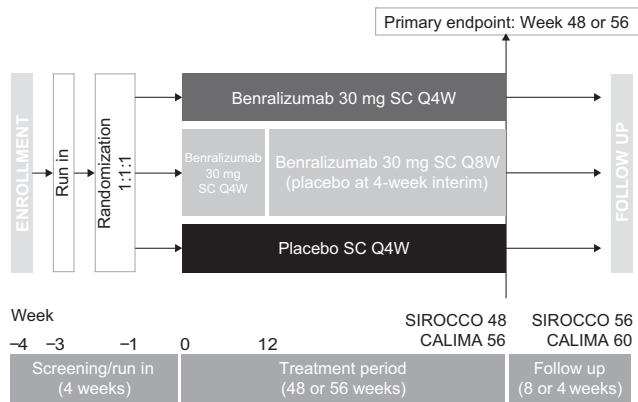


Figure 1. SIROCCO and CALIMA trial designs. Q4W = every 4 weeks; Q8W = every 8 weeks (first three doses were Q4W); SC = subcutaneously.

after. In two phase III clinical trials, SIROCCO (NCT01928771)⁹ and CALIMA (NCT01914757),¹⁰ benralizumab significantly reduced asthma exacerbations and increased lung function for patients with severe, uncontrolled asthma and baseline blood eosinophil counts of ≥ 300 cells/ μ L. In the ZONDA (NCT02075255) phase III trial, asthma exacerbations were reduced by 55–70% for patients who received benralizumab while the median oral corticosteroid dosage was gradually titrated down by 75%.¹¹

The effect of benralizumab on seasonal asthma exacerbation peaks has not been reported. Seasonal exacerbation peaks are numerically higher for patients with higher blood eosinophil counts than for patients with low eosinophil counts,³ and, therefore, we hypothesized that benralizumab, which depletes eosinophils, may be effective in reducing or eliminating seasonal asthma exacerbation peaks. The primary aim of this *post hoc* analysis was to evaluate the effect of benralizumab treatment on seasonal asthma exacerbation rates for patients with severe, uncontrolled asthma and with baseline blood eosinophil counts of ≥ 300 cells/ μ L.

METHODS

Study Design and Participants

The SIROCCO⁹ and CALIMA¹⁰ trials were multinational, randomized, double-blind, placebo-controlled, phase III clinical trials. The studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice guidelines. Studies were approved by the ethics committee at each participating site.

Descriptions of both studies have been published.^{9,10} Briefly, each study comprised a 4-week screening/run-in period, a 48-week (SIROCCO) or 56-week

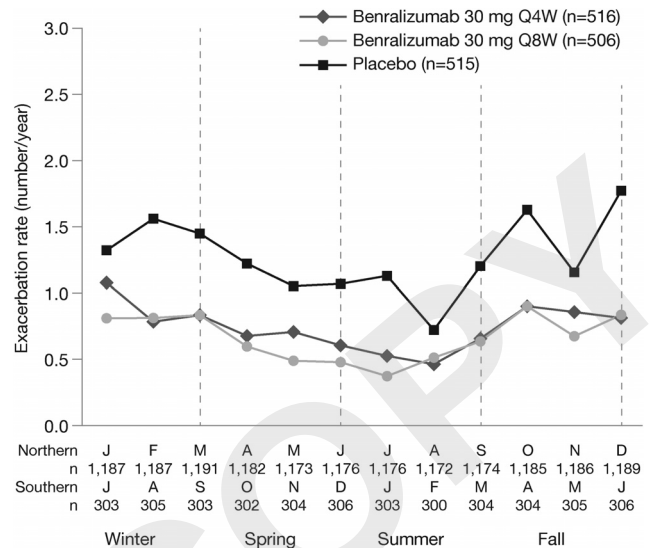


Figure 2. Asthma exacerbation rates by season: pooled results from the patients who received high-dosage ICS and with eosinophil counts of ≥ 300 cells/ μ L in the SIROCCO and CALIMA trials. Exacerbations were counted in the month when they began. Data from Brazil were included in the Southern Hemisphere. ICS = inhaled corticosteroid; Northern = Northern Hemisphere; Q4W = every 4 weeks; Q8W = every 8 weeks (first three doses were Q4W); Southern = Southern Hemisphere.

