

Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial



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Summary

Background Eosinophilia is associated with worsening asthma severity and decreased lung function, with increased exacerbation frequency. We assessed the safety and efficacy of benralizumab, a monoclonal antibody against interleukin-5 receptor α that depletes eosinophils by antibody-dependent cell-mediated cytotoxicity, for patients with severe, uncontrolled asthma with eosinophilia.

Methods We did a randomised, double-blind, parallel-group, placebo-controlled phase 3 study at 374 sites in 17 countries. We recruited patients (aged 12–75 years) with a physician-based diagnosis of asthma for at least 1 year and at least two exacerbations while on high-dosage inhaled corticosteroids and long-acting β_2 -agonists (ICS plus LABA) in the previous year. Patients were randomly assigned (1:1:1) by an interactive web-based voice response system to benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses every 4 weeks) or placebo Q4W for 48 weeks as add on to their standard treatment. Patients were stratified 2:1 according to blood eosinophil counts of at least 300 cells per μ L and less than 300 cells per μ L. All patients and investigators involved in patient treatment or clinical assessment were masked to treatment allocation. The primary endpoint was annual exacerbation rate ratio versus placebo, and key secondary endpoints were prebronchodilator forced expiratory volume in 1 s (FEV₁) and total asthma symptom score at week 48, for patients with blood eosinophil counts of at least 300 cells per μ L. Efficacy analyses were by intention to treat (based on the full analysis set); safety analyses included patients according to study drug received. This study is registered with ClinicalTrials.gov, number NCT01928771.

Findings Between Sept 19, 2013, and March 16, 2015, 2681 patients were enrolled, 1205 of whom met the study criteria and were randomly assigned: 407 to placebo, 400 to benralizumab 30 mg Q4W, and 398 to benralizumab 30 mg Q8W. 267 patients in the placebo group, 275 in the benralizumab 30 mg Q4W group, and 267 in the benralizumab 30 mg Q8W group had blood eosinophil counts at least 300 cells per μ L and were included in the primary analysis population. Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when given Q4W (rate ratio 0.55, 95% CI 0.42–0.71; $p < 0.0001$) or Q8W (0.49, 0.37–0.64; $p < 0.0001$). Both benralizumab dosing regimens significantly improved prebronchodilator FEV₁ in patients at week 48 compared with placebo (least-squares mean change from baseline: Q4W group 0.106 L, 95% CI 0.016–0.196; Q8W group 0.159 L, 0.068–0.249). Compared with placebo, asthma symptoms were improved by the Q8W regimen (least-squares mean difference –0.25, 95% CI –0.45 to –0.06), but not the Q4W regimen (–0.08, –0.27 to 0.12). The most common adverse events were worsening asthma (105 [13%] of 797 benralizumab-treated patients vs 78 [19%] of 407 placebo-treated patients) and nasopharyngitis (93 [12%] vs 47 [12%]).

Interpretation These results confirm the efficacy and safety of benralizumab for patients with severe asthma and elevated eosinophils, which are uncontrolled by high-dosage ICS plus LABA, and provide support for benralizumab to be an additional option to treat this disease in this patient population.

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Introduction

Asthma has been estimated to affect more than 315 million people worldwide, with approximately 10% having severe or uncontrolled asthma.^{1,2} The worldwide prevalence of asthma continues to increase, and is projected to reach more than 400 million by 2020,³ representing a growing unmet need for the treatment of patients with uncontrolled disease.

Patients with severe asthma need high-dosage inhaled corticosteroids in combination with long-acting β_2 -agonists to control their disease.⁴ Despite the proven effectiveness of this approach for most asthmatics, many patients continue to have uncontrolled disease and are at risk for severe asthma exacerbations. Patients with severe, uncontrolled asthma experience a high disease burden, including recurrent exacerbations and hospital

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See Online for appendix

Research in context

Evidence before this study

Benralizumab is a humanised, anti-eosinophil monoclonal antibody against interleukin-5 receptor α that is intended for patients with severe, uncontrolled asthma with eosinophilic inflammation. We searched PubMed on June 7, 2016, for articles with the terms “asthma”, “anti-interleukin-5”, and “eosinophil” in the title or abstract. This search yielded 29 results, including one study describing a randomised, controlled, double-blind, dose-ranging phase 2b trial of benralizumab for patients with uncontrolled eosinophilic asthma. Based on this systematic review, benralizumab is the only monoclonal antibody against interleukin-5 receptor α used to treat asthma. Benralizumab induces direct, rapid, and nearly complete depletion of eosinophils in the bone marrow, blood, and target tissue via enhanced antibody-dependent cell-mediated cytotoxicity. Given the promising results obtained in the phase 2b trial, we undertook the phase 3 SIROCCO study to confirm the efficacy

and safety of benralizumab 30-mg dosage for patients with severe, uncontrolled, eosinophilic asthma, and to seek regulatory approval in the USA, Europe, and Japan.

Added value of this study

This study is, to our knowledge, the first phase 3 trial of benralizumab in patients with severe, uncontrolled asthma with eosinophilic inflammation. Benralizumab given once every 4 or 8 weeks decreased exacerbations and improved lung function, with improvement in asthma symptoms noted with the once every 8 weeks dosage.

Implications of all the available evidence

Severe asthma affects the health and wellbeing of millions of people worldwide. Exacerbations are life threatening for these patients, and their health-related quality of life is substantially diminished. These findings show the potential for benralizumab to improve outcomes for patients with severe asthma.

admissions (defined as admission to an inpatient facility and/or assessment and treatment in a health-care facility for ≥ 24 h).^{5,6} As a result, most health-care resources used for asthma care are attributable to those patients with severe disease.^{5,6} Furthermore, the cost of asthma increases proportionally with disease severity.⁷

Eosinophilic inflammation is present in approximately 50% of patients with asthma⁸ and is associated with asthma severity, greater frequency of exacerbations, and decreased lung function.^{9,10} Additionally, poor asthma control is associated with progressive increases in sputum and blood eosinophil counts.¹¹

Interleukin 5 is one of several cytokine mediators involved in eosinophil development, activation, proliferation, and survival, and concentrations of this cytokine in the lungs are increased in patients with asthma.^{12,13} Findings from clinical trials have shown efficacy and safety of treatment with monoclonal antibodies against interleukin 5 in patients with asthma and have led to the approval of mepolizumab and reslizumab in the USA and mepolizumab in Europe as add-on maintenance treatment for patients with severe asthma aged 18 years (reslizumab) or 12 years (mepolizumab) and older with an eosinophilic phenotype.^{14–17}

Benralizumab is a humanised, afucosylated, monoclonal antibody against interleukin-5 receptor α that induces direct, rapid, and nearly complete depletion of eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity, an apoptotic process of eosinophil elimination involving natural killer cells.^{18,19} This mechanism is in contrast to current treatments, which target interleukin 5 directly and act through a passive (ie, indirect) mechanism that ultimately results in eosinophil reduction but not depletion.¹² Benralizumab has a broad efficacy profile for patients with severe, uncontrolled asthma with eosinophilic inflammation.^{20–22} In a phase 2b study,²²

benralizumab 100 mg Q8W for 1 year seemed to reduce exacerbation rates compared with placebo (0·34 vs 0·57; 41% reduction, 80% CI 11–60; $p=0\cdot096$) for patients with uncontrolled asthma treated with medium-dosage or high-dosage inhaled corticosteroids and long-acting β_2 -agonists (ICS plus LABA). A lower 20 mg dosage was efficacious in reducing exacerbation rates (0·30 vs 0·68 in placebo, 57% reduction, 80% CI 33–72; $p=0\cdot015$) in patients with blood eosinophil counts at least 300 cells per μL .²² Results from this study prompted the decision to investigate a 30 mg dosage in phase 3 trials.^{22,23}

We report the results from SIROCCO, one of two phase 3 trials that investigated the efficacy and safety of benralizumab in patients with severe asthma with eosinophilia inadequately controlled with high-dosage ICS plus LABA.

Methods

Study design and participants

SIROCCO was a phase 3, randomised, double-blind, parallel-group, placebo-controlled study done at 374 clinical research centres in Australia, Brazil, Bulgaria, Czech Republic, France, Italy, Mexico, Peru, Poland, Russia, South Africa, South Korea, Spain, Turkey, the UK, the USA, and Vietnam (appendix pp 2–6).

Patients aged 12–75 years who weighed at least 40 kg and who were diagnosed by a physician to have had asthma needing treatment with medium-dosage or high-dosage ICS plus LABA for at least 1 year before enrolment (week –4) were included in the study. Patients must have had at least two documented asthma exacerbations needing systemic corticosteroid treatment or a temporary increase in their usual maintenance dosages of oral corticosteroids within 1 year before enrolment. To be eligible for participation, patients must have had documented treatment of ICS plus LABA with or without

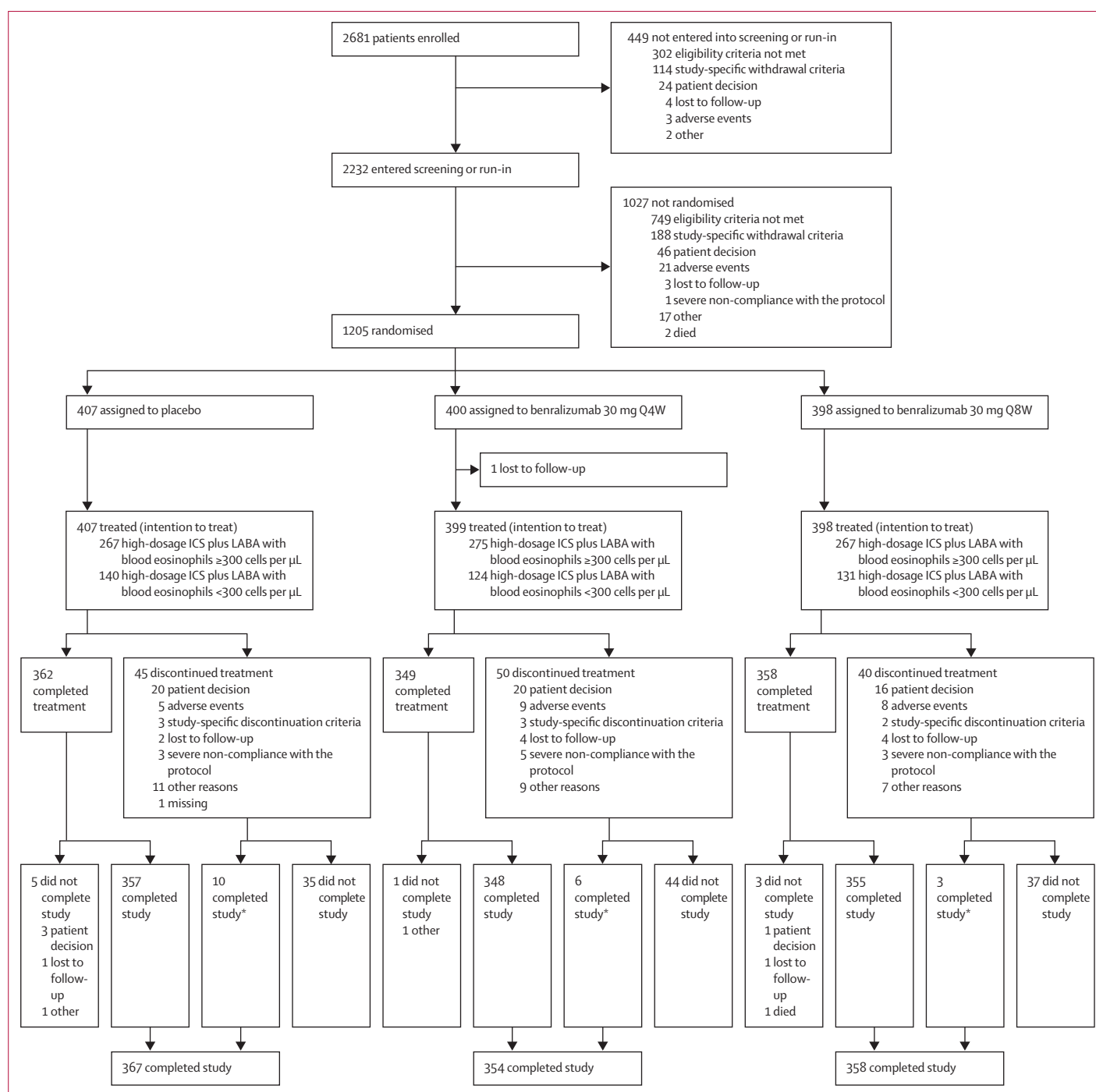


Figure 1: Trial profile

*Discontinued treatment but attended all study visits. ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonist. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

oral corticosteroids and additional asthma controllers for at least 3 months before enrolment. Patients aged 18 years or older were permitted only high-dosage inhaled corticosteroid treatment, whereas patients aged 12–17 years could have been receiving medium-dosage or high-dosage inhaled corticosteroids.

Additional inclusion criteria included a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) of less than 80% predicted (<90% predicted for patients aged 12–17 years) at screening (week -3); a documented post-bronchodilator reversibility of at least 12% and at least 200 mL in FEV_1 within 12 months before enrolment

	All patients (n=1204)			High-dosage ICS plus LABA with baseline blood eosinophils ≥ 300 cells per μL (n=809)			High-dosage ICS plus LABA with baseline blood eosinophils < 300 cells per μL (n=395)		
	Placebo (n=407)	Benralizumab 30 mg Q4W (n=399)	Benralizumab 30 mg Q8W (n=398)	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=124)	Benralizumab 30 mg Q8W (n=131)
Age (years)	48.7 (14.9)	50.1 (13.4)	47.6 (14.5)	48.6 (14.7)	49.2 (13.1)	47.6 (14.6)	49.0 (15.3)	52.0 (13.9)	47.8 (14.3)
Age group (years)									
≥ 12 to < 18	23 (6%)	11 (3%)	19 (5%)	12 (4%)	8 (3%)	10 (4%)	11 (8%)	3 (2%)	9 (7%)
≥ 18 to 75	384 (94%)	388 (97%)	379 (95%)	255 (96%)	267 (97%)	257 (96%)	129 (92%)	121 (98%)	122 (93%)
Sex									
Male	138 (34%)	124 (31%)	146 (37%)	87 (33%)	102 (37%)	93 (35%)	51 (36%)	22 (18%)	53 (40%)
Female	269 (66%)	275 (69%)	252 (63%)	180 (67%)	173 (63%)	174 (65%)	89 (64%)	102 (82%)	78 (60%)
Race									
White	302 (74%)	285 (71%)	287 (72%)	191 (72%)	191 (69%)	192 (72%)	111 (79%)	94 (76%)	95 (73%)
Black or African American	16 (4%)	15 (4%)	15 (4%)	10 (4%)	11 (4%)	10 (4%)	6 (4%)	4 (3%)	5 (4%)
Asian	50 (12%)	54 (14%)	50 (13%)	36 (13%)	39 (14%)	35 (13%)	14 (10%)	15 (12%)	15 (11%)
Other*	39 (10%)	45 (11%)	46 (12%)	30 (11%)	34 (12%)	30 (11%)	9 (6%)	11 (9%)	16 (12%)
Ethnic group									
Hispanic or Latino	77 (19%)	73 (18%)	80 (20%)	57 (21%)	52 (19%)	52 (19%)	20 (14%)	21 (17%)	28 (21%)
Not Hispanic or Latino	330 (81%)	326 (82%)	318 (80%)	210 (79%)	223 (81%)	215 (81%)	120 (86%)	103 (83%)	103 (79%)
Body-mass index (kg/m^2)	28.9 (7.1)	29.2 (7.1)	28.2 (6.2)	28.7 (7.0)	28.9 (6.9)	27.7 (6.1)	29.3 (7.1)	29.9 (7.3)	29.3 (6.2)
Missing data	0	2	0	0	2	0	0	0	0
Eosinophil count (cells per μL)	370 (0–2690)	390 (0–3440)	360 (0–3100)	500 (300–2690)	500 (300–3440)	500 (300–3100)	130 (0–290)	160 (0–297)	180 (0–290)
Missing data	4	4	6	3	1	4	1	3	2
Central eosinophil count (cells per μL)	350 (0–3580)	360 (0–3170)	325 (0–3110)	480 (70–2220)	470 (40–3170)	460 (10–3110)	130 (0–3580)	160 (0–760)	150 (0–460)
Missing data	12	12	16	9	6	10	3	6	6
Prebronchodilator FEV_1 (L)	1.660 (0.584)	1.655 (0.553)	1.680 (0.582)	1.654 (0.580)	1.673 (0.577)	1.660 (0.574)	1.672 (0.594)	1.615 (0.493)	1.721 (0.597)
Predicted normal (%)	56.6% (15.0)	57.4% (14.1)	56.1% (14.6)	56.4% (14.6)	56.5% (14.4)	55.5% (14.6)	57.0% (15.7)	59.4% (13.2)	57.3% (14.7)
Missing data	7	6	1	5	2	1	2	4	0
Prebronchodilator FEV_1/FVC	61 (13)	62 (12)	61 (13)	61 (13)	62 (12)	60 (13)	62 (13)	63 (12)	62 (14)
Missing data	7	6	1	5	2	1	2	4	0
Reversibility (%)	20% (–26 to 154)	18% (–7 to 136)	22% (–12 to 157)	20% (–26 to 154)	18% (–7 to 136)	21% (–10 to 157)	20% (–7 to 138)	17% (–2 to 96)	22% (–12 to 134)
Missing data	26	24	23	16	13	14	10	11	9
ACQ-6 score†	2.87 (0.94)	2.77 (0.96)	2.80 (0.88)	2.90 (0.95)	2.77 (0.95)	2.81 (0.89)	2.82 (0.93)	2.78 (1.00)	2.78 (0.85)

(Table 1 continues on next page)

or identified at screening; and an Asthma Control Questionnaire, six-question version (ACQ-6) score of at least 1.5 at enrolment.²⁴ The ACQ-6 is a six-item questionnaire to assess daytime and night-time symptoms and rescue β -agonist use on a 0–6 scale. Patients were excluded from the study if they had a history of anaphylaxis with any biologic drug, a clinically important pulmonary disease other than asthma, or a helminthic parasitic infection diagnosed within 24 weeks before enrolment that had either not been treated or did not respond to standard-of-care treatment. Full inclusion and exclusion criteria are included in the appendix (pp 7–10).

Because the aim of the SIROCCO trial was to establish the effect of benralizumab as an add-on treatment, patients continued receiving their background asthma controller treatments at a stable

dosage during the study. Short-acting β_2 -agonists were permitted as rescue drugs to control worsening asthma symptoms; the appendix (pp 11–13) lists restricted asthma drugs.

Before any patient was enrolled, an independent ethics committee or institutional review board at each study centre 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 enrolment. The study was done in accordance with the principles of the Declaration of Helsinki and was consistent with the International Council for Harmonisation/Good Clinical Practice and applicable regulatory requirements and AstraZeneca company policy on bioethics.

	All patients (n=1204)			High-dosage ICS plus LABA with baseline blood eosinophils ≥ 300 cells per μL (n=809)			High-dosage ICS plus LABA with baseline blood eosinophils < 300 cells per μL (n=395)		
	Placebo (n=407)	Benralizumab 30 mg Q4W (n=399)	Benralizumab 30 mg Q8W (n=398)	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=124)	Benralizumab 30 mg Q8W (n=131)
(Continued from previous page)									
Time since asthma diagnosis (years)	14.2 (1.1–72.4)	15.3 (1.1–70.4)	14.4 (1.1–66.9)	13.4 (1.1–65.2)	14.9 (1.1–62.6)	14.6 (1.1–66.9)	16.8 (1.1–72.4)	17.4 (1.2–70.4)	14.0 (1.2–58.8)
Number of exacerbations in the past 12 months	3.0 (1.8)	2.9 (1.8)	2.8 (1.5)	3.1 (2.0)	3.0 (2.0)	2.8 (1.5)	2.7 (1.5)	2.7 (1.2)	2.6 (1.3)
Number resulting in ED visit	0.3 (0.8)	0.3 (1.0)	0.2 (0.8)	0.3 (0.8)	0.4 (1.0)	0.3 (0.9)	0.2 (0.8)	0.2 (0.9)	0.2 (0.6)
Patients with ≥ 1 exacerbations resulting in ED visit	67 (16%)	64 (16%)	53 (13%)	48 (18%)	51 (19%)	40 (15%)	19 (14%)	13 (10%)	13 (10%)
Number resulting in hospital admission	0.4 (0.8)	0.4 (0.7)	0.4 (0.8)	0.4 (0.8)	0.3 (0.7)	0.4 (0.9)	0.4 (0.8)	0.4 (0.9)	0.3 (0.8)
Patients with ≥ 1 exacerbations resulting in hospital admission	107 (26%)	98 (25%)	100 (25%)	67 (25%)	66 (24%)	71 (27%)	40 (29%)	32 (26%)	29 (22%)
Total asthma symptom score	2.68 (1.07)	2.72 (1.02)	2.70 (1.11)	2.74 (1.08)	2.67 (1.01)	2.68 (1.09)	2.57 (1.07)	2.84 (1.02)	2.73 (1.14)
Missing data	0	1	3	0	1	2	0	0	1
Diagnosis of allergic rhinitis	220 (54%)	207 (52%)	219 (55%)	156 (58%)	148 (54%)	150 (56%)	64 (46%)	59 (48%)	69 (53%)
Nasal polyps	79 (19%)	84 (21%)	74 (19%)	62 (23%)	66 (24%)	62 (23%)	17 (12%)	18 (15%)	12 (9%)
Atopic (based on Phadiatop test)	230 (57%)	231 (58%)	244 (61%)	152 (57%)	156 (57%)	169 (63%)	78 (56%)	75 (60%)	75 (57%)
History of omalizumab treatment	31 (8%)	29 (7%)	28 (7%)	22 (8%)	16 (6%)	18 (7%)	9 (6%)	13 (10%)	10 (8%)
Missing data	3	1	1	2	1	1	1	0	0
AQLQ(S)+12 score†	3.90 (1.02)	3.93 (0.98)	3.94 (1.00)	3.87 (0.99)	3.93 (1.00)	3.93 (0.97)	3.97 (1.07)	3.92 (0.95)	3.97 (1.04)
Missing data	15	17	17	12	12	12	3	5	5
Smoker	5 (1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)	4 (3%)	0	0
Nicotine pack-years	5.0 (0–9)	5.0 (0–9)	5.0 (0–9)	5.0 (0–9)	6.0 (0–9)	5.0 (0–9)	5.0 (0–9)	5.0 (1–9)	5.0 (0–9)

Data are mean (SD), number (%), or median (range). Some percentages do not add up to 100 because of rounding. ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonists. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). ACQ-6=Asthma Control Questionnaire, six-question version. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. ED=emergency department. FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. *Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or other. †Low numbers represent better symptom control. ‡High numbers suggest better quality of life. §Current smoker or former smoker with a smoking history of ≥ 10 packs per year.

Table 1: Baseline demographics and clinical characteristics (full analysis set)

Randomisation and masking

All adult patients, and adolescent patients enrolled at non-European Union (EU) sites, were randomly assigned (1:1:1) to one of three 48-week treatment groups: subcutaneous benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses given 4 weeks apart), or matching placebo. This dosing regimen was chosen based on an exposure–response analysis of data from the phase 2b study with benralizumab involving patients with uncontrolled asthma.^{22,23} Adolescent patients enrolled at sites in the EU were randomly assigned to one of two treatment groups: subcutaneous benralizumab 30 mg Q8W (first three doses given Q4W) or matching placebo to accommodate a request by the Paediatric Committee at the European Medicines Agency to limit drug burden in adolescents.

Each patient was assigned a unique enrolment number and randomisation code by an interactive web-based voice response system. Randomisation was stratified by age

group (adult or adolescent), country (in adults) or region (within the EU and outside the EU for adolescents), and blood eosinophil counts. The randomisation stratified patients (2:1) for blood eosinophil counts of at least 300 cells per μL and less than 300 cells per μL , which were measured at a local laboratory. The randomisation was stratified to enrich the study population with patients most likely to benefit from benralizumab treatment and to provide insight into efficacy in patients with low baseline blood eosinophil counts. Randomisation codes were assigned by the study investigator sequentially in each stratum as patients became eligible for randomisation, until each stratum was full.

The study was planned with a double-blind, double-dummy design to ensure masking throughout. The identity of the treatment allocation was not made available to the patients, investigators involved in patient treatment or clinical assessment, or study funder. Placebo solution was visually matched with benralizumab solution.

	High-dosage ICS plus LABA with baseline blood eosinophils ≥ 300 cells per μL			High-dosage ICS plus LABA with baseline blood eosinophils < 300 cells per μL		
	Placebo	Benralizumab 30 mg Q4W	Benralizumab 30 mg Q8W	Placebo	Benralizumab 30 mg Q4W	Benralizumab 30 mg Q8W
Primary endpoint						
Annual asthma exacerbation rate over 48 weeks*						
Number of patients analysed	267	275	267	140	124	131
Rate estimate (95% CI)	1.33 (1.12–1.58)	0.73 (0.60–0.89)	0.65 (0.53–0.80)	1.21 (0.96–1.52)	0.85 (0.65–1.11)	1.00 (0.78–1.28)
Absolute difference estimate (95% CI)	..	–0.60 (–0.87 to –0.33)	–0.68 (–0.95 to –0.42)	..	–0.36 (–0.71 to –0.00)	–0.21 (–0.58 to 0.16)
Rate ratio vs placebo (95% CI; p value)	..	0.55 (0.42–0.71; <0.0001)	0.49 (0.37–0.64; <0.0001)	..	0.70 (0.50–1.00; 0.0471)	0.83 (0.59–1.16; 0.2685)
Key secondary endpoints (48 weeks)						
Prebronchodilator FEV ₁ (L)†						
Number of patients analysed‡	261	271	264	138	120	129
LS mean change (number of patients§)	0.239 (233)	0.345 (236)	0.398 (235)	0.145 (125)	0.120 (105)	0.248 (119)
LS mean difference vs placebo (95% CI; p value)	..	0.106 (0.016 to 0.196; 0.0215)	0.159 (0.068 to 0.249; 0.0006)	..	–0.025 (–0.134 to 0.083; 0.6438)	0.102 (0.003 to 0.208; 0.568)
Total asthma symptom score†¶						
Number of patients analysed‡	267	273	263	139	123	127
LS mean change (number of patients§)	–1.04 (180)	–1.12 (197)	–1.30 (178)	–0.77 (99)	–0.97 (93)	–1.06 (91)
LS mean difference vs placebo (95% CI; p value)	..	–0.08 (–0.27 to 0.12; 0.4420)	–0.25 (–0.45 to –0.06; 0.0118)	..	–0.20 (–0.48 to 0.08; 0.1688)	–0.29 (–0.57 to –0.01; 0.0431)
ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonists. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). FEV ₁ =forced expiratory volume in 1 s. LS=least squares. *Estimates calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations. †Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit $\times$ treatment. ‡Patients with a baseline and at least one post-baseline assessment. §Numbers of patients at 48 weeks. ¶A decrease in score suggests an improvement.						

Table 2: Primary and key secondary endpoints

Procedures

Benralizumab and placebo were provided in pre-filled syringes (accessorised with needle guards and finger phalanges) containing a deliverable volume of 1 mL containing 30 mg/mL solution or matching placebo solution for injection (manufactured by AstraZeneca, Gaithersburg, MD, USA). Patients assigned to the benralizumab Q4W dosing schedule or placebo were given their randomly assigned treatments at study centre visits at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44, whereas patients assigned to the benralizumab Q8W dosing schedule were given benralizumab at study centre visits on weeks 0, 4, 8, 16, 24, 32, and 40 and placebo at the intervening visits. The site of injection was rotated between different anatomical sites at each visit.

Data were collected from all patients at enrolment, screening, randomisation (week 0), every 4-week interval during the treatment period (weeks 4–48), and follow-up (week 56, for patients not continuing in BORA [NCT02258542], an open-label extension study). Study investigators at each site did prebronchodilator spirometry at screening, then weeks 0, 4, 8, 16, 24, 32,

40, and 48. Lung function assessments (FEV₁ and forced vital capacity) were done according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.²⁵ Properly certified personnel did the spirometry testing using equipment that was supplied by a central spirometry vendor (eResearch Technology GmbH, Estenfeld, Germany) and met ATS/ERS recommendations. Additional assessments included asthma symptom score, ACQ-6,²⁴ Standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12; a 32-item questionnaire to assess asthma-related quality of life scored on a 1–7 scale), anti-drug antibodies, and overall measurement of response to treatment (appendix pp 14–15). Patient-reported outcomes and daily metrics, including ACQ-6, AQLQ(S)+12, and asthma symptom scores, were recorded using an electronic Asthma Daily Diary. The Asthma Daily Diary, ACQ-6, and AQLQ(S)+12 have been validated for use in clinical trials.²⁴ Safety was monitored at each study centre visit from enrolment, during the screening or run-in period, during the treatment period, and at a follow-up visit on week 56.

Outcomes

The primary efficacy endpoint was the annual asthma exacerbation rate ratio versus placebo, which is summarised as total number of exacerbations $\times$ 365 $\cdot$ 25 / total duration of follow-up within the treatment group (days). An exacerbation was defined as a worsening of asthma that led to one of the following: (1) use of systemic corticosteroids, or temporary increase in a stable oral corticosteroid background dosage, for at least 3 days or a single injectable dose of corticosteroids; (2) emergency department or visit to an urgent care centre (<24 h) because of asthma that needed systemic corticosteroids; or (3) inpatient hospital stay (≥ 24 h) because of asthma. Worsening of asthma was defined as any new or increased symptoms or signs that were concerning to the patient or related to an Asthma Daily Diary alert (appendix p 16).

Key secondary endpoints (ie, multiplicity [type I error]–protected endpoints) for the primary analysis population were prebronchodilator FEV₁ and total asthma symptom score (a composite of daytime and night-time symptoms scored 0–6 overall) at week 48. The primary and key secondary analyses of efficacy included patients with blood eosinophil counts at least 300 cells per μ L. Additional secondary endpoints were time to first asthma exacerbation, annual rate of asthma exacerbations that were associated with a visit to an emergency department or urgent care centre or admission to hospital, post-bronchodilator FEV₁, ACQ-6 score,²⁴ and AQLQ(S)+12 score. All efficacy endpoints were also assessed in patients with blood eosinophil counts less than 300 cells per μ L, with statistical comparisons not done for patients with less than 300 eosinophils per μ L for non-key secondary outcomes (except ACQ-6) and summarised descriptively. Safety outcomes were adverse events, serious adverse events, laboratory variables, electrocardiograms, vital signs, and immunogenicity.

Statistical analysis

We calculated that for the primary analysis of efficacy, approximately 252 patients with blood eosinophil counts at least 300 cells per μ L per treatment group (756 total) were needed for 90% power to detect a 40% reduction in annual exacerbation rate in both benralizumab dosage regimens compared with placebo, assuming a two-sided 4% α (appendix p 18) and an annual placebo exacerbation rate of 0.88 events per patient, based on published phase 2b data.^{22,23} The sample size calculation was based on simulations and a negative binomial shape parameter of 0.9, on the basis of corresponding data from phase 2b trial results.²² A total enrolment of 1134 adults and adolescents for randomisation was needed, including the enrolment of 126 patients per group (378 total) for the less than 300 cells per μ L blood eosinophil cohort.

We analysed the primary efficacy endpoint using a negative binomial model, with adjustment for treatment,

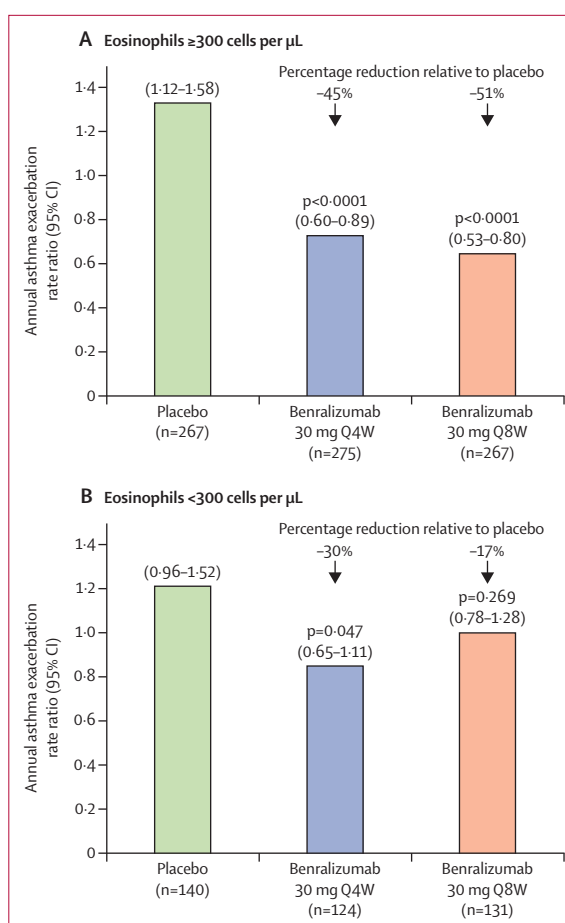


Figure 2: Annual asthma exacerbation rate estimates at 48 weeks according to baseline blood eosinophil concentrations

Data for patients with baseline blood eosinophils (A) ≥ 300 cells per μ L and (B) < 300 cells per μ L in the full analysis set are shown. Estimates were calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomisation, and previous exacerbations. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

region, exacerbations in the previous year (two, three, or four or more), and oral corticosteroid use at time of randomisation. The estimated treatment effect (ie, rate ratio of benralizumab vs placebo), corresponding 95% CI, and two-sided p value for the rate ratio were calculated. The annual exacerbation rate and corresponding 95% CIs within each treatment group were also calculated. We also did prespecified subgroup analyses to assess the exacerbation rate in subgroups of clinical relevance (appendix p 17). We did a post-hoc analysis in the primary analysis population to assess the treatment effect of a history of at least three exacerbations experienced by patients in the previous year using a separate negative binomial model with adjustment for treatment, region, oral corticosteroid use, and number of previous exacerbations.

We analysed the key secondary endpoints using a mixed-effects model for repeated measures analysis, with

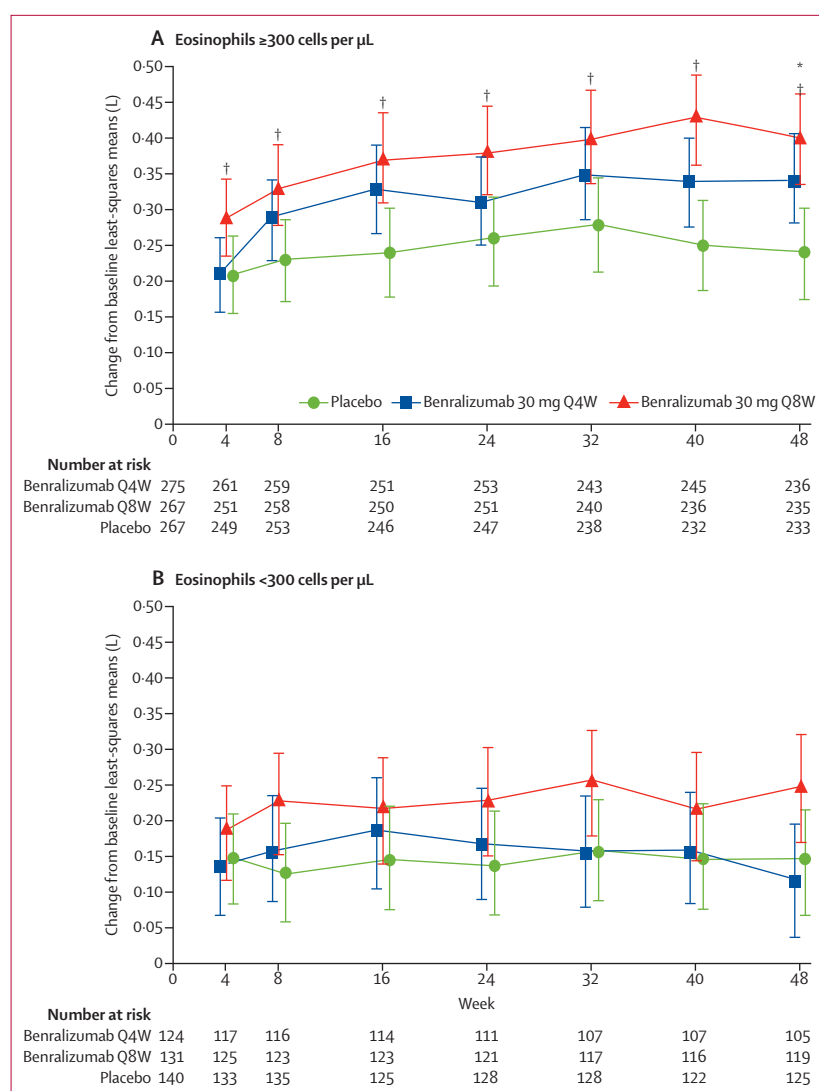


Figure 3: Change from baseline in prebronchodilator forced expiratory volume in 1 s according to baseline blood eosinophil concentrations

Data for patients with baseline blood eosinophils (A) ≥ 300 cells per μL and (B) < 300 cells per μL in the full analysis set are shown. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). * $p < 0.05$ for benralizumab 30 mg Q4W vs placebo. † $p < 0.05$ for benralizumab 30 mg Q8W vs placebo.

adjustment for treatment, region, baseline value, oral corticosteroid use at time of randomisation, visit, and visit $\times$ treatment. Least-squares means, treatment differences in least-squares means, 95% CIs, and p values were calculated. We analysed the other continuous secondary efficacy endpoints using a mixed-effects model for repeated measures analysis. Time to first asthma exacerbation was analysed using a Cox proportional hazard model, with adjustment for treatment, region, exacerbations in the previous year, and oral corticosteroid use at time of randomisation.

To account for multiplicity to test the primary endpoint and two key secondary endpoints (ie, change from baseline in FEV₁ and asthma symptom score) for each of

the two benralizumab dosing regimens, we followed a multiple testing procedure to control the overall type I error rate (appendix p 18). The testing procedure permitted two tests of annual asthma exacerbation rate (one test for each dosing regimen vs placebo) at the family-wise error rate of 0.04 using a Hochberg procedure. If both p values were less than 0.04, then the two key secondary endpoints could be tested for both dosing regimens at a family-wise error rate of 0.05 using a Holm procedure.

All efficacy analyses were done in the intention-to-treat population; that is, all randomly assigned patients who received any study treatment, regardless of their protocol adherence and continued participation in the study. Safety analyses were based on the actual treatment regimen received and included all patients who received at least one dose of study drug. All analyses were done using SAS version 9.2.

A data safety monitoring board and two independent adjudication committees (one for asthma-associated emergency department visits and/or hospital admissions; the other for major adverse cardiovascular events or malignancies) oversaw the study (appendix p 19). This study is registered with ClinicalTrials.gov, number NCT01928771.

Role of the funding source

The funders of the study participated in the study design. All authors, including those employed by the funders of the study, participated in the data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 19, 2013, and March 16, 2015, we enrolled 2681 patients, 2232 of whom were screened for eligibility (figure 1). 1205 patients who met study entry criteria were randomly assigned to treatment: 407 to placebo, 400 to benralizumab 30 mg Q4W, and 398 to benralizumab Q8W. One patient in the benralizumab 30 mg Q4W group was lost to follow-up before treatment; all other patients received their assigned treatments. 267 patients in the placebo group, 275 in the benralizumab 30 mg Q4W group, and 267 in the benralizumab 30 mg Q8W group had blood eosinophil counts at least 300 cells per μL (figure 1). 1069 (89%) of 1204 patients completed treatment with the study drug and 135 (11%) discontinued treatment. The proportions of patients who discontinued treatment were similar across groups. The most common reason for discontinuation of treatment was patient decision (56 patients [5%]; figure 1). Baseline characteristics were similar across randomised treatment groups and between patients with blood eosinophil counts at least 300 cells per μL and less than 300 cells per μL (table 1). Use of

	High-dosage ICS plus LABA with baseline blood eosinophils ≥ 300 cells per μL			High-dosage ICS plus LABA with baseline blood eosinophils < 300 cells per μL		
	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=124)	Benralizumab 30 mg Q8W (n=131)
ACQ-6 score (week 48)*†						
Number of patients analysed‡	267	274	263	138	124	130
LS mean change	-1.17 (186)	-1.32 (198)	-1.46 (191)	-0.89 (97)	-0.89 (89)	-1.11 (94)
LS mean difference vs placebo (95% CI; p value)	..	-0.15 (-0.34 to 0.04; 0.1107)	-0.29 (-0.48 to -0.10; 0.0028)	..	0.00 (-0.27 to 0.27; 0.9903)	-0.22 (-0.48 to 0.05; 0.1066)
AQLQ(S)+12 score*§						
Number of patients analysed‡	254	261	252	..	..	..
LS mean change	1.26 (180)	1.44 (192)	1.56 (187)	..	..	..
LS mean difference vs placebo (95% CI; p value)	..	0.18 (-0.02 to 0.37; 0.0811)	0.30 (0.10-0.50; 0.0036)	..	..	..

We did not do a formal statistical analysis of the data from the < 300 cells per μL group for AQLQ(S)+12 score. ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonists. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). ACQ-6=Asthma Control Questionnaire, six-question version. LS=least squares. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. *Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit $\times$ treatment. †Low numbers represent better control. ‡Patients with a baseline and at least one post-baseline assessment. §High numbers suggest better quality of life.

Table 3: Changes in health-related quality of life, and productivity at week 48 (secondary endpoints)

maintenance asthma treatment use was similar across groups, with a mean fluticasone propionate or equivalent total daily dosage of 899 μg (range 125–3000; appendix p 20). 196 (16%) patients were receiving oral corticosteroids, with similar dosing between cohorts.

Unless otherwise specified, all results are presented for patients with baseline blood eosinophil counts at least 300 cells per μL . For the primary endpoint, both dosing regimens of benralizumab significantly decreased the annual asthma exacerbation rate compared with placebo at week 48 (table 2; figure 2). For the Q4W cohort, the rate ratio versus placebo was 0.55 (95% CI 0.42–0.71; $p < 0.0001$), and for the Q8W cohort, it was 0.49 (0.37–0.64; $p < 0.0001$).

Both benralizumab dosing regimens significantly improved prebronchodilator FEV₁ in patients at week 48 compared with placebo (table 2). The difference in least-squares mean change from baseline between the benralizumab Q4W and placebo cohorts was 0.106 L (95% CI 0.016–0.196; $p = 0.0215$) and between the benralizumab Q8W and placebo cohorts it was 0.159 L (0.068–0.249; $p = 0.0006$). Benralizumab treatment Q8W also resulted in improved asthma symptoms, as indicated by a greater decrease in total asthma symptom score at week 48 compared with placebo treatment (least-squares mean difference -0.25, 95% CI -0.45 to -0.06; $p = 0.0118$); however, the difference was not significant for the Q4W regimen (-0.08, -0.27 to 0.12; $p = 0.4420$; table 2).

During the 48-week period, the curves for the cumulative number of exacerbations in the benralizumab-treated and placebo cohorts diverged as early as 4 weeks (the first sampling timepoint; appendix p 21). Additionally, the time to first asthma exacerbation was longer for both

benralizumab treatment cohorts compared with placebo, with the probability of having an asthma exacerbation reduced by 37% (hazard ratio 0.63, 95% CI 0.49–0.82; $p = 0.0005$) for the Q4W cohort and by 40% (0.60, 0.46–0.78; $p = 0.0002$) for the Q8W cohort (appendix p 22). The prebronchodilator FEV₁ increase relative to baseline for the benralizumab Q8W cohort was greater than for the placebo cohort throughout the treatment period starting at week 4 ($p < 0.05$; figure 3). Post-bronchodilator FEV₁ also increased at week 48 with both treatment regimens (Q4W cohort $p = 0.0369$; Q8W cohort $p = 0.0357$; appendix p 23). The decrease in total asthma score for the Q8W cohort also began early in treatment, with the decrease being consistently greater than placebo treatment ($p < 0.05$ from week 36; appendix p 24); however, differences between placebo and the benralizumab Q4W cohort were not statistically significant.

The benralizumab Q8W cohort had reduced asthma exacerbations leading to emergency department visits or hospital admissions compared with placebo treatment (rate ratio 0.37, 95% CI 0.20–0.67; $p = 0.0010$), and for the Q4W cohort, the rate ratio was 0.61 (0.37–1.01; $p = 0.0529$; appendix p 25). Compared with placebo, benralizumab treatment Q8W also improved ACQ-6 (least-squares mean difference -0.29, 95% CI -0.48 to -0.10; $p = 0.0028$) and health-related quality of life (AQLQ(S)+12 score; 0.30, 0.10–0.50; $p = 0.0036$), but findings for the benralizumab Q4W group were not significant (ACQ-6 $p = 0.1107$; AQLQ(S)+12 $p = 0.0811$; table 3).

Patients who had blood eosinophil counts less than 300 cells per μL and received benralizumab Q4W achieved improvements in exacerbation rate ($p = 0.0471$), and those who received the Q8W dosage had improvements in asthma symptoms ($p = 0.0431$); no

	Placebo (n=407)	Benralizumab 30 mg Q4W (n=403)*	Benralizumab 30 mg Q8W (n=394)
Any adverse event	311 (76%)	293 (73%)	281 (71%)
Any adverse event leading to treatment discontinuation	3 (<1%)	9 (2%)	8 (2%)†
Any serious adverse event	55 (14%)	47 (12%)	52 (13%)
Deaths	2 (1%)	2 (<1%)	1 (<1%)
Adverse events in >3% of patients‡			
Asthma	78 (19%)	60 (15%)	45 (11%)
Nasopharyngitis	47 (12%)	47 (12%)	46 (12%)
Upper respiratory tract infection	36 (9%)	44 (11%)	32 (8%)
Headache	21 (5%)	30 (7%)	37 (9%)
Bronchitis	30 (7%)	24 (6%)	19 (5%)
Sinusitis	28 (7%)	17 (4%)	22 (6%)
Influenza	23 (6%)	17 (4%)	19 (5%)
Pharyngitis	14 (3%)	17 (4%)	23 (6%)
Rhinitis	15 (4%)	16 (4%)	10 (3%)
Arthralgia	10 (2%)	11 (3%)	18 (5%)
Cough	10 (2%)	15 (4%)	13 (3%)
Pyrexia	8 (2%)	16 (4%)	12 (3%)
Back pain	15 (4%)	11 (3%)	8 (2%)
Acute sinusitis	10 (2%)	10 (2%)	13 (3%)
Rhinitis allergic	8 (2%)	11 (3%)	12 (3%)
Nausea	8 (2%)	8 (2%)	12 (3%)
Gastroenteritis	6 (1%)	9 (2%)	12 (3%)
Pain in extremity	5 (1%)	3 (1%)	13 (3%)
Injection-site reactions	8 (2%)	16 (4%)	9 (2%)
Hypersensitivity adverse events§	11 (3%)	13 (3%)	11 (3%)
Causally related¶	2 (<1%)	2 (<1%)	2 (<1%)
Urticaria	2 (<1%)	1 (<1%)	2 (<1%)
Allergic granulomatous angiitis	0	1 (<1%)	0

Data are number of patients (%). The on-treatment period was defined as the day of first dose of study treatment to the scheduled end-of-treatment visit. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Includes four patients in the Q8W cohort who received extra doses of benralizumab. †One additional patient discontinued the study after receiving their last dose but before attending the end-of-treatment visit. ‡Medical Dictionary for Regulatory Activities version 18.1. §High-level term. ¶In the opinion of the investigator.

Table 4: Adverse events, injection-site reactions, and hypersensitivity during the on-treatment period in the safety population

other secondary endpoints were significant in patients who had blood eosinophil counts less than 300 cells per μL (tables 2 and 3). However, this study was not powered to detect differences within this group.

Findings from prespecified subgroup analyses suggested that geographical region might affect treatment response (appendix p 27). Patients from each region displayed substantial heterogeneity of baseline characteristics between regions, particularly with regard to exacerbation history (appendix p 28).

In the at least 300 cells per μL population, blood eosinophil counts were reduced in both benralizumab groups by week 4 to a median of 0 cells per μL (IQR 0–10) from similar baseline values (450 cells per μL [300–720] for Q4W and 440 cells per μL [280–691] for Q8W), whereas blood eosinophil counts in the placebo cohort remained similar between baseline and week 4 (appendix p 29). This reduction was maintained at week 48. Findings were similar for patients with blood eosinophil counts less than 300 cells per μL (appendix p 29).

In a post-hoc analysis of patients who had at least three exacerbations in the previous year, patients in the benralizumab Q8W cohort who had at least 300 blood eosinophils per μL had greater improvements relative to placebo in annual exacerbation rate ($p<0.0001$), FEV_1 ($p=0.0018$), total asthma symptom score ($p=0.0420$), and ACQ-6 ($p=0.0458$) than the overall population with at least 300 cells per μL (appendix). Patients in the benralizumab Q4W cohort also had greater improvements relative to placebo in annual exacerbation rate ($p=0.0010$); whereas FEV_1 , total asthma symptom score, ACQ-6, and AQLQ(S)+12 were similar to placebo (see appendix for results for patients with a history of two exacerbations in the previous year).

Adverse events during the treatment period were reported by similar percentages of patients who received benralizumab (574 [72%] of 797) or placebo (311 [76%] of 407; table 4). Percentages of patients experiencing adverse events were also similar between treatment groups, irrespective of baseline eosinophil counts (appendix p 30). The most common adverse events in patients treated with benralizumab were worsening asthma (105 [13%]), nasopharyngitis (93 [12%]), and upper respiratory tract infection (76 [10%]); adverse events related to asthma were reported by proportionally less patients in the benralizumab-treated groups than in the placebo group (table 4). Serious adverse events were also reported by similar percentages of patients who received benralizumab (99 [12%]) or placebo (55 [14%]). The most common serious adverse event in all patients was worsening asthma (31 [8%] in the placebo group vs 22 [5%] in the benralizumab Q4W group vs 24 [6%] in the benralizumab Q8W group); no other serious adverse event was experienced by more than 1% of patients. Four serious adverse events were judged by the investigator to be related to treatment: three in the benralizumab Q4W cohort (allergic granulomatous angiitis, panic attack, and paraesthesia) and one in the placebo cohort (injection-site erythema). 18 patients (2%) receiving benralizumab and three (1%) receiving placebo discontinued treatment because of adverse events. Five patients died during treatment: two in the benralizumab Q4W cohort (cerebral haemorrhage and asthma), one in the benralizumab Q8W cohort (accidental opioid overdose), and two in the placebo cohort (pulmonary embolism and cause unknown). Additionally, one patient with a post-treatment adverse event died in the Q8W

cohort (sudden death of unknown cause). None of the deaths was considered related to treatment.

33 patients (3%) experienced injection-site reactions: 16 (4%) of 403 patients on benralizumab Q4W, nine (2%) of 394 on benralizumab Q8W, and eight (2%) of 407 on placebo (table 4). Similar percentages of patients experienced hypersensitivity adverse events: 13 (3%) on benralizumab Q4W, 11 (3%) on benralizumab Q8W, and 11 (3%) on placebo. Six patients reported hypersensitivity adverse events that the investigator deemed to be causally related to treatment (five with urticaria and one with allergic granulomatous angiitis). Positive anti-drug antibody response was noted in 105 (13%) of 797 patients in the benralizumab groups (appendix p 31). There was no suggestion that positive anti-drug antibody response was associated with hypersensitivity or affected efficacy outcomes (data not shown).

Discussion

In the phase 3 SIROCCO study, the anti-eosinophil monoclonal antibody benralizumab significantly reduced the annual rate of exacerbations by up to 51% after 48 weeks of treatment in patients with severe, uncontrolled asthma with eosinophilia (blood eosinophil counts ≥ 300 cells per μL). Benralizumab also significantly improved pulmonary function, with a 0.106–0.159 L increase in prebronchodilator FEV₁ relative to placebo, depending on the dosing regimen. Differences from placebo were generally greater for the Q8W cohort than the Q4W cohort, especially for symptom endpoints; for example, patient-reported asthma symptoms were significantly reduced in the Q8W cohort, but not in the Q4W cohort, compared with placebo at week 48. Our findings suggest that the clinical benefit obtained with benralizumab translates into better asthma control and, for the Q8W dosage, improved health-related quality of life. Benralizumab treatment resulted in direct, rapid, and nearly complete eosinophil depletion at 4 weeks, the first sampling timepoint, consistent with phase 1 and 2 study results that showed such depletion to occur as early as day 1.^{20–22}

These results are consistent with those presented from the similarly designed 56-week CALIMA phase 3 trial²⁶ of benralizumab for patients with severe, uncontrolled asthma with eosinophilia (table 5). After assignment to the same treatment groups as the SIROCCO study, both benralizumab regimens significantly decreased the annual exacerbation rate and improved prebronchodilator FEV₁ compared with placebo for patients with blood eosinophil counts at least 300 cells per μL . These improvements in asthma symptoms were also substantial compared with baseline.²⁶ Furthermore, both studies indicated improvements in patient-reported asthma symptoms with benralizumab Q8W, a prespecified outcome measure. Consistent with findings from previous studies,^{19,23} both dosage regimens of benralizumab

	SIROCCO		CALIMA ²⁶	
	Benralizumab Q4W	Benralizumab Q8W	Benralizumab Q4W	Benralizumab Q8W
Annual rate of exacerbations	↓ 45%	↓ 51%	↓ 36%	↓ 28%
Prebronchodilator FEV ₁ (L)	↑ 0.106	↑ 0.159	↑ 0.125	↑ 0.116
Total asthma symptom score (score 0–6)*	↓ 0.08†	↓ 0.25	↓ 0.12†	↓ 0.23

All results are differences from placebo; week 48 results for SIROCCO and week 56 results for CALIMA. FEV₁=forced expiratory volume in 1 s. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W). *Reduced score suggests improvement. †Non-significant.

Table 5: Efficacy results for patients who received high-dosage inhaled corticosteroids plus long-acting β_2 -agonists with baseline blood eosinophils at least 300 cells per μL in the CALIMA and SIROCCO studies

reduced blood eosinophil counts rapidly and extensively.^{19,22}

Similar to findings from previous studies,^{20,22} benralizumab was well tolerated, with approximately 90% of patients assigned to benralizumab still receiving treatment after 48 weeks, and only 2% of patients stopping treatment because of adverse events. The safety profile was consistent with that anticipated from previous studies of similar patient populations.^{20,22} Injection-site reactions were low overall, reported by 3% of patients receiving benralizumab.

Two monoclonal antibody treatments against interleukin 5 (mepolizumab and reslizumab) have been approved in the European Union and the USA by the European Medicines Agency and the US Food and Drug Administration, respectively, for the treatment of severe asthma.^{16,17} Unlike benralizumab, both these antibodies target the interleukin-5 ligand directly, rather than the receptor. Therefore, benralizumab is likely to circumvent potential issues with cytokine-directed antibodies, such as the induction of increased cytokine production.²⁷ Furthermore, benralizumab depletes eosinophils directly, whereas mepolizumab and reslizumab work through a passive mechanism, which seems to reduce eosinophils rather than deplete them entirely.^{14,15} Studies for mepolizumab and reslizumab generally involved similar patients to those included in this study, although for mepolizumab, patients included in the MENSA²⁸ and DREAM²⁹ phase 3 studies had more severe exacerbation phenotypes than those in the SIROCCO study, as noted by a greater mean baseline number of exacerbations in the previous year (2.8–3.0 for the SIROCCO cohorts vs 3.4–3.8 for DREAM and MENSA cohorts) and a greater annual exacerbation rate in the placebo group. Similar to benralizumab, clinical efficacy of mepolizumab was related to baseline blood eosinophil counts. In a post-hoc analysis of DREAM and MENSA,¹⁴ in which mepolizumab was given Q4W for at least 32 weeks to patients with severe, uncontrolled asthma with evidence of eosinophilic airway inflammation, the reduction of the annualised exacerbation rate compared with placebo was 52% for patients with baseline eosinophil counts of at least 150 cells per μL and 59%

for counts of at least 300 cells per μL . Efficacy of intravenous reslizumab treatment was reported in two duplicate phase 3 studies¹⁵ only for patients with blood eosinophil counts at least 400 cells per μL , with a reduction of 54% in the annual exacerbation rate relative to placebo when given once Q4W for 52 weeks. Although studies of different biologics are not directly comparable, increases in lung function with benralizumab treatment seemed to be greater than those reported for mepolizumab and reslizumab,^{14,15} with improvements noted as early as 4 weeks, the first timepoint assessed.

An additional biologic drug in clinical development for the treatment of uncontrolled asthma is dupilumab, a human monoclonal antibody against the interleukin-4 receptor α that inhibits interleukin-4 and interleukin-13 signalling. The results of a phase 2b study³⁰ showed that this drug increases lung function and reduces severe exacerbations in patients with uncontrolled, persistent asthma.

The finding that the Q8W dosage was efficacious suggests that benralizumab has the potential to lower disease burden and reduce health-care costs relative to other biologics that are required to be administered more regularly.

Patients with blood eosinophil counts less than 300 cells per μL had a substantial but smaller treatment effect; the size of this cohort was limited because of protocol-mandated enrichment for the at least 300 cells per μL cohort. Therefore, the threshold eosinophil count that results in significant therapeutic improvement with benralizumab treatment should be investigated in larger populations of severe or uncontrolled patients with asthma and different degrees of eosinophilia. An additional study limitation was that long-term safety with benralizumab treatment cannot be ascertained in a 1-year trial; this will be addressed in the BORA extension study (NCT02258542), in which patients from this study and CALIMA²⁶ will be followed up for up to 2 additional years. Also, because of the small sample size, differences noted in subgroup analyses need to be confirmed in a larger patient population.

The SIROCCO study validates and expands on the results from the phase 2b study²² of the use of biologic treatments to deplete eosinophils through antibody-dependent cell-mediated cytotoxicity to treat patients with severe, uncontrolled asthma with eosinophilia. In the phase 2b study,²² benralizumab 100 mg Q8W reduced the annual exacerbation rate by 41% relative to placebo at 52 weeks, while improving lung function and asthma symptoms for patients with uncontrolled eosinophilic asthma. Although not directly comparable, the magnitudes of improvements in exacerbations, lung function, asthma symptoms, and health-related quality of life in SIROCCO were even greater than in the phase 2b study. Moreover, positive findings from these studies support the assessment of benralizumab in the treatment of other diseases with an eosinophilic component, such

as chronic obstructive pulmonary disease, chronic rhinosinusitis, and hypereosinophilic syndrome.

Both the SIROCCO and CALIMA studies met their primary endpoints, and confirm their respective results. Benefits were noted not only through asthma exacerbation reductions, but also through improvements in lung function and asthma symptoms. Improvements in these variables occurred early in the study, after 4 weeks, which is earlier than reported for improvements in studies of mepolizumab and reslizumab.^{15,28,29} Furthermore, these benefits were obtained with dosages provided once Q8W, unlike other biologic treatments for asthma, which are given once every 2–4 weeks.

Contributors

ERB, JMF, and MG conceived and designed the study. PB, SS, GG, MA, VW, and MG acquired the data. All authors analysed and interpreted the data. All authors participated in the development and review of the manuscript and gave approval to submit for publication.

Declaration of interests

ERB has undertaken clinical trials through his employer, Wake Forest School of Medicine, for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, Cephalon/Teva, Forest, Genentech, GSK, Johnson & Johnson (Janssen), Novartis, and Sanofi. He has also served as a paid consultant for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, GSK, Forest, Novartis, Regeneron, and Sanofi. JMF reports being a member of advisory boards for AstraZeneca, Novartis, Teva, ALK, and Boehringer Ingelheim, and has been paid honoraria for lecturing at symposia organised by these companies. PC has provided consultancy services for Almirall, Boehringer Ingelheim, Johnson & Johnson, GlaxoSmithKline, Merck Sharp & Dohme, AstraZeneca, Novartis, Teva, Chiesi, and SNCF; has served on advisory boards for Almirall, Boehringer Ingelheim, Johnson & Johnson, GlaxoSmithKline, AstraZeneca, Novartis, Teva, Chiesi, Schering Plough, and ALK; has received lecture fees from Almirall, Boehringer Ingelheim, Centocor, GlaxoSmithKline, AstraZeneca, Novartis, Teva, Chiesi, and Merck Sharp & Dohme; and has received industry-sponsored grants from Almirall, Boston Scientific, Boehringer Ingelheim, Centocor, GlaxoSmithKline, AstraZeneca, Novartis, Teva, and Chiesi. AP reports grants, personal fees, and travel expenses reimbursement from Chiesi Farmaceutici, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, Pfizer, Takeda, Mundipharma, Menarini, Zambon, and Teva. SFW reports being a consultant for Teva and has received research grants from AstraZeneca, GSK, Merck, Teva, Mylan, Roxane, and Sanofi. SS is an employee of Optimum Statistics (LaSalle, MB, Canada), and provided statistical analyses and support under contract to AstraZeneca, through inVentiv Health Clinical. PB, GG, MA, VW, and MG are employees of AstraZeneca.

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Supplementary appendix

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Pioneer Research Solutions Inc: Subodh Bhuchar; Metroplex Pulmonary & Sleep Medicine Center, PA: Shahrukh Kureishy; AAPRI Clinical Research Institute; John Zwetchkenbaum; Panama Clinical Research Associates: Sohail Khan; Gwinnett Biomedical Research: Paul Weinberg; Advanced Biomedical Research of America: Yekaterina Khronusova; Florida Center for Allergy and Asthma Research: Jaime Landman; Wake Forest University Health Sciences School of Medicine: Eugene Bleecker; Clinical Research of Charleston: James Carswell; G & L Research LLC: Nidal Morrar; Santiago Reyes MD; Clinical Research of Lake Norman: Christopher Poor; Feasterville Family Health Care Cntr: John Peniston; Florida Pulmonary Res Institute: Faisal Fakih; Chest Diseases of Northwestern PA: Stephen Kovacs; CHI Group Inc: Marvin Heuer; Newport Native MD, Inc: Ryan Klein; San Gabriel Clinical Research; John Willis; The Asthma & Allergy Center, PC: Linda Ford; Doctors Care Research: Carlos Bello; Michael Marcus MD; Vital Prospects Clinical Research Institute: Iftikhar Hussain; Kern Allergy and Medical Research, Inc: Tonny Tanus; University of Arizona – Respiratory Center: Tara Carr; University of New Mexico: Hengameh Heidarian-Raissy; Clinical Research Trials of Florida Inc: Sady Alpizar; Sooner Clinical Research: Robert Gordon; Carolina Research Center Inc: Stephen Jones; San Marcus Research Clinic Inc: Hector Rodriguez; University of Utah Hospital: Gerald Gleich; Office of John P Lavery MD PA; Georgia Pollens Clinical Research Centers Inc: Tracy Bridges; United Care Research: Sergio Rodriguez, Rafael Palmerola; Longwood Research: Saadat Ansari; Centex Studies Inc: Joe Pouzar; Centex Studies Inc: Hiram Garcia; Clinical Trials of Orange County: Chao Lin; Allergy Asthma & Sinus Center SC: Gary Steven; IMC Diagnostic & Medical Clinic Mobile Infirmary: Blesilda Ellis; Syrentis Clinical Research: Kenneth Rich; Vero Lung Center: John Suen; Chesapeake Clinical Research Inc: Jonathan Matz; Detroit Clinical Research Center PC: Michael Basha, Shana Krstevska; MedStar Clinic Research Associates: Rachel Kientcha-Tita; Medical Education and Research Management Of New England: Lawrence Dubuske; Pulmonary and Sleep Center of the Valley: Adolfo Kaplan; Family Allergy and Asthma Research Institute: James Sublett; Allergy & Clinical Immunology Associates; James DeAngelo; Oklahoma Institute of Allergy & Asthma Clinical Research LLC: Amy Darter; Clinical Investigation Specialists Inc: John Agaiby; Mayo Clinic: John Hagan; Oregon Clinic: Mahmood Darr; Novel Research of New York: Enrique Davis; St. Francis Hospital & Medical Cntr.: Daniel Gerardi; Sneeze Wheeze & Itch Associates LLC: Dareen Siri; Health Partners Institute for Education and Research: Charlene McEvoy; Kentucky Lung Clinic PSC: Firas Koura; Southwest Family Medicine Associates; Chrisette Dharma; East Montgomery County Clinic: Najmuddin Karimjee; Gonzalez Family and Occupational Medicine: Julian Gonzales; Temple University Hospital-Lung Center: Steven Kelsen; Life Spring Research Foundation LLC: Juan Frias, Bryan Robbins; Arizona Pulmonary Specialists, Ltd.: Amy Silverthorn; Professional Healthcare Care of Pinellas Inc: Fadi Saba; University of Iowa Hospital and Clinics: Joel Kline; Palmetto Professional Research Corp: Esperanza Arce-Nunez; Pulmonary and Critical Care Assoc of the Tricities: Muhammed Farooq; Mid Hudson: Medical Research: Rabi Sinha; Direct Helpers Medical Center Inc: Alberto Manzor; Saint Francis Sleep Allergy and Lung Institute: Francis Averill; Top Medical Research Inc: Jose Ruiz; Pulmonary Research of Abingdon LLC: Emory Robinette; East Coast Institute for Research: Mitchell Rothstein; Aspen Clinical Research, LLC: Talaat Al Shuqairat; PMA Medical Specialists LLC: Raymond Kovalski; Sealy Clinical Research Foundation: Kannappan Krishnaswamy; Toledo Institute of Clinical Research: Syed Rehman; Robert V. Sibilia M.D., Inc.; Southwest Clinical Trials: Zeeshan Shaikh; Allergy & Asthma Specialists Medical Group: Steven F Weinstein; St Mark Clinical Trials, LLC: Joseph Zaky; Medsol Clinical Research Ctr: Elvin Mendez; Elite Clinical Research: Carlos Aguilar; South Florida Clinical Trials: Hernando Alvarez; Calvin Dixon MD; New York Clinical Trials: Scott Bloom; South Florida Clinical Trials: Norma Roche; Joseph A. Montes, MD, PA; Integrated Research Group Inc: Amit Patel; Northeast GA Physicians Group Allergy & Asthma: William Nish; Mainland Medical Research Institute: Susan Andrew; Clinical Research of Brandon, LLC: German Alvarez; Integrity Clinical Trials, LLC: Maria del Carmen Valdes; Altru Health Main: Wayne Breitwieser; Aviisha Medical Institute LLC; Abraham Ishaaya: Syed Research Consultants LLC: Faizullah Syed; Allphase Clinical Research INC: Luis Mas; Allergy and Asthma Care Mid-South – Germantown: Phillip Lieberman; Jimin Wang MD PA; Riser Medical Associates: James Riser; Exemplar Research Inc: Sally Dee; Billings Clinic Research Endocrinology: Kathleen Davis; Clinical Research of Rock Hill: Michael Denenberg; Scottsboro Quick Care Clinic: Younus Ismail; Parikh Institute for Research LLC: Purvi Parikh; Delaware Valley Clinical Research: Eugene Gatti; Pediatric Pulmonary & Asthma Associates of South Jersey: Mila Leong; Bassetti Medical Research: Dennis Bassetti; Advanced Research Associates Self Medical Group: Dennis Murphy; American Institute of Research/NewPort Children's Medical Gr: Zachariah Reda; Sacred Heart Medical Research LLC: Juan Ortiz, Yvelice Villaman-Bencosme; Advance Research Institute: Michael Lucia; Midland Florida Clinical Research: Godson Oguchi; Infinity Medical Research Inc: Curtis Mello; Clinsearch LLC: Richard Krause; National Allergy and Asthma Research LLC: John Ramey; Allergy & Asthma Associates of Santa Clara Valley: Alan Goldsobel; Southeastern Medical

Integrated: Mercedes Pernice; Vista Health Research, LLC: Antonio Blanco; Indago Research and Health Center: Jose Cardona; Acadiana Medicine Clinic: Jose Santiago; National Clinical Resources: Edward Campbell; BioMed Research Institute: Guido Perez; Yale University School of Medicine: Geoffrey Chupp; Paradigm Clinical Research Institute: Ramprasad Dandillaya; Easley Clinical Research: Abbas Mansour; Beacon Clinical Research, LLC: Sara Penn, Toby Bates, Maxim Lutskiy; The Research Center Inc: Vandely Perez; DCT-Genesis-Baxter, LLC dba Discovery Clinical Trials: Barbara Baxter; Florida Institute for Clinical Research, LLC: Humberto Cruz; AZ Perfection Clinical, LLC: Ilia Segal; Abraham Research, PLLC: Manuel Villareal

Vietnam

Bach Mai Hospital: Chau Ngo; Cho Ray Hospital: Ngoc Tran; Department of Management and Treatment, Pham Ngoc Thach Hosp: Lan Nguyen; Respiratory dept – Gia Dinh People Hospital: Huong Le; Respiratory Care Center, HCMC University Medical Center: Le Thi Tuyet Lan

Appendix 2. Inclusion and exclusion criteria

Inclusion criteria

Patients must have met all of the following criteria:

- Written informed consent, and assent when applicable, for study participation had to be obtained prior to any study-related procedures being performed (local regulations were to be followed in determining the assent/consent requirements for children and parent[s]/guardian[s]) and according to international guidelines and/or applicable European Union guidelines.
- Female and male aged 12 to 75 years, inclusively, at the time of visit 1.
 - Patients who were 17 on the day of visit 1 but turned 18 after this day were considered an adolescent for the purposes of this trial.
- Women of childbearing potential (after menarche) had to use a highly effective form of birth control (confirmed by the investigator or designee).
 - Highly effective forms of birth control included: true sexual abstinence, a vasectomised sexual partner, Implanon®, female sterilisation by tubal occlusion, any effective intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™ or Nuvaring™.
- Women of childbearing potential (after menarche) had to agree to use a highly effective method of birth control, as defined above, from enrolment, throughout the study duration, and within 16 weeks after last dose of investigational product, and have a negative serum pregnancy test result on visit 1.
- Women not of childbearing potential were defined as women who were either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who were postmenopausal.
 - Women were considered postmenopausal if they had been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age specific requirements applied:
 - Women <50 years old were considered postmenopausal if they had been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone concentrations in the postmenopausal range.
 - Women ≥50 years old were considered postmenopausal if they had been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- All male patients who were sexually active had to agree to use a double barrier method of contraception (condom with spermicide) from the first dose of investigational product until 16 weeks after their last doses.
- Weight of ≥40 kg.
- History of physician-diagnosed asthma requiring treatment with medium- to high-dosage inhaled corticosteroids (ICS; >250-µg fluticasone dry powder formulation equivalents total daily dosage) and a long-acting β₂-agonist (LABA), for at least 12 months prior to visit 1.
- Documented treatment with ICS and long-acting β₂-agonists for at least 3 months prior to visit 1 with or without oral corticosteroids (OCS) and additional asthma controllers.
 - The ICS and LABA could be parts of a combination product or given by separate inhalers.
 - For patients 18 years of age and older, the ICS dosage had to be >500 µg/day fluticasone propionate dry powder formulation or equivalent daily. For ICS/LABA combination preparations, the highest approved maintenance dosage in the local country would have met this ICS criterion.
 - For patients ages 12–17, the ICS dosage had to be ≥500 µg/day fluticasone propionate dry powder formulation or equivalent daily. For ICS/LABA combination preparations, the mid-strength approved maintenance dosage in the local country would have met this ICS criterion.
 - If patients used more than one type of ICS-containing therapy, each should have been converted to fluticasone propionate equivalents and summed to derive the patient's total daily dosage.
 - For patients ≥18 years of age, if that sum was >500 µg of fluticasone propionate equivalents dry powder formulation daily, the patient was eligible for the study.
 - For patients 12–17 years of age, if that sum was ≥500 µg of fluticasone propionate equivalents dry powder formulation daily, the patient was eligible for the study.
- Additional maintenance asthma controller medications that were locally approved in a country for the treatment of asthma (e.g., leukotriene receptor antagonists [LTRA], tiotropium, cromone, theophylline, OCS), and had been used for at least 30 days prior to visit 1 were allowed.

- Pre-bronchodilator forced expiratory volume in 1 second (FEV₁) of <80% predicted (<90% predicted for patients 12 to 17 years of age) at visit 2 (week –3).
- At least two documented asthma exacerbations in the 12 months prior to the date informed consent, and assent when applicable, was obtained that required use of a systemic corticosteroid or a temporary increase from the patient's usual maintenance dosage of OCS.
 - For patients who were re-screened within 30 days of their screen failure date, the calculation of the 12-month period should have been done from the original informed consent, and assent when applicable, date.
- Asthma Control Questionnaire-6 score ≥ 1.5 at visit 1 (week –4).
- Documented post-bronchodilator reversibility in FEV₁ of >12% and >200 mL in FEV₁ within 12 months prior to visit 1.
 - If historical documentation was not available, reversibility had to be demonstrated and documented at visit 2.

Inclusion criteria at randomisation:

- For women not of childbearing potential only: have a negative urine pregnancy test prior to administration of the investigational product at visit 4.
- Fulfilment of at least one of the following conditions over the 7 days prior to randomisation:
 - >2 days with a daytime or night-time symptoms score ≥ 1 .
 - Rescue short-acting β_2 -agonist use on >2 days.
 - ≥ 1 nocturnal awakening due to asthma.
- Pre-bronchodilator FEV₁ of <80% (<90% predicted for patients 12 to 17 years of age) predicted at day of randomisation visit.
- Patients demonstrate acceptable inhaler, peak flow meter, and spirometry techniques during run-in (from visit 2 to visit 4).
- At least 70% compliance with usual asthma controller ICS/LABA during run-in period (from visit 2 to visit 4) based on Asthma Daily Diary.
 - Patients who experienced an asthma exacerbation during run-in may have temporarily been unable to complete their diary due to illness or hospitalisation.
 - In these cases, ICS/LABA compliance was calculated for the period after systemic corticosteroid therapy was complete.
- Minimum 80% compliance with electronic patient-reported outcome completion.
 - 80% compliance was defined as completing Asthma Daily Diary for any 8 mornings and any 8 evenings of the last 10 days of the run-in period.

Exclusion criteria

Any of the following excluded the patient from participation in the study:

- Clinically important pulmonary disease other than asthma (e.g., active lung infection, chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, $\alpha 1$ antitrypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease other than asthma that was associated with elevated peripheral eosinophil counts (e.g., allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).
- Any disorder, including but not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that was not stable in the opinion of the investigator and could have:
 - Affected the safety of the patient throughout the study.
 - Influenced the findings of the studies or their interpretations.
 - Impede the patient's ability to complete the entire duration of study.
- Known history of allergy or reaction to the investigational product formulation.
- History of anaphylaxis to any biologic therapy.
- A helminthic parasitic infection diagnosed within 24 weeks prior to the date informed consent, and assent when applicable, was obtained that had not been treated with, or has failed to respond to, standard of care therapy.

- Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent, and assent when applicable, was obtained or during the screening/run-in period.
- Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis during screening/run-in period that, in the opinion of the investigator, may have put the patient at risk because of his/her participation in the study, or may have influenced the results of the study or the patient's ability to complete entire duration of the study.
- Any clinically significant cardiac disease or any electrocardiogram (ECG) abnormality obtained during the screening/run-in period that, in the opinion of the investigator, may have put the patient at risk or interfered with study assessments.
- History of alcohol or drug abuse within 12 months prior to the date informed consent, and assent when applicable, was obtained.
- Positive hepatitis B surface antigen or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C.
 - Patients with a history of hepatitis B vaccination without history of hepatitis B were allowed to enrol.
- A history of known immunodeficiency disorder including a positive human immunodeficiency virus test.
- Current smokers or former smokers with a smoking history of ≥ 10 pack-years.
- History of cancer:
 - Patients who have had basal cell carcinoma, localised squamous cell carcinoma of the skin, or in situ carcinoma of the cervix were eligible provided that the patient was in remission and curative therapy was completed at least 12 months prior to the date informed consent, and assent when applicable, was obtained.
 - Patients who have had other malignancies were eligible provided that the patient was in remission and curative therapy was completed at least 5 years prior to the date informed consent, and assent when applicable, was obtained.
- Use of immunosuppressive medication (including but not limited to methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, or any experimental anti-inflammatory therapy) within 3 months prior to the date informed consent, and assent when applicable, was obtained.
 - Chronic maintenance prednisone for the treatment of asthma was allowed.
- Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent, and assent when applicable, was obtained.
- Receipt of any marketed (e.g., omalizumab) or investigational biologic within 4 months or 5 half-lives prior to the date informed consent, and assent when applicable, was obtained, whichever was longer.
- Receipt of live attenuated vaccines 30 days prior to the date of randomisation; the exception was for adolescent patients from the European Union within 4 months or within 5 half-lives prior to the date informed consent and assent was obtained, whichever was longer:
 - Receipt of inactive/killed vaccinations (e.g., inactive influenza) was allowed provided they were not administered within 1 week before/after any investigational product administration.
- Receipt of any investigational nonbiologic within 30 days or 5 half-lives prior to randomisation, whichever was longer.
- Previously randomised in any benralizumab (MEDI-563) study.
- Initiation of new allergen immunotherapy was not allowed within 30 days prior to the date of informed consent, and assent, when applicable.
 - Immunotherapy initiated prior to this period or as a routine part of the patient's seasonal treatment was allowed.
 - If the immunotherapy was delivered as an injection, there should have been a gap of 7 days between the immunotherapy and investigational product administration.
- Current use of any oral or ophthalmic nonselective β -adrenergic antagonist (e.g., propranolol).
- Planned surgical procedures during the conduct of the study.
- Currently breastfeeding or lactating women.
- Previous randomisation in the present study.
- Concurrent enrolment in another clinical trial.
- AstraZeneca staff involved in the planning and/or conduct of the study.

- Employees of the study centre or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
- Alanine aminotransferase or aspartate aminotransferase concentration ≥ 2.5 times the upper limit of normal confirmed during screening period.
- Five-lipoxygenase inhibitors (e.g., Zileuton[®]) and roflumilast were prohibited.

Appendix 3. Asthma medication restrictions

Use of short-acting β_2 -agonists (SABAs)

- Regularly scheduled SABA use in the absence of any asthma symptoms and/or planned exercise was discouraged from enrolment and throughout the study duration.
- Prophylactic use of SABAs in the absence of symptoms (e.g., prior to planned exercise) was discouraged.
 - However, if deemed necessary by the patient and investigator, it could be used, but prophylactic inhalations were not to be recorded in the Asthma Daily Diary.
 - Such use should have been documented in medical notes and recorded in the electronic case report form (eCRF).
- SABAs via a metered dose device were permitted as needed for worsening asthma symptoms (i.e., rescue use) and were recorded in the Asthma Daily Diary as number of inhalations.
- Rescue use of SABAs administered via jet or ultrasonic nebulisation was allowed.
 - Occasions where SABAs were administered via nebulisation were to be recorded separately from metered-dose inhaler (MDI) inhalations in the Asthma Daily Diary.

Use of short-acting anticholinergics

- Use of short-acting anticholinergics (e.g., ipratropium) as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event was not allowed from enrolment and throughout the study duration.

Use of long-acting β_2 -agonists (LABAs)

- Use of long-acting β_2 -agonists (LABAs) as a reliever (e.g., Symbicort® Maintenance and Reliever Treatment) was not allowed from enrolment and throughout the study duration.

Maintenance of asthma controller medications

- The patient's usual pre-study ICS/LABA formulation, dosage, and regimen, and any other additional allowed asthma controllers that he/she may have been taking prior to enrolment should have been continued unchanged throughout the run-in and treatment period.
- Additional maintenance asthma controller medications that were locally approved in a country for the treatment of asthma (e.g., tiotropium, LTRAs, chromone, theophylline, and OCS), that had been used for at least 30 days prior to visit 1, were allowed.
- Patients on theophylline should have had blood theophylline concentrations checked, assessed, and documented prior to randomisation.
 - The theophylline concentration must not have exceeded the upper limit of the therapeutic range.
- Changes to the patient's background controller regimen were discouraged during the treatment period, unless judged medically necessary by the investigator; ideally such changes should have been discussed with the AstraZeneca Study Team Physician.
 - All changes in the patient's background medication should have been documented in the source along with rationale for change and recorded in the eCRF.
- Asthma exacerbations should have been treated with oral or other systemic corticosteroids according to standard practice.

Asthma medication restrictions on the days of scheduled spirometry visit

- Pre- and/or post-bronchodilator spirometry assessments were performed at the study centre at scheduled visits: restrictions to patient's background medication were required prior to the spirometry.
- Screening visit 2:
 - Patients should have withheld their usual ICS, LABA, or long-acting muscarinic receptor antagonist (LAMA) medications on the morning of the screening FEV₁ measurement and reversibility test.
 - Twice-daily ICS and LABA therapies should have been withheld for 12 to 24 hours; once-daily therapies containing ICS, LABAs, or long-acting antimuscarinic therapies should have been withheld for ≥ 24 hours for eligibility assessment.

- In case the patient did not meet the reversibility eligibility criterion or FEV₁ (<80% or <90%) eligibility criterion, and a second re-test was done (not earlier than next calendar day and not later than 7 calendar days after the failed attempt), asthma medication restrictions described above should have been applied.
- In addition, SABA should not have been used within 6 hours of these spirometry assessments.
- The patient's usual asthma medications may have been administered following completion of the screening lung function procedures.
- Treatment visits 4–17:
 - Patients should have withheld their usual ICS, LABA, or LAMA medications on the morning of the scheduled spirometry, as indicated above for screening visit 2.
 - This was especially important prior to scheduled spirometry assessments in order to maintain the integrity of planned efficacy analyses around lung function improvement.
 - In addition, SABA should not have been used within 6 hours prior to the spirometry assessments.
 - The patient's usual asthma controller medications may have been administered following completion of the pre-bronchodilator spirometry.
 - If the patient had taken his/her usual ICS/LABA or LAMA asthma controller medication on the morning of the scheduled spirometry visit, the investigator/authorised delegate should have reminded the patient of the importance of withholding his/her usual morning asthma medication and rescheduled the visit for another day within the allowed window.
- If the patient had taken rescue SABA within 6 hours of the planned centre visit spirometry, he/she should have ideally remained at the centre until such time that the 6-hour withholding time had been reached if it did not exceed the 1.5-hour spirometry window or returned on another day within the visit window.

Asthma medication restrictions prior to home peak expiratory flow (PEF) testing

- Patients should have avoided taking their morning asthma controllers prior to the morning home PEF testing, and should have conducted the evening home PEF testing before taking evening asthma controllers.
 - When possible, home PEF testing should have been taken at least 6 hours after the last dose of SABA rescue medication.

Asthma medication restrictions on unscheduled visits

- Asthma medication restrictions on unscheduled visits may not have been feasible, and may have been applied at the discretion of the investigator.
 - Timing of recent controller and rescue SABA use relative to the unscheduled spirometry should have been noted in the record.

Asthma medication restrictions at centre visits with scheduled ECG assessment

- Patients should have been instructed not to take their usual asthma controller medication (i.e., LABA) prior to scheduled ECG assessment.
 - Use of SABA should have been avoided within 6 hours before ECG assessments.
 - The medication restriction was waived for the screening ECG and visit 1.

Other medication restrictions

- Use of immunosuppressive medication (other than prior, stable OCS for the maintenance treatment of asthma) or administration of live/attenuated vaccines was not permitted.
 - Topical administration of immunosuppressive medication may have been permitted at the discretion of the investigator after discussion with the AstraZeneca Study Physician.
- Receipt of live attenuated vaccines within 30 days prior to randomisation, during the treatment period, and for 16 weeks (5 half-lives) after the last dose of the study treatment was not permitted.
 - For adolescent patients from Europe: within 4 months or within 5 half-lives prior to the date of informed consent, and assent when applicable, was obtained, whichever was longer.
- Patients should not have received allergen immunotherapy injection on the same day as study treatment administration.

- When enrolling a patient who was on theophylline, digoxin, or other drugs with a narrow therapeutic range, the investigator should have ensured the concentrations of each of these medications did not exceed the upper limit of therapeutic range.
 - The investigator was also responsible for ensuring that these concentrations were regularly checked, assessed, and documented as per local practice.
- Patients should not have taken any other excluded medications:
 - Five-lipoxygenase inhibitors (e.g., Zileuton®).
 - Roflumilast.
 - Oral or ophthalmic non-selective β -adrenergic antagonist (e.g., propranolol).

Appendix 4. Efficacy assessments

Spirometry

- Lung function (FEV₁ and forced vital capacity [FVC]) at the study centre was measured by spirometry using equipment provided by a central vendor.
- Spirometry was performed by the investigator or authorised delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.
- All post-randomisation spirometry assessments should have been performed within ± 1.5 hours of the time that the randomisation spirometry was performed.

Home PEF testing

- An electronic, hand-held spirometer (peak flