Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial

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Summary

Background Benralizumab is an interleukin-5 receptor α-directed cytolytic monoclonal antibody that has been shown to safely reduce exacerbations and improve lung function for patients with asthma. We assessed the long-term safety and efficacy of benralizumab for patients with severe, uncontrolled eosinophilic asthma.

Methods We conducted a randomised, double-blind, parallel-group, phase 3 extension study at 447 sites in 24 countries. Eligible patients had to have completed the SIROCCO or CALIMA trials and remained on subcutaneous benralizumab 30 mg every 4 weeks (Q4W) or every 8 weeks (Q8W). Patients who had received placebo in those trials were re-randomised in a 1:1 ratio, using an interactive web-based system, to benralizumab 30 mg either Q4W or Q8W (first three doses 4 weeks apart). Treatment lasted for 56 weeks for adult patients (age ≥18 years) and 108 weeks for adolescent patients (age 12–17 years). The primary endpoint was the safety and tolerability of the two dosing regimens of benralizumab up to 68 weeks for adult patients (including the follow-up visit post-treatment) and up to 56 weeks for adolescent patients. This endpoint was assessed in the full analysis set, which included all patients from the SIROCCO and CALIMA predecessor studies who received at least one dose of study treatment in BORA and did not continue into another trial. This study is registered with ClinicalTrials.gov (NCT02258542).

Findings Between Nov 19, 2014, and July 6, 2016, we enrolled 1926 patients, of whom 633 had received benralizumab Q4W and 639 had received benralizumab Q8W in SIROCCO or CALIMA. The remaining 654 patients had received placebo in those trials and were randomly re-assigned in this trial to receive benralizumab Q4W (n=320) or Q8W (n=334). 1576 patients, including 783 who received benralizumab Q4W (265 newly assigned) and 793 who received benralizumab Q8W (281 newly assigned), were included in the full analysis set. The most common adverse events in all groups were viral upper respiratory tract infection (14–16%) and worsening asthma (7–10%). The most common serious adverse events were worsening asthma (3–4%), pneumonia (<1% to 1%), and pneumonia caused by bacterial infection (0–1%). The percentages of patients who had any on-treatment adverse event, any serious adverse event, or any adverse event leading to treatment discontinuation during BORA were similar between patients originally assigned benralizumab and those originally assigned placebo and between benralizumab treatment regimens. The percentage of patients who had any adverse event was similar between SIROCCO or CALIMA (71–75%; benralizumab group only) and BORA (65–71%), as was the percentage of patients who had an adverse event that led to treatment discontinuation (2% in SIROCCO and CALIMA *vs* 2–3% in BORA).

Interpretation The 2 years of safety results validate that observations observed in the first year of benralizumab continued through a second year of treatment. No new consequences of long-term eosinophil depletion occurred, and the incidence of other adverse events, including opportunistic infections, were similar during the second year.

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Introduction

Asthma affects more than 315 million people worldwide, with about 10% having severe or uncontrolled asthma.[1,2] For patients with severe asthma, high-dosage inhaled corticosteroids and long-acting β_2-agonists are commonly used to control their disease.[3] However, despite the general effectiveness of this approach, many patients remain uncontrolled and experience a high disease burden, including recurrent exacerbations and hospitalisations.[4] Therefore, drugs with novel mechanisms of action are needed to address this unmet medical need. One approach is to target eosinophilic inflammation, which is present in about 50% of patients with asthma[5] and associated with asthma severity, as reflected by an increased frequency of exacerbations and decreased lung function in patients with eosinophilic asthma.[6,7]

Benralizumab is an interleukin-5 receptor α-directed cytolytic monoclonal antibody that induces direct, rapid, and nearly complete depletion of eosinophils by enhancing antibody-dependent cell-mediated cytotoxicity,

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for English-language reports of clinical trials published from May 1, 2008, to May 22, 2018, that investigated the use of biologics targeting interleukin-5 or the interleukin-5 receptor for the treatment of patients with asthma. We used the search terms "asthma" AND "interleukin 5" AND "antibody", as well as the independent terms "benralizumab", "mepolizumab", and "reslizumab". The search yielded 43 results, including four multicentre, randomised, double-blind, placebo-controlled phase 3 trials of benralizumab for patients with asthma published in 2016–17, three of which were in patients with severe, uncontrolled asthma with eosinophilic inflammation. In these studies, benralizumab significantly reduced exacerbations, increased lung function, improved asthma symptoms, and reduced the need for oral corticosteroids compared with placebo and had an acceptable safety and tolerability profile. Along with the improved efficacy outcomes, benralizumab completely depleted blood eosinophil counts.

Added value of this study

This first report from the BORA phase 3 long-term safety and efficacy extension trial presents the complete and final results for adult patients and the first-year results for adolescent patients. We present the safety and efficacy of benralizumab for patients with severe, uncontrolled asthma who completed either the SIROCCO or CALIMA phase 3 trials and received a second year of benralizumab or, for those previously in the placebo group, received benralizumab for 1 year. Benralizumab administered either once every 4 or 8 weeks for a second year maintained the safety and tolerability profiles observed in the preceding primary studies. No new adverse consequences of long-term eosinophil depletion were observed. The incidence of other adverse events, including opportunistic infections, did not change during the second year. Efficacy benefits with benralizumab were maintained, with exacerbation rates and lung function improvements observed in the phase 3 studies for patients continuously on therapy sustained through 2 years of benralizumab treatment. Additionally, patients who received placebo for the first year and were then treated with benralizumab during year 2 had exacerbation rates and lung function improvements that were similar to the patients who had been receiving benralizumab for 2 years.

Implications of all the available evidence

There is an unmet medical need for effective treatments for patients with severe, uncontrolled asthma that have safety and tolerability profiles that allow their long-term use. Our findings demonstrate that long-term use of benralizumab can improve outcomes for patients with severe asthma, with an acceptable safety profile. These results should reassure respiratory care physicians of the long-term safety and efficacy of benralizumab for the treatment of asthma.

which is an apoptotic process of eosinophil elimination that involves natural killer cells.[8,9] Benralizumab 30 mg every 8 weeks (Q8W; first three doses received 4 weeks apart) has recently been approved in Canada, Europe, Japan, the USA, and other countries for the treatment of patients with severe asthma.[10–13] In the USA, it is indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older with an eosinophilic phenotype.[10] In Europe, benralizumab is indicated for add-on maintenance treatment of adult patients with severe eosinophilic asthma that is inadequately controlled despite treatment with high-dosage inhaled corticosteroids and long-acting β_2-agonists.[11]

Two phase 3 trials, the 48-week SIROCCO trial (NCT01928771)[14] and the 56-week CALIMA trial (NCT01914757),[15] investigated the effect of benralizumab 30 mg every 4 weeks (Q4W) or Q8W compared with placebo on the annual rate of exacerbations in patients aged 12–75 years with severe, uncontrolled asthma.[14,15] The studies demonstrated that benralizumab combined with high-dosage inhaled corticosteroids and long-acting β_2-agonists significantly reduced asthma exacerbations and improved lung function and disease control in patients with blood eosinophil counts of 300 cells per µL or greater at baseline.[14,15] For patients who received benralizumab 30 mg Q8W, the annual exacerbation rate was reduced by 51% (in the SIROCCO trial) or 28% (in the CALIMA trial) compared with placebo.[14,15]

Another phase 3 trial of benralizumab 30 mg (Q4W or Q8W) versus placebo, the 28-week ZONDA trial (NCT02075255),[16] included adult patients with severe, uncontrolled asthma and blood eosinophil counts of 150 cells per µL or greater, and had a primary endpoint of percentage change from baseline to week 28 in oral glucocorticoid dosage.[16] At week 28, benralizumab reduced the oral glucocorticoid dosage by 75% versus baseline and placebo by 25% versus baseline ($p<0·001$ for the difference between groups).[16]

Because benralizumab represents a new class of compounds to treat asthma, it is important to understand and present data on the long-term safety and efficacy of this drug. The BORA phase 3 extension trial was designed to assess the safety and efficacy of benralizumab over 2 years for patients with severe eosinophilic asthma that has been inadequately controlled with inhaled corticosteroids and long-acting β_2-agonists.

All patients who previously participated in and completed the SIROCCO, CALIMA, or ZONDA trials were eligible for enrolment in BORA. Patients were treated in BORA for 56 weeks (adults) or 108 weeks (adolescents) with benralizumab 30 mg, either Q4W or Q8W. Once the trial size objective was achieved, adult patients who had completed 16–40 weeks in BORA and wanted to continue

treatment for a longer period of time had the option to continue therapy in MELTEMI (NCT02808819), an open-label, 130-week, safety extension study, without completing the full, planned follow-up in BORA.

We present the adult completion results from the BORA extension study, which includes the full results for adults and the first-year results for adolescents. These results include patients who were previously in the similar-length SIROCCO or CALIMA studies. Results for ZONDA patients will be reported as part of a later integrated analysis.

Methods

Study design and participants

BORA was a randomised, double-blind, parallel-group, phase 3 extension study conducted at 447 clinical research centres in Argentina, Australia, Brazil, Bulgaria, Canada, Chile, Czech Republic, France, Germany, Japan, Peru, Philippines, Poland, Romania, Russia, South Africa, South Korea, Spain, Sweden, Turkey, Ukraine, the UK, the USA, and Vietnam (appendix).

A summary of the BORA study design is in the appendix. Briefly, all patients who completed treatment in the SIROCCO, CALIMA, or ZONDA trials were eligible for enrolment. Patients were aged 12–75 years and had physician-diagnosed asthma requiring treatment with medium-dosage or high-dosage inhaled corticosteroids and long-acting β_2-agonists for at least 12 months before enrolment. Exclusion criteria for this study included any medical disorder that affected either interpretation of study results or a patient's safety or ability to complete the study and a current malignancy or malignancy that developed during the preceding primary study. Full inclusion and exclusion criteria are listed in the appendix.

In this study, we present only the results for patients enrolled from the SIROCCO or CALIMA trials. The results for patients from the ZONDA trial are not reported because the trial was shorter (28 weeks) and smaller than SIROCCO and CALIMA; about 50% of patients in ZONDA transitioned into MELTEMI (NCT02808819), an open-label, 130-week, safety extension study, without completing the full planned follow-up in BORA; and ZONDA differed in design from the other two studies in that it was an oral corticosteroid reduction study. The results for the patients from ZONDA will be reported elsewhere as part of an integrated analysis of all three trials.

A protocol amendment on Sept 1, 2015, required patient entrance into the BORA study at visit 1 to coincide with the end-of-treatment visit in the preceding primary study. In the original protocol, patients were allowed a delay of up to 16 weeks after the last dose of study drug in the preceding primary study before entering BORA. A total of 80 patients had a gap of more than 30 days after completion of the preceding primary study before entering BORA, with the longest gap being 84 days. As in SIROCCO, CALIMA, and ZONDA, patients in BORA were encouraged to remain on a stable dose of background asthma medication unless a change was medically warranted. Restrictions on the use of these medications are described in the appendix.

An independent ethics committee at each study centre approved the study protocol, and the national regulatory authority of each country either approved the study protocol or received notification of the study per local regulations. An independent data safety monitoring board reviewed ongoing data from the phase 3 asthma trials, including BORA, and made no changes to trial conduct based on their review. An independent adjudication committee reviewed all major adverse cardiac events and malignancies. All patients provided written informed consent before participation. The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation's Good Clinical Practice guidelines, applicable regulatory requirements, and AstraZeneca's policy on bioethics and human biological samples.

Randomisation and masking

All adult (age ≥18 years) and adolescent (age 12–17 years and from non-EU countries) patients who were previously assigned subcutaneous benralizumab 30 mg Q4W or Q8W in the SIROCCO or CALIMA trials continued to receive their assigned treatments in this study. Adult and adolescent patients who were previously assigned placebo in SIROCCO or CALIMA were randomly re-assigned in a 1:1 ratio to receive subcutaneous benralizumab 30 mg either Q4W or Q8W. Patients who were newly assigned benralizumab Q8W were required to have their first three doses 4 weeks apart. Patients assigned benralizumab Q8W in BORA received placebo injections at the 4-week interim to ensure masking of regimen assignment. Adolescent patients who were enrolled at sites in EU countries and who previously received subcutaneous benralizumab 30 mg Q8W continued to receive the same treatment in this study; those who received placebo in the primary trial received open-label subcutaneous benralizumab 30 mg Q8W. Patients who were adolescents at initiation of the preceding primary study were considered adolescents for this study, irrespective of age at enrolment to BORA.

We assigned each patient a unique enrolment number and randomisation code using an interactive, web-based, voice-response system. Randomisation for adult patients from any country and adolescents from non-EU countries was stratified by the preceding primary study, age group (adults *vs* adolescents), and country (for adults only).

The study sponsor became unmasked to treatment allocation following completion of the preceding primary studies. Masking of treatment regimen was maintained for both investigators and patients in BORA. Treatment regimen allocation was not made available to patients or to investigators involved in patient treatment or clinical

evaluation (except for adolescent patients in EU countries). Placebo solution was visually matched with benralizumab solution.

Procedures

Benralizumab and placebo were provided by AstraZeneca in accessorised, pre-filled syringes containing a 1 mL deliverable volume of 30 mg/mL benralizumab solution or matching placebo solution. Patients received injections with benralizumab during study centre visits, which started at baseline and continued to week 52 (for adults) or week 104 (for adolescents); placebo was administered at 4-week intervals for adult and non-EU adolescent patients who were assigned the Q8W dosing schedule. The site of injection was rotated between different anatomical sites at each visit.

Safety and efficacy data were collected from all patients at 4-week intervals during the treatment period (weeks 0–52 for adults and weeks 0–104 for adolescents), at the end of treatment (week 56 for adults and week 108 for adolescents), and at a follow-up visit (week 68 for adults and week 120 for adolescents). Study investigators at each site performed pre-bronchodilator spirometry at weeks 0, 16, 32, 48, and 56 for adult patients and at weeks 0, 16, 32, 48, 64, 80, 96, and 108 for adolescent patients. Measurement of eosinophil and anti-drug antibody concentrations was described previously.[14,15]

Outcomes

The primary endpoint was the safety and tolerability of the two dosing regimens of benralizumab over 56 weeks of treatment for adult patients and over 108 weeks of treatment for adolescent patients. This was an adult completion analysis that included data for adolescents up to the 56-week timepoint only (data cutoff). Adolescent patients will continue to receive treatment up to week 108, with the results at that timepoint presented as part of a later integrated analysis. Additional results for adults at the week 68 follow-up visit are reported for certain efficacy endpoints.

Safety assessments included adverse events (coded with the Medical Dictionary for Regulatory Activities version 20.0), serious adverse events, clinical laboratory assessments (haematological, clinical chemistry, and urinalysis), physical examinations, vital sign measurements, and electrocardiograms.

Secondary endpoints included a subset of efficacy outcomes that were the primary and secondary endpoints in SIROCCO and CALIMA. These included the effect of the two benralizumab dosing regimens on asthma exacerbations (annual asthma exacerbation rate), lung function (pre-bronchodilator and post-bronchodilator FEV_1), scores on the Asthma Quality of Life Questionnaire (standardised) for individuals aged 12 years and older (AQLQ[S]+12) and the Asthma Control Questionnaire 6 (ACQ-6), concomitant use of medications for asthma control (including total daily doses of inhaled corticosteroids and numbers of other concomitant drugs), eosinophil concentrations, and concentrations of antibodies to the study drug.

The annual asthma exacerbation rate was summarised as the total number of exacerbations multiplied by 365·25 and divided by the total number of days of follow-up within the treatment group. For other efficacy endpoints, change from baseline (week 0) was determined. Additional information about the secondary endpoints is in the appendix.

Statistical analysis

Because BORA did not include a placebo comparator group, no formal statistical hypothesis testing was planned or performed. Thus, formal sample size calculations to achieve statistical power were not required. This study was not powered to test any null hypothesis. However, a sample size was established as a clinical judgment goal, consistent with regulatory guidance. With an estimated rollover rate of greater than 90%, about 1800–2000 patients (maximum of 2200) were anticipated to be enrolled worldwide. A minimum of 1200 patients were estimated to be required to address the primary safety and tolerability objectives of the study.

Adult patients who had enrolled in BORA after the minimum sample size of 1200 patients had been obtained and completed 16–40 weeks in BORA had the option to exit the study and enrol in the MELTEMI trial without completing the full planned follow-up in BORA. These patients were not included in the full analysis set for BORA because of their truncated follow-up period. In MELTEMI, patients received active drug on the same dosing regimen as they received in BORA. To maintain masking of regimen assignment in BORA, patients who entered the MELTEMI study will remain masked to treatment regimen allocation until they have completed all end-of-treatment assessments in BORA and signed informed consent for participation in MELTEMI. Of note, about half of patients in the shorter (28 weeks) and smaller ZONDA study went into MELTEMI without completing the planned 56-week treatment period in BORA, and therefore were not included in this analysis, and will be reported separately according to the analysis plan.

Primary safety and secondary endpoints were conducted on the full analysis set, which included all patients from the SIROCCO and CALIMA predecessor studies who received at least one dose of study treatment and remained in BORA (did not transition into MELTEMI). Data are summarised with descriptive statistics (mean [SD] or median [range]), qualitative summaries, and 95% CIs. Unless otherwise stated, baseline reflects the measurement at the time the patient entered the BORA study (not the measurement at the time the patient entered the preceding primary trial). All analyses were done with SAS version 9.4 or higher.

The study is registered with ClinicalTrials.gov, number NCT02258542.

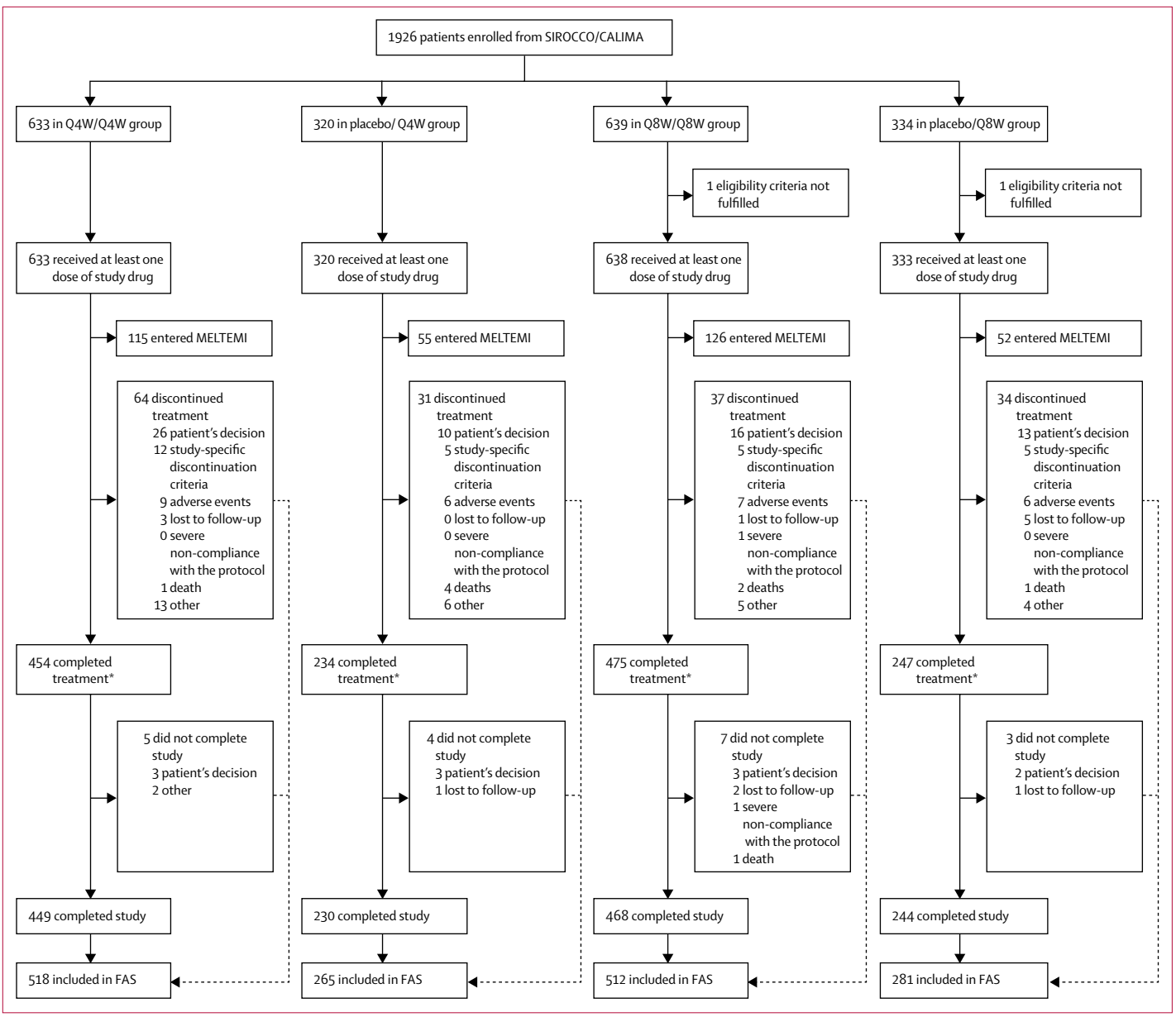

Figure 1: **Trial profile**
All participants received benralizumab 30 mg Q4W or Q8W. Group names are what patients received in the preceding SIROCCO or CALIMA trials/what they received in this trial. FAS=full analysis set. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Includes adolescent patients who were still receiving treatment at the cutoff date.

Role of the funding source
The funders of this study participated in the study design. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
2226 patients completed treatment in SIROCCO or CALIMA, of whom 1926 were enrolled in this study between Nov 19, 2014, and July 6, 2016 (figure 1). 1272 patients continued to receive the benralizumab treatment regimen assigned in SIROCCO or CALIMA, whereas 654 who had previously been assigned to placebo were randomly re-assigned to benralizumab 30 mg Q4W (n=320) or Q8W (n=334). 1758 patients completed treatment with the study drug during BORA or were ongoing (including 348 patients who enrolled in MELTEMI).

The full analysis set included 1576 patients: 783 who received benralizumab Q4W (including 265 newly assigned) and 793 who received benralizumab Q8W (including 281 newly assigned). Mean treatment

	Benralizumab 30 mg Q4W			Benralizumab 30 mg Q8W		
	Q4W/Q4W group (n=518)	Placebo/Q4W group (n=265)	Total (n=783)	Q8W/Q8W group (n=512)	Placebo/Q8W group (n=281)	Total (n=793)
Age (years)	51·7 (13·3)	49·9 (14·7)	51·1 (13·8)	49·3 (14·8)	48·2 (16·8)	48·9 (15·5)
Age group						
12–17 years	12 (2%)	9 (3%)	21 (3%)	25 (5%)	26 (9%)	51 (6%)
18–75 years	504 (97%)	254 (96%)	758 (97%)	486 (95%)	253 (90%)	739 (93%)
>75 years	2 (<1%)	2 (1%)	4 (1%)	1 (<1%)	2 (1%)	3 (<1%)
Sex						
Male	179 (35%)	101 (38%)	280 (36%)	205 (40%)	118 (42%)	323 (41%)
Female	339 (65%)	164 (62%)	503 (64%)	307 (60%)	163 (58%)	470 (59%)
Race						
White	398 (77%)	201 (76%)	599 (77%)	388 (76%)	224 (80%)	612 (77%)
Black or African American	6 (1%)	10 (4%)	16 (2%)	12 (2%)	7 (2%)	19 (2%)
Asian	94 (19%)	44 (17%)	138 (18%)	92 (18%)	44 (16%)	136 (17%)
Other*	20 (4%)	10 (4%)	30 (4%)	20 (4%)	6 (2%)	26 (3%)
Ethnicity						
Hispanic or Latino	103 (20%)	53 (20%)	156 (20%)	102 (20%)	46 (16%)	148 (19%)
Not Hispanic or Latino	415 (80%)	212 (80%)	627 (80%)	410 (80%)	235 (84%)	645 (81%)
Body-mass index (kg/m²)	29·0 (7·0)	29·1 (6·7)	29·1 (6·9)	28·4 (6·2)	28·9 (7·1)	28·6 (6·5)
Missing data	0	0	0	0	1	1
Eosinophil count (cells per μL)†	20 (0–1050)	400 (0–2270)	149 (0–2270)	33 (0–1690)	399 (0–2430)	162 (0–2430)
Missing data	2	1	3	4	5	9
Baseline blood eosinophil count in previous study‡						
<300 cells per μL	171 (33%)	93 (35%)	264 (34%)	173 (34%)	93 (33%)	266 (34%)
≥300 cells per μL	347 (67%)	172 (65%)	519 (66%)	339 (66%)	188 (67%)	527 (66%)
Pre-bronchodilator FEV_1 (L)	1·95 (0·70)	1·89 (0·79)	1·93 (0·73)	2·02 (0·75)	2·00 (0·82)	2·01 (0·78)
Pre-bronchodilator FEV_1 (% predicted normal)	67·1% (17·9)	62·8% (19·7)	65·7% (18·6)	66·9% (19·0)	66·2% (20·0)	66·7% (19·3)
Pre-bronchodilator FEV_1/FVC ratio	63·5 (11·7)	62·0 (13·7)	63·0 (12·4)	63·0 (13·3)	64·0 (13·2)	63·0 (13·3)
ACQ-6 score	1·5 (1·2)	1·6 (1·2)	1·5 (1·2)	1·4 (1·1)	1·6 (1·2)	1·5 (1·1)
Missing data	1	1	2	3	1	4
Time since asthma diagnosis (years)	16·4 (2·2–70·3)	19·1 (2·1–73·3)	17·0 (2·1–73·3)	16·3 (2·1–59·3)	14·4 (2·1–71·0)	15·7 (2·1–71·0)
Number of exacerbations in the past 12 months	0·9 (1·6)	1·4 (2·2)	1·1 (1·8)	0·8 (1·2)	1·2 (1·8)	1·0 (1·4)
Patients with ≥1 exacerbation in the past 12 months	218 (42%)	139 (52%)	357 (46%)	227 (44%)	150 (53%)	377 (48%)
Number of exacerbations in the past 12 months resulting in ED visit	0·1 (0·4)	0·1 (0·5)	0·1 (0·4)	0·1 (0·3)	0·1 (0·3)	0·1 (0·3)
Missing data	0	1	1	1	0	1
Patients with ≥1 exacerbation in the past 12 months resulting in ED visit	19 (4%)	16 (6%)	35 (4%)	21 (4%)	23 (8%)	44 (6%)
Missing data	0	1	1	1	0	1
Number of exacerbations in the past 12 months resulting in hospitalisation	0·1 (0·3)	0·1 (0·4)	0·1 (0·3)	0·1 (0·3)	0·1 (0·3)	0·1 (0·3)
Missing data	0	1	1	1	0	1
Patients with ≥1 exacerbation in the past 12 months resulting in hospitalisation	33 (6%)	19 (7%)	52 (7%)	25 (5%)	13 (5%)	38 (5%)
Missing data	0	1	1	1	0	1
Diagnosis of allergic rhinitis	294 (57%)	161 (61%)	455 (58%)	296 (58%)	160 (57%)	456 (58%)
Nasal polyps	92 (18%)	49 (18%)	141 (18%)	82 (16%)	39 (14%)	121 (15%)
AQLQ(S)+12 score	5·39 (1·19)	5·28 (1·32)	5·36 (1·23)	5·48 (1·14)	5·27 (1·21)	5·40 (1·17)

Data are mean (SD), median (range), n, or n (%). Group names are what patients received in the preceding SIROCCO or CALIMA trials/what they received in this trial. Eosinophil counts are mean (range). ACQ-6=Asthma Control Questionnaire 6. AQLQ(S)+12=Asthma Quality of Life Questionnaire (standardised) for 12 years and older. ED=emergency department. FVC=forced vital capacity. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other. †Baseline eosinophil counts in BORA. ‡Baseline blood eosinophil counts in the preceding primary study.

Table 1: **Baseline demographics and clinical characteristics at BORA study entry (full analysis set)**

durations were 338·5 days (SD 79·1) for patients who previously received benralizumab Q4W and 350·5 days (66·1) for patients who previously received benralizumab Q8W in the SIROCCO or CALIMA trials, 340·8 days (78·4) for patients who were newly assigned benralizumab Q4W in this trial, and 345·1 days (73·6) for patients who

	Benralizumab 30 mg Q4W			Benralizumab 30 mg Q8W		
	Q4W/Q4W group (n=518)	Placebo/Q4W group (n=265)	Total (n=783)	Q8W/Q8W group (n=512)	Placebo/Q8W group (n=281)	Total (n=793)
Any AE	364 (70%)	181 (68%)	545 (70%)	361 (71%)	183 (65%)	544 (69%)
Any AE leading to treatment discontinuation	10 (2%)	8 (3%)	18 (2%)	8 (2%)	5 (2%)	13 (2%)
AEs in ≥5% of patients*						
Viral upper respiratory tract infection	78 (15%)	36 (14%)	114 (15%)	80 (16%)	41 (15%)	121 (15%)
Asthma	49 (9%)	27 (10%)	76 (10%)	41 (8%)	19 (7%)	60 (8%)
Upper respiratory tract infection	30 (6%)	21 (8%)	51 (7%)	31 (6%)	20 (7%)	51 (6%)
Bronchitis	26 (5%)	18 (7%)	44 (6%)	33 (6%)	15 (5%)	48 (6%)
Headache	25 (5%)	13 (5%)	38 (5%)	31 (6%)	9 (3%)	40 (5%)
Acute sinusitis	18 (3%)	9 (3%)	27 (3%)	27 (5%)	13 (5%)	40 (5%)
Any SAE	58 (11%)	29 (11%)	87 (11%)	53 (10%)	30 (11%)	83 (10%)
SAEs in ≥1% of patients						
Worsening asthma	19 (4%)	10 (4%)	29 (4%)	16 (3%)	9 (3%)	25 (3%)
Pneumonia	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	2 (1%)	3 (<1%)
Pneumonia caused by bacterial infection	1 (<1%)	0	1 (<1%)	2 (<1%)	2 (1%)	4 (1%)
Influenza	1 (<1%)	1 (<1%)	2 (<1%)	0	2 (1%)	2 (<1%)
Ischaemic stroke	0	0	0	0	2 (1%)	2 (<1%)
SAEs associated with infections	7 (1%)	4 (2%)	11 (1%)	9 (2%)	8 (3%)	17 (2%)
Deaths	1 (<1%)	3 (1%)	4 (1%)	2 (<1%)	1 (<1%)	3 (<1%)
Injection-site reactions	8 (2%)	6 (2%)	14 (2%)	10 (2%)	3 (1%)	13 (2%)
Hypersensitivity AEs†	12 (2%)	7 (3%)	19 (2%)	6 (1%)	7 (2%)	13 (2%)
Causally related‡	1 (<1%)	0	1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
Urticaria	0	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Anaphylactic reaction	1 (<1%)	0	1 (<1%)	0	0	0

Data are n (%), where n is the number of patients. Group names are what patients received in the preceding SIROCCO or CALIMA trials/what they received in this trial. The on-treatment period was defined as the day of the first dose of study treatment to the scheduled end-of-therapy visit. AE=adverse event. SAE=serious adverse event. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *As defined in Medical Dictionary for Regulatory Activities version 20.0. †High-level term. ‡Investigator's opinion.

***Table 2*: Adverse events, injection-site reactions, and hypersensitivity during the on-treatment period (full analysis set)**

were newly assigned benralizumab Q8W in this trial. Baseline characteristics, measured at the time patients entered BORA and presented for the full analysis set, were generally similar between patients who had been assigned placebo and those who had been assigned benralizumab in the preceding primary studies (table 1).

166 patients (about 10% of patients in each group) discontinued treatment. The primary reasons for treatment discontinuation were patient's decision (n=65), adverse events (n=28), and study-specific discontinuation criteria (n=27). The percentages of patients who had any on-treatment adverse event, any serious adverse event, or any adverse event leading to treatment discontinuation during BORA were similar between patients originally assigned benralizumab and those originally assigned placebo (ie, regardless of treatment with benralizumab for 1 year or 2 years) and between benralizumab treatment regimens (table 2). The most common adverse events in all groups were viral upper respiratory tract infections and worsening asthma (table 2). No cases of helminth infection were reported in BORA.

There were 170 serious adverse events in BORA, and the percentage of patients with serious adverse events was similar between groups (table 2), with the most common being worsening asthma (n=54), pneumonia (n=5), and pneumonia caused by bacterial infection (n=5; non-overlapping with pneumonia serious adverse events; table 2). Serious adverse events associated with infections were reported for 11 (1%) of 783 patients who received benralizumab Q4W and for 17 (2%) of 793 patients who received benralizumab Q8W (table 2). Serious adverse events that were considered by the investigator to be related to benralizumab occurred in four patients treated with benralizumab Q4W (including anaphylactic reaction in one patient who remained on this regimen from the previous study and interstitial lung disease, syncope, and hepatitis or multiple organ dysfunction syndrome in three different patients who switched to benralizumab Q4W in this study) and five patients treated with benralizumab Q8W (including chronic kidney disease and prostate cancer in two separate patients who remained on this regimen from the previous study and arthralgia, asthma, and pneumonia caused by bacterial infection in three different patients who were newly assigned benralizumab Q8W in this study; table 2).

	Benralizumab 30 mg Q4W			Benralizumab 30 mg Q8W		
	Q4W/Q4W group	Placebo/Q4W group	Total	Q8W/Q8W group	Placebo/Q8W group	Total
≥300 cells per μL*						
Number of patients	347	172	519	339	188	527
Asthma exacerbations						
≥1 exacerbation	89 (26%)	56 (33%)	145 (28%)	88 (26%)	60 (32%)	148 (28%)
Crude annual rate (95% CI)	0·48 (0·42–0·56)	0·53 (0·43–0·65)	0·50 (0·44–0·56)	0·46 (0·39–0·53)	0·57 (0·47–0·68)	0·49 (0·44–0·56)
Exacerbations per patient	0·5 (1·1)	0·5 (1·0)	0·5 (1·1)	0·5 (1·0)	0·6 (1·2)	0·5 (1·1)
Exacerbations leading to ED visits						
≥1 exacerbation	7 (2%)	5 (3%)	12 (2%)	13 (4%)	7 (4%)	20 (4%)
Crude annual rate (95% CI)	0·03 (0·02–0·05)	0·03 (0·02–0·08)	0·03 (0·02–0·05)	0·04 (0·03–0·07)	0·06 (0·04–0·11)	0·05 (0·03–0·07)
Exacerbations per patient	0·0 (0·3)	0·0 (0·2)	0·0 (0·2)	0·0 (0·2)	0·1 (0·4)	0·1 (0·3)
Exacerbations leading to hospitalisation						
≥1 exacerbation	11 (3%)	7 (4%)	18 (3%)	11 (3%)	8 (4%)	19 (4%)
Crude annual rate (95% CI)	0·05 (0·03–0·07)	0·04 (0·02–0·08)	0·04 (0·03–0·07)	0·03 (0·02–0·06)	0·05 (0·03–0·10)	0·04 (0·03–0·06)
Exacerbations per patient	0·0 (0·3)	0·0 (0·2)	0·0 (0·3)	0·0 (0·2)	0·1 (0·3)	0·0 (0·2)
<300 cells per μL*						
Number of patients	171	93	264	173	93	266
Asthma exacerbations						
≥1 exacerbation	59 (35%)	42 (45%)	101 (38%)	59 (34%)	31 (33%)	90 (34%)
Crude annual rate (95% CI)	0·74 (0·62–0·88)	0·80 (0·64–1·00)	0·76 (0·66–0·87)	0·59 (0·49–0·71)	0·74 (0·59–0·94)	0·64 (0·55–0·74)
Exacerbations per patient	0·7 (1·8)	0·8 (1·3)	0·8 (1·6)	0·6 (1·1)	0·8 (1·7)	0·7 (1·3)
Exacerbations leading to ED visits						
≥1 exacerbation	5 (3%)	3 (3%)	8 (3%)	6 (4%)	3 (3%)	9 (3%)
Crude annual rate (95% CI)	0·03 (0·01–0·07)	0·04 (0·02–0·11)	0·03 (0·02–0·07)	0·03 (0·01–0·07)	0·04 (0·02–0·11)	0·04 (0·02–0·07)
Exacerbations per patient	0·0 (0·2)	0·0 (0·3)	0·0 (0·2)	0·0 (0·2)	0·0 (0·3)	0·0 (0·2)
Exacerbations leading to hospitalisation						
≥1 exacerbation	9 (5)	7 (8)	16 (6)	7 (4)	4 (4)	11 (4)
Crude annual rate (95% CI)	0·05 (0·03–0·10)	0·09 (0·04–0·17)	0·06 (0·04–0·10)	0·05 (0·03–0·10)	0·05 (0·02–0·13)	0·05 (0·03–0·09)
Exacerbations per patient	0·1 (0·2)	0·1 (0·3)	0·1 (0·3)	0·1 (0·3)	0·1 (0·3)	0·1 (0·3)

Data are n (%) or mean (SD), unless otherwise stated. Group names are what patients received in the preceding SIROCCO or CALIMA trials/what they received in this trial. ED=emergency department. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Eosinophil counts at baseline in SIROCCO or CALIMA.

***Table 3*: Asthma exacerbation rates by baseline blood eosinophil count (full analysis set)**

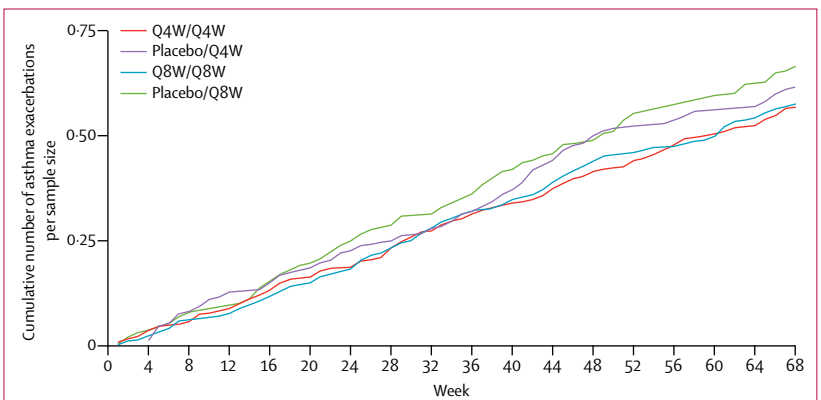

***Figure 2*: Cumulative number of new exacerbations over time for patients with baseline blood eosinophil counts ≥300 cells per μL (full analysis set)**
Group names are what patients received in the preceding SIROCCO or CALIMA trials/what they received in this trial. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

Independently adjudicated new malignancies occurred in 12 (1%) of 1576 patients (four in each group [1–2%] except for the group newly assigned benralizumab Q8W in this study, for which no new malignancies were reported). Malignancies were chronic myeloid leukaemia (n=1), colon cancer (n=1), pancreatic cancer (n=1; diagnosed post-treatment), and stage II diffuse large B-cell lymphoma (n=1; diagnosed post-treatment) in the group that remained on benralizumab Q4W from the preceding studies; basal cell carcinoma (n=2; one diagnosed post-treatment), colon adenocarcinoma (n=1), and stage II diffuse large B-cell lymphoma (n=1) in the group that was newly assigned benralizumab Q4W; and B-cell lymphoma (n=1), nasal cavity cancer (n=1), and prostate cancer (n=2; one diagnosed post-treatment) in the group that remained on benralizumab Q8W. Only one malignancy (prostate cancer in a patient who remained on the Q8W regimen) was considered to be related to treatment with the study drug by the investigator (for more information about this patient, see the appendix).

	Benralizumab 30 mg Q4W			Benralizumab 30 mg Q8W		
	Q4W/Q4W group	Placebo/Q4W group	Total	Q8W/Q8W group	Placebo/Q8W group	Total
≥300 cells per µL*						
Baseline						
Number of patients	347	172	519	339	188	527
Pre-bronchodilator FEV_1 (L)	2·012 (0·680)	1·990 (0·811)	2·005 (0·725)	2·066 (0·746)	1·988 (0·770)	2·038 (0·755)
Week 48						
Number of patients	308	150	458	310	169	479
Pre-bronchodilator FEV_1 (L)	1·992 (0·706)	2·142 (0·791)	2·041 (0·738)	2·111 (0·765)	2·117 (0·808)	2·113 (0·780)
Mean change from baseline (L)	−0·011 (0·323; −0·047 to 0·025)	0·129 (0·449; 0·057 to 0·200)	0·035 (0·374; 0·001 to 0·069)	0·053 (0·345; 0·015 to 0·092)	0·125 (0·402; 0·065 to 0·186)	0·079 (0·367; 0·046 to 0·112)
Week 56†						
Number of patients	297	142	439	291	151	442
Pre-bronchodilator FEV_1 (L)	1·963 (0·670)	2·050 (0·785)	1·991 (0·710)	2·055 (0·777)	2·005 (0·780)	2·038 (0·777)
Mean change from baseline (L)	−0·006 (0·295; −0·039 to 0·028)	0·131 (0·422; 0·061 to 0·200)	0·038 (0·346; 0·006 to 0·071)	0·019 (0·317; −0·018 to 0·055)	0·081 (0·419; 0·014 to 0·148)	0·040 (0·356; 0·007 to 0·073)
<300 cells per µL*						
Baseline						
Number of patients	171	93	264	173	93	266
Pre-bronchodilator FEV_1 (L)	1·835 (0·721)	1·709 (0·733)	1·790 (0·726)	1·916 (0·758)	2·034 (0·905)	1·957 (0·813)
Week 48						
Number of patients	150	83	233	162	80	242
Pre-bronchodilator FEV_1 (L)	1·853 (0·691)	1·771 (0·786)	1·824 (0·725)	1·936 (0·763)	2·159 (0·959)	2·010 (0·837)
Mean change from baseline (L)	0·016 (0·332; −0·037 to 0·069)	0·017 (0·514; −0·094 to 0·127)	0·016 (0·405; −0·036 to 0·068)	0·001 (0·304; −0·046 to 0·048)	0·073 (0·407; −0·016 to 0·162)	0·025 (0·342; −0·018 to 0·068)
Week 56†						
Number of patients	147	79	226	149	69	218
Pre-bronchodilator FEV_1 (L)	1·786 (0·692)	1·687 (0·710)	1·751 (0·698)	1·812 (0·695)	1·855 (0·831)	1·826 (0·739)
Mean change from baseline (L)	−0·021 (0·376; −0·081 to 0·040)	−0·011 (0·280; −0·073 to 0·051)	−0·017 (0·345; −0·062 to 0·028)	−0·015 (0·293; −0·062 to 0·032)	0·030 (0·350; −0·053 to 0·112)	−0·001 (0·312; −0·042 to 0·040)

Data are n, mean (SD), or mean (SD; 95% CI). Group names are what patients received in the preceding SIROCCO or CALIMA trials/what they received in this trial. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Eosinophil counts at baseline of preceding primary studies. †Week 56 data are for adults only.

Table 4: **Changes in pre-bronchodilator FEV_1 by baseline blood eosinophil count (full analysis set)**

31 (2%) of 1576 patients discontinued treatment because of adverse events, with similar percentages of patients discontinuing treatment in each group (2–3%). Seven patients died during treatment, including three newly assigned benralizumab Q4W (one because of asthma and two because of unknown reasons), one newly assigned benralizumab Q8W (because of ischaemic stroke), one who remained on benralizumab Q4W from the predecessor study (because of cardiac arrest), and two who remained on benralizumab Q8W (one because of pulmonary sepsis and the other because of sepsis; table 2). A further two adult patients died during the post-treatment period because of asthma or multiple organ dysfunction syndrome. No adolescent patient died during the study. One death (multiple organ dysfunction syndrome in a patient who was newly assigned benralizumab Q4W) was considered related to treatment with the study drug by the investigator (for more information about this patient, see the appendix).

Overall, 27 (2%) of 1576 patients experienced injection-site reactions (table 2). The percentages of patients who had hypersensitivity adverse events were similar across the four groups (table 2). Three patients reported hypersensitivity adverse events that the investigator considered to be causally related to treatment (table 2). Positive test results for anti-drug antibodies were reported for 39 (8%) of 518 patients who remained on benralizumab Q4W, 41 (15%) of 265 patients who were newly assigned benralizumab Q4W, 57 (11%) of 512 patients who remained on the Q8W regimen, and 36 (13%) of 281 patients newly assigned benralizumab Q8W (appendix). A slight decrease in eosinophil-depleting activity due to high titres of anti-drug antibodies was noted only at very low trough concentrations of benralizumab in all groups (data not shown). There was no indication that positivity for anti-drug antibodies was associated with hypersensitivity or affected efficacy outcomes (data not shown).

The primary efficacy analyses in SIROCCO and CALIMA focussed on patients with baseline blood eosinophil counts of 300 cells per µL or greater and demonstrated that these patients responded better to

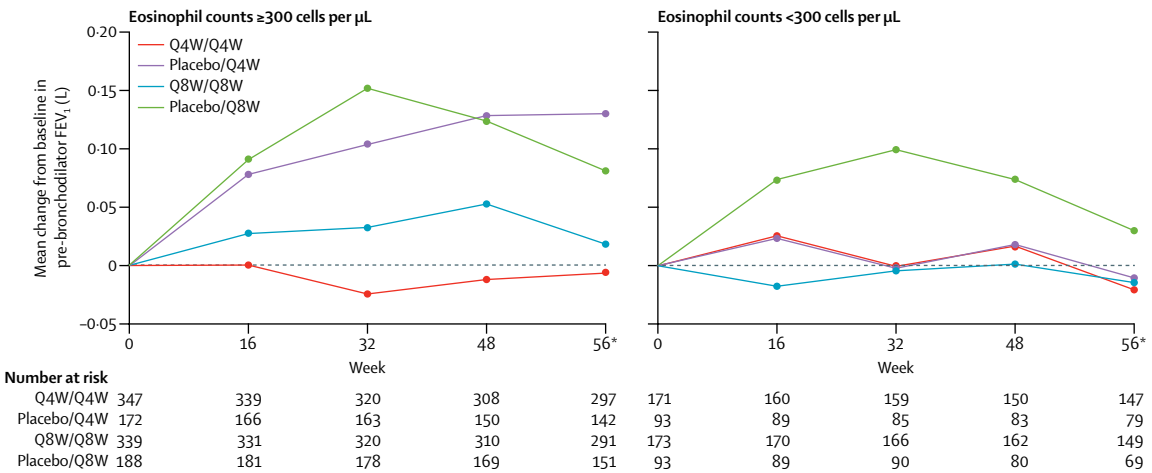

***Figure 3*: Change from baseline in pre-bronchodilator FEV_1 by baseline blood eosinophil counts (full analysis set)**
Group names are what patients received in the preceding SIROCCO or CALIMA trials/what they received in this trial. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Data at this timepoint are from adult patients only.

	Benralizumab 30 mg Q4W			Benralizumab 30 mg Q8W		
	Q4W/Q4W group	Placebo/Q4W group	Total	Q8W/Q8W group	Placebo/Q8W group	Total
≥300 cells per µL*						
Baseline						
Number of patients	346	172	518	336	188	524
ACQ-6 score	1·34 (1·14)	1·49 (1·18)	1·39 (1·16)	1·28 (1·05)	1·55 (1·19)	1·38 (1·11)
Week 48						
Number of patients	320	158	478	316	173	489
ACQ-6 score	1·32 (1·06)	1·26 (1·07)	1·30 (1·06)	1·25 (1·06)	1·30 (1·02)	1·27 (1·05)
Mean change from baseline†	0·01 (0·89; −0·09 to 0·10)	−0·27 (0·94; −0·42 to −0·13)	−0·09 (0·92; −0·17 to 0·00)	0·00 (0·81; −0·09 to 0·09)	−0·23 (1·07; −0·39 to −0·07)	−0·08 (0·92; −0·16 to 0·00)
Week 56‡						
Number of patients	299	146	445	297	153	450
ACQ-6 score	1·30 (1·03)	1·36 (1·14)	1·32 (1·07)	1·20 (1·04)	1·30 (1·02)	1·23 (1·03)
Mean change from baseline†	−0·04 (0·83; −0·14 to 0·05)	−0·20 (1·04; −0·37 to −0·03)	−0·09 (0·91; −0·18 to −0·01)	−0·06 (0·82; −0·15 to 0·03)	−0·25 (1·06; −0·41 to −0·08)	−0·12 (0·91; −0·21 to −0·04)
<300 cells per µL*						
Baseline						
Number of patients	171	92	263	173	92	265
ACQ-6 score	1·77 (1·10)	1·94 (1·17)	1·83 (1·13)	1·64 (1·09)	1·75 (1·31)	1·68 (1·17)
Week 48						
Number of patients	157	83	240	164	85	249
ACQ-6 score	1·58 (1·16)	1·90 (1·13)	1·69 (1·16)	1·58 (1·11)	1·56 (1·07)	1·57 (1·09)
Mean change from baseline†	−0·19 (0·91; −0·33 to −0·05)	−0·04 (0·87; −0·23 to 0·14)	−0·14 (0·90; −0·25 to −0·03)	−0·07 (0·79; −0·19 to 0·05)	−0·29 (0·98; −0·50 to −0·08)	−0·14 (0·86; −0·25 to −0·04)
Week 56‡						
Number of patients	149	79	228	150	67	217
ACQ-6 score	1·59 (1·08)	1·81 (1·07)	1·67 (1·08)	1·60 (1·09)	1·84 (1·15)	1·68 (1·11)
Mean change from baseline†	−0·16 (0·90; −0·31 to −0·02)	−0·12 (0·80; −0·29 to 0·06)	−0·15 (0·86; −0·26 to −0·03)	−0·10 (0·83; −0·23 to 0·04)	−0·09 (1·06; −0·35 to 0·16)	−0·10 (0·90; −0·22 to 0·02)

Data are n, mean (SD), or mean (SD; 95% CI). Group names are what patients received in the preceding SIROCCO or CALIMA trials/what they received in this trial. ACQ-6=Asthma Control Questionnaire 6. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Eosinophil counts at baseline of preceding primary studies. †Data not available for all patients. ‡Week 56 data are for adults only.

***Table 5*: Changes in ACQ-6 score by baseline blood eosinophil count (full analysis set)**

treatment than did patients with baseline blood eosinophil counts of less than 300 cells per µL.[14,15] Unless otherwise stated, efficacy results focus on patients with baseline blood eosinophil counts of 300 cells per µL or greater, with the count based on the eosinophil measurement at the time patients entered SIROCCO or CALIMA and not on the count recorded on entry to BORA. Only the results for patients with blood eosinophil counts of 300 cells per µL or greater are presented in the text; the results for patients with blood eosinophil counts of less than 300 cells per µL at baseline are presented in the tables and figures.

753 (72%) of 1046 patients with blood eosinophil counts of 300 cells per µL or greater at baseline did not have asthma exacerbations during benralizumab treatment in BORA, including 251 (74%) of 339 patients who continued on benralizumab Q8W (table 3). The crude asthma exacerbation rate for patients who received benralizumab in SIROCCO or CALIMA was 0·48 (95% CI 0·42–0·56; Q4W group) or 0·46 (0·39–0·53; Q8W group). For patients who previously received placebo, the crude exacerbation rate was 0·53 (0·43–0·65; Q4W group) or 0·57 (0·47–0·68; Q8W group). The cumulative number of new exacerbations remained constant over time during BORA (figure 2) and, after allowing for differences in the number of patients between groups, was similar between patients who were previously or newly treated with benralizumab. For patients who previously received benralizumab, exacerbation frequencies and rates were maintained into the second year of treatment (table 3). 37 (4%) of 1046 patients who received benralizumab in BORA had exacerbations that led to hospital admission, which is similar to the percentages in SIROCCO and CALIMA (4–6%, unpublished).

For patients who had previously received benralizumab, pre-bronchodilator FEV_1 values were maintained into the second year of treatment, whereas for patients who previously received placebo, benralizumab treatment increased pre-bronchodilator FEV_1 to values comparable with other cohorts (table 4). Improvements in pre-bronchodilator FEV_1 for patients who were newly assigned benralizumab in this study were observed as early as week 16, the first post-baseline measurement (figure 3).

Benralizumab also maintained (for patients who received benralizumab in SIROCCO or CALIMA) or improved (for patients who received placebo in these studies) ACQ-6 and AQLQ(S)+12 scores (tables 5, 6). Improvements in ACQ-6 and AQLQ(S)+12 scores were observed by week 12 of treatment for patients who previously received placebo (appendix).

Blood eosinophil depletion was maintained through the second year of treatment with benralizumab, with negligible serum concentrations for patients who remained on benralizumab from the predecessor trials (appendix). Blood eosinophil counts of patients who previously received placebo were reduced to 0 cells per µL with benralizumab treatment by week 12, and this depletion was maintained throughout the treatment period. Blood eosinophil counts began to increase after treatment discontinuation for adult patients (week 68; adolescent patients were still receiving treatment at the data cutoff), with the rate of increase between week 56 and week 68 similar for patients who were newly treated with benralizumab (preceding primary trial placebo patients) and those who were previously treated with benralizumab, within each dosing regimen.

Discussion

This first report of the BORA safety and efficacy extension trial presents the complete and final results for adult patients and the first-year results for adolescent patients. Patients who completed the phase 3 SIROCCO or CALIMA trials and then received a second year of benralizumab had safety and efficacy results that were similar to those of patients from the placebo cohorts of SIROCCO or CALIMA who then received benralizumab for 1 year in this trial. Safety results were similar between the different treatment regimens and between patients who received 1 year of benralizumab in either SIROCCO or CALIMA and those who received a second year of benralizumab in BORA. 65–71% of patients had an adverse event in BORA, which led to treatment discontinuation in 2–3% of patients. In SIROCCO or CALIMA, 71–75% of patients treated with benralizumab had an adverse event, with 2% of patients discontinuing as a result of the event.[14,15] The most common adverse events in BORA were also the most common events in SIROCCO and CALIMA, except for nasopharyngitis (in 1% of patients in BORA and 12–21% of patients in SIROCCO or CALIMA) and viral upper respiratory tract infection (in 15–16% of patients in BORA and in no patients in SIROCCO or CALIMA).[14,15]

Serious adverse events were reported by 10–11% of patients in BORA compared with 9–13% of patients treated with benralizumab in SIROCCO or CALIMA. Nine (1%) of 1576 patients in BORA had serious adverse events considered by the investigator to be associated with benralizumab treatment compared with six (<1%) of 1663 patients in SIROCCO and CALIMA, with worsening asthma being the only serious adverse event that was reported in all three trials. In BORA, the investigators were aware that their patients were receiving benralizumab, whereas, in the preceding primary studies, patients could have been receiving benralizumab or placebo. This knowledge might have biased the investigators towards identifying a serious adverse event as being related to the investigational drug.

1–2% of patients experienced serious adverse events associated with infections during the 1-year period in BORA, which was similar to the percentages in the SIROCCO and CALIMA trials. This finding is

	Benralizumab 30 mg Q4W			Benralizumab 30 mg Q8W		
	Q4W/Q4W group	Placebo/Q4W group	Total	Q8W/Q8W group	Placebo/Q8W group	Total
≥300 cells per μL*						
Baseline						
Number of participants	346	172	518	337	188	525
AQLQ(S)+12 score	5·39 (1·19)	5·28 (1·32)	5·36 (1·23)	5·48 (1·14)	5·27 (1·21)	5·40 (1·17)
Week 48						
Number of participants	317	157	474	316	171	487
AQLQ(S)+12 score	5·41 (1·18)	5·44 (1·30)	5·42 (1·22)	5·53 (1·15)	5·51 (1·13)	5·52 (1·15)
Mean change from baseline†	−0·00 (0·90; −0·10 to 0·10)	0·19 (0·95; 0·04 to 0·34)	0·06 (0·92; −0·02 to 0·15)	0·02 (0·89; −0·08 to 0·12)	0·26 (1·02; 0·10 to 0·41)	0·10 (0·95; 0·02 to 0·19)
Week 56‡						
Number of participants	297	146	443	295	153	448
AQLQ(S)+12 score	5·42 (1·16)	5·42 (1·22)	5·42 (1·18)	5·58 (1·14)	5·47 (1·13)	5·54 (1·14)
Mean change from baseline†	0·02 (0·80; −0·07 to 0·11)	0·21 (0·98; 0·05 to 0·37)	0·08 (0·87; 0·00 to 0·16)	0·08 (0·91; −0·02 to 0·19	0·26 (1·00; 0·10 to 0·42)	0·15 (0·94; 0·06 to 0·23)
<300 cells per μL*						
Baseline						
Number of participants	171	92	263	173	92	265
AQLQ(S)+12 score	4·97 (1·18)	4·78 (1·18)	4·91 (1·18)	5·07 (1·17)	5·10 (1·28)	5·09 (1·21)
Week 48						
Number of participants	155	83	238	164	85	249
AQLQ(S)+12 score	5·16 (1·24)	4·82 (1·12)	5·04 (1·20)	5·23 (1·19)	5·10 (1·21)	5·18 (1·20)
Mean change from baseline†	0·16 (0·84; 0·02 to 0·29)	0·04 (1·00; −0·18 to 0·25)	0·12 (0·90; 0·00 to 0·23)	0·14 (0·85; 0·01 to 0·27)	0·08 (0·96; −0·12 to 0·29)	0·12 (0·89; 0·01 to 0·23)
Week 56‡						
Number of participants	148	79	227	149	67	216
AQLQ(S)+12 score	5·12 (1·13)	4·81 (1·15)	5·01 (1·15)	5·21 (1·14)	4·93 (1·17)	5·12 (1·16)
Mean change from baseline†	0·11 (0·84; −0·02 to 0·25)	0·03 (0·89; −0·16 to 0·23)	0·09 (0·85; −0·03 to 0·20)	0·15 (0·90; 0·00 to 0·29)	0·02 (1·06; −0·23 to 0·28)	0·11 (0·95; −0·02 to 0·24)

Data are n, mean (SD), mean (SD; 95% CI). Group names are what patients received in the preceding SIROCCO or CALIMA trials/what they received in this trial. AQLQ(S)+12=Asthma Quality of Life Questionnaire (standardised) for 12 years and older. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Eosinophil counts at baseline of preceding primary studies. †Data not available for all patients. ‡Week 56 data are for adults only.

Table 6: **Changes in AQLQ(S)+12 score by baseline blood eosinophil count (full analysis set)**

consistent with previous reports that indicated that patients with low blood eosinophil counts due to disease or treatments do not have an apparent increased risk of infections.[17,18] These results support the observation that eosinophil depletion by benralizumab does not increase the risk of infection. Furthermore, peripheral blood eosinophil counts recovered after discontinuation of benralizumab, indicating that the effects on eosinophil depletion are not associated with long-term bone marrow suppression after medication withdrawal.

The adjudicated malignancy rate in BORA was low (12 of 1576 patients). One malignancy deemed by the investigator to be related to benralizumab (prostate cancer in a patient who remained on benralizumab Q8W from the preceding trial) occurred 3 days after the second dose of benralizumab. The patient had a history of prostatic hypertrophy and elevated prostate-specific antigen. There was insufficient evidence in a review of the data for these malignancies to support a causal relationship between benralizumab and cancer.

The percentage of patients who died in BORA (n=9 [1%]) was similar to the percentages of patients who died in the benralizumab groups in SIROCCO and CALIMA (n=9 [1%]). Unlike SIROCCO or CALIMA, one death in BORA (in a patient who was newly assigned benralizumab Q4W in this study) was deemed by the investigator to be related to benralizumab treatment. This patient was admitted to the hospital with severe hepatitis, and the cause of death was multi-organ failure (judged by the investigator), which occurred 40 days after the last treatment dose. The patient had a history of alcohol intake and liver steatosis.

Positive anti-drug antibody responses occurred in 8–11% of patients receiving benralizumab for a second year compared with 12–15% of patients in SIROCCO or CALIMA.[14,15] Similar to SIROCCO and CALIMA, there was no indication that the positive anti-drug response was associated with hypersensitivity or affected efficacy

outcomes in BORA.

Improvements in efficacy outcomes with benralizumab observed in SIROCCO and CALIMA were maintained with an additional year of treatment in BORA. Patients who previously received placebo in SIROCCO and CALIMA appeared to have improvements in efficacy outcomes with benralizumab, consistent with what was observed with active treatment in the preceding primary studies.[14,15] As the analyses in BORA were performed without a placebo control, all conclusions are descriptive. The annual asthma exacerbation rate estimate after 1 year of benralizumab Q8W for patients with blood eosinophil counts of 300 cells per μL or greater at baseline was 0·65–0·66 in SIROCCO and CALIMA compared with a crude rate of 0·57 in BORA.[14,15] 379 (72%) of 527 patients with baseline blood eosinophil counts of 300 cells per μL or greater who received benralizumab Q8W in this study had not experienced a disease exacerbation by week 56, with the percentage greater for patients who were in their second year of treatment than for those who were in their first (74% *vs* 68%). 176 (66%) of 266 patients with blood eosinophil counts of less than 300 cells per μL at baseline who received benralizumab Q8W were exacerbation-free, with an annual exacerbation rate of 0·59 for patients who had received this dosage for 2 years. These results indicate that benralizumab benefits patients across a broad range of baseline blood eosinophil counts, but that patients with elevated eosinophil counts might derive greater benefit from treatment, consistent with previous findings using the pooled results of SIROCCO and CALIMA.[19,20] These studies observed that additional manifestations of eosinophilic airway inflammation, such as baseline exacerbation frequency, might be needed to identify patients with moderately elevated blood eosinophil counts who might respond to treatment with benralizumab.[19,20]

Pre-bronchodilator FEV_1 improved by 0·125 L between baseline and week 48 for patients in the benralizumab Q8W group with blood eosinophil counts of 300 cells per μL or greater who previously received placebo. Improvements in lung function that were obtained with benralizumab treatment in SIROCCO or CALIMA were maintained after 1 year of treatment in BORA. Consistent with previous studies, greater improvements were observed for patients with blood eosinophil counts of 300 cells per μL or greater at baseline than for those with baseline counts of less than 300 cells per μL.[14,15] Similar findings were also noted for improvements in ACQ-6 and AQLQ(S)+12 scores. These improvements in efficacy were accompanied by nearly complete depletion of blood eosinophil counts, as was observed in SIROCCO and CALIMA,[14,15] and maintained over the 2-year treatment period. Overall, these results indicate that improvements in exacerbation frequency, lung function, and symptoms obtained with 1 year of benralizumab can be sustained with longer treatment, while maintaining safety and tolerability. For patients who entered BORA, integrated analyses are ongoing to describe efficacy and safety measures over the entire 2-year treatment period. These analyses will be the focus of a future publication.

In BORA, the safety and efficacy profiles for benralizumab Q8W were similar to, if not numerically better than, the Q4W regimen, with the caveat that this study was not designed to assess differences between treatment groups. These findings are consistent with SIROCCO and CALIMA results and support the use of this regimen for the treatment of patients with severe, uncontrolled eosinophilic asthma.[14,15]

This study has some limitations. There was no placebo control group (although patients were masked to regimen assignment) and so improvements over placebo beyond 1 year could not be demonstrated. Although investigators and patients in the preceding primary trials were masked to treatment assignment, they could have inferred that they were giving or receiving benralizumab based on efficacy, leading to rollover bias. However, rollover from the preceding primary studies into BORA was high (about 86%).[14,15] The safety profile of benralizumab and reasons for treatment discontinuation were similar between BORA and the SIROCCO and CALIMA trials,[14,15] supporting the maintenance of efficacy and safety commensurate with that described in SIROCCO and CALIMA. This study is an extension trial for 1 year in adults and 2 years for adolescents. Longer-term safety with benralizumab treatment beyond this period cannot be ascertained and will be addressed for adults in the extension MELTEMI study, which will include patients from this study.

Because ZONDA was a shorter (28 weeks) and smaller study than SIROCCO (48 weeks) or CALIMA (56 weeks) and about 50% of patients in ZONDA went into the MELTEMI long-term safety trial without completing the 1-year follow up in BORA, the patients from ZONDA were not included in this analysis. Moreover, these patients were not included because ZONDA differed from the other two studies in that it was an oral corticosteroid reduction study. Results for ZONDA patients will be reported as part of a later, larger integrated analysis of all three studies.

In conclusion, this study indicates that benralizumab, when administered for 2 years, has a safety and tolerability profile similar to that observed over 1 year in SIROCCO and CALIMA. Furthermore, we demonstrated that long-term eosinophil depletion by benralizumab did not lead to any new adverse consequences. This extension study reaffirms that treatment with benralizumab Q8W potently decreases eosinophil counts. Improvements in efficacy measures (exacerbation rate, lung function, and asthma symptoms) demonstrated in the preceding primary randomised controlled trials were maintained over longer-term follow-up for patients in BORA with severe, uncontrolled asthma and an eosinophilic phenotype.

Conceptually, longer treatment with benralizumab might affect pathophysiological mechanisms, such as eosinophilic mucous plug formation and inflammatory changes, and decrease the rate of lung function decline that is associated with exacerbations. These effects would be of interest to investigate in the future. The results of this study support the use of benralizumab for the add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype not controlled with inhaled corticosteroids and long-acting β_2-agonists.

Contributors

WWB, ERB, JMF, GTF, and MG conceived and designed the study. PB, SS, RFO, UJM, and MG acquired the data. All authors had access to and analysed and interpreted the data, participated in the development and critical review of the manuscript, approved submission of the manuscript for publication, and are accountable for the accuracy and integrity of the work.

Declaration of interests

WWB reports personal fees from 3M, AstraZeneca, Boehringer Ingelheim, Boston Scientific, Circassia, Genentech, GlaxoSmithKline (GSK), ICON, Novartis, Roche, Sanofi, and Teva. ERB has performed clinical trials through his former employer, the Wake Forest School of Medicine, and his current employer, the University of Arizona, and has served as a paid consultant for AstraZeneca/MedImmune, GSK, Novartis, Regeneron, and Sanofi Genzyme. JMF is an advisory board member for AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Sanofi Regeneron, and Teva, and has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Cephalon/Teva, and Novartis. GTF reports grants and personal fees from Novartis, AstraZeneca, Pearl Therapeutics, and Sunovian, as well as grants from Forest and personal fees from GSK. PB, RFO, UJM, and MG are employees of AstraZeneca. SS is an employee of Optimum Statistics, and provided statistical analyses and support under contract to AstraZeneca through inVentiv Health Clinical.

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