(CALIMA) treatment period, and a follow-up period of 8 weeks (SIROCCO) or 4 weeks (CALIMA) (Fig. 1). Patients were ages 12–75 years, male and female, and had physician-diagnosed asthma that was uncontrolled despite treatment with medium- to high-dosage inhaled corticosteroids and long-acting β_2 -agonists. Inclusion criteria required that patients had experienced two or more asthma exacerbations in the previous year. Patients in both studies were enrolled 2:1 by baseline blood eosinophil counts of ≥ 300 cells/ μ L and < 300 cells/ μ L, and were randomized 1:1:1 to receive benralizumab 30 mg subcutaneously Q4W or Q8W (first three doses were Q4W) or placebo Q4W. The primary efficacy end point in both trials was the annual exacerbation rate (AER) for patients who received high-dosage inhaled corticosteroids and long-acting β_2 -agonists and with baseline blood eosinophil counts of ≥ 300 cells/ μ L.^{9,10}

Assessments

This *post hoc* analysis used pooled data from the patients in the SIROCCO⁹ and CALIMA¹⁰ clinical trials with baseline blood eosinophil counts of ≥ 300 cells/ μ L. Asthma exacerbations were defined as a worsening of asthma that led to the use of systemic corticosteroids or a temporary increase in oral corticosteroid dosage for ≥ 3 days, an asthma-related emergency department or urgent care visit for < 24 hours that required the use of systemic corticosteroids, or an asthma-related inpatient hospital-

Table 1 Seasonal exacerbation rates for patients who received benralizumab and placebo: pooled results from patients who received high-dosage ICS and with a baseline eosinophil count of ≥ 300 cells/ μ L in the SIROCCO and CALIMA trials*

Season	No. Patients with Any Data in the Specified Season			Crude Exacerbation Rate, events/patient-year		Marginal Annual Exacerbation Rate (95% CI)			Rate Ratio (95% CI)#	
	Benra Q4W	Benra Q8W	Placebo	Benra Q4W	Benra Q8W	Placebo	Benra Q4W	Benra Q8W	Benra Q4W	Benra Q8W
Winter§	505	495	513	0.91	0.82	1.44	0.91 (0.75–1.11)	0.87 (0.70–1.07)	1.45 (1.23–1.70)	0.63 (0.49–0.81)
	505	490	504	0.66	0.52	1.11	0.66 (0.53–0.84)	0.55 (0.42–0.72)	1.11 (0.92–1.34)	0.60 (0.44–0.81)
	508	487	500	0.55	0.51	1.02	0.56 (0.43–0.73)	0.57 (0.43–0.75)	1.02 (0.83–1.27)	0.54 (0.39–0.78)
	506	493	510	0.86	0.81	1.52	0.88 (0.71–1.08)	0.84 (0.67–1.04)	1.54 (1.30–1.81)	0.57 (0.44–0.74)

ICS = inhaled corticosteroid; CI = confidence interval; Benra = benralizumab; Q4W = every 4 weeks; Q8W, every 8 weeks (first three doses were Q4W).

*Marginal asthma exacerbation rates and exacerbation rate ratios were estimated directly from a negative binomial model adjusted by study code, treatment, region, use of oral corticosteroids, and number of exacerbations in the previous year.

$p < 0.001$ for all rate ratios.

§January, February, and March in the Northern Hemisphere; July, August, and September in the Southern Hemisphere.

¶April, May, and June in the Northern Hemisphere; October, November, and December in the Southern Hemisphere.

||July, August, and September in the Northern Hemisphere; January, February, and March in the Southern Hemisphere.

**October, November, and December in the Northern Hemisphere; April, May, and June in the Southern Hemisphere.

ization for ≥ 24 hours. Crude exacerbation rates are expressed as the number of exacerbation events per patient-year that occurred during each month or season.

Marginal AERs and exacerbation rate ratios were determined by using a negative binomial model that included covariates for study code, treatment, region, use of maintenance oral corticosteroids, and the number of exacerbations in the previous year. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for the different exposure times during which the events occurred. Exacerbation rates were estimated by season or month, and hemispheric seasons were accounted for by normalizing study site location (with data from Brazil included in the Southern Hemisphere). Because these analyses were not part of the formal testing strategy, all p values were nominal.

The patient population for each season or month included all the patients who had at least 1 day of follow up during that period. Patients in the CALIMA trial¹⁰ (56-week duration) could have data for the same month in 2 consecutive years. When this occurred, the patients were counted only once in the patient population for that month.

RESULTS

The analysis included nearly four times as many patients who lived in the Northern Hemisphere than the Southern Hemisphere (Fig. 2). The numbers of patients in the pooled population with available data were similar across months, with 1172–1191 patients in the Northern Hemisphere and 300–306 patients in the Southern Hemisphere (Fig. 2). Patients with data for any of the 3 months that comprise a season were included in analyses by season (Table 1), which is why these patient populations were slightly larger than those for each individual month.

The observed crude exacerbation rates for patients with severe, uncontrolled eosinophilic asthma in all the treatment groups were higher in the fall and winter than in the spring and summer (Table 1). Crude exacerbation rates and marginal AERs were similar between the two benralizumab treatment arms and were higher for the placebo group than for patients who received benralizumab. Improvements with both benralizumab Q4W and Q8W at every season versus placebo were observed (all nominal $p < 0.001$). The rate reductions in AER for benralizumab Q4W and Q8W, respectively, versus placebo were as follows: spring, 40% and 50%, respectively; summer, 46% and 45%, respectively; fall, 43% and 46%, respectively; and winter, 37% and 40%, respectively. Compared with the placebo group, the patients who received benralizumab experienced fewer exacerbations during each month. Results from both benralizumab dosing regi-

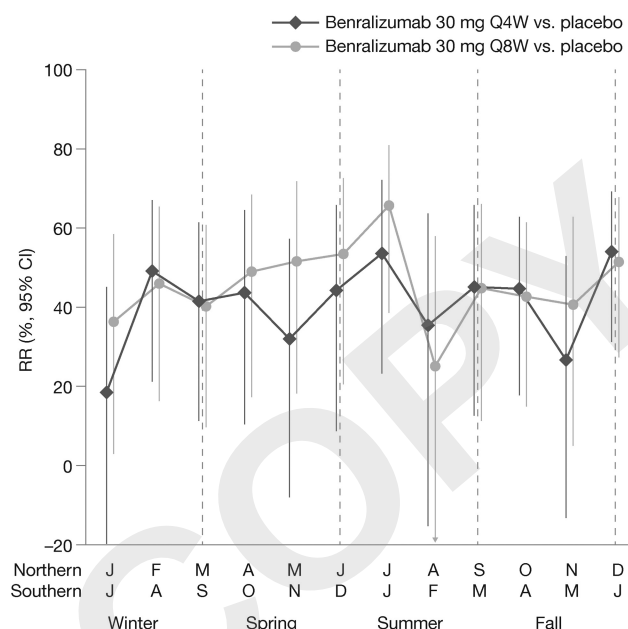


Figure 3. Rate ratio (benralizumab to placebo) by month. Data from Brazil were included in the Southern Hemisphere. CI = confidence interval; Northern = Northern Hemisphere; Q4W = every 4 weeks; Q8W = every 8 weeks (first three doses were Q4W); RR = rate reduction; Southern = Southern Hemisphere.

mens were similar (Figs. 2 and 3). Seasonal exacerbation peaks also were reduced (Fig. 2).

DISCUSSION

The patients who received benralizumab experienced fewer asthma exacerbations during all months and seasons than those who received placebo. Benralizumab treatment reduced, but did not eliminate, seasonal exacerbation peaks and reduced AER by 37–50% during each season.

Other biologics that impact type 2 or eosinophilic inflammation have also been studied for effects on seasonal peak exacerbations in asthma. In a recent *post hoc* analysis of data from a multinational study of adolescents and adults with asthma, mepolizumab treatment resulted in fewer exacerbations than placebo but did not reduce the magnitude of the seasonal peak in asthma exacerbations.⁴ In contrast, in a *post hoc* analysis of adults with moderate-to-severe asthma, lebrikizumab treatment was most efficacious during exacerbation peaks.³ Rate reductions were 44.4% in September and 49.3% in April. However, during the exacerbation nadir in July, lebrikizumab had essentially no effect on the exacerbation rate (rate increase of 2.0%).³

Two studies, one *post hoc*⁶ and one prospective trial,¹² of inner-city school-age children and young adults evaluated omalizumab for the treatment of exacerbation peaks. The *post hoc* study compared rates across seasons and found that omalizumab, like lebrikizumab, substan-

tially reduced exacerbations during peak times versus placebo (mean monthly percentage of participants who experienced exacerbations: fall, 4.3% versus 9.0%; spring, 4.2% versus 8.1%) but had less effect during exacerbation nadirs (summer, 3.3% versus 4.6%).

In the prospective study, which focused on the fall asthma season, the percentage of patients treated with omalizumab who experienced at least one exacerbation decreased compared with the placebo group (11.3% versus 21.0%, odds ratio 0.48 [95% confidence interval, 0.25–0.92]).¹² This prospective study was examined in a recent Cochrane review that concerned the reduction of asthma exacerbations for children during the fall,⁵ along with studies of leukotriene receptor antagonist tablets, increased dosages of inhaled steroids, and medication reminder letters. The review concluded that, of those interventions, omalizumab was the only one with sufficient evidence of effect on seasonal asthma exacerbations for this population.

Efficacy comparisons across studies are problematic. In comparing our results with other studies, one must consider the large and diverse geographic area covered by study sites in this and other multinational studies. Diversity in geography, climate, and culture is generally a strength in clinical trial design, but, at any given time, patients in a single multinational study may have substantially different exposures to asthma triggers based on factors such as pollen counts and the prevalence of molds and viruses, and even the date when the school year begins.

Thus, seasonal exacerbations may occur at different times for patients in the same study. Peak exacerbation rates for diverse study populations may be blunted compared with peaks for more homogeneous populations from seasonal variation studies, and, therefore, the effects of treatment on these peaks may be less obvious. Comparisons across studies are further complicated by how the seasons are defined. Seasons change on approximately the 21st day of March, June, September, and December, but most studies, including this one, categorize seasons as full months. Thus, some studies include all of September in summer, whereas other studies include September in fall. Also, values derived from statistical analyses would be affected by differences in the covariates and models used in each study.

The chief limitation of this study was the *post hoc* nature of the analysis. In addition, no corrections were made for multiple statistical comparisons. However, these limitations are shared by other *post hoc* analyses of the effect of treatment on seasonal asthma exacerbations,^{3,4,6} which suggests a need for more prospective studies on this topic. The dosage approved by the U.S. Food and Drug Administration of benralizumab (30 mg subcutaneously Q4W for the first three doses and Q8W thereafter) provided a consistent reduction in asthma exacerbations compared with placebo across

all seasons, with rate reductions that ranged from 40% to 50%. This impact was seen even in the peak periods of asthma exacerbation, the fall and winter, when exacerbations are often triggered by viral respiratory infections. Analysis of these data indicated that near-complete depletion of eosinophils by benralizumab was an effective strategy for reducing asthma exacerbations across all seasons.

CONCLUSION

The patients who received benralizumab experienced fewer asthma exacerbations, measured in events per patient-year, during all months, and had reduced seasonal asthma exacerbation peaks compared with placebo. Benralizumab treatment provided a consistent reduction of 37–50% in AER across all seasons.

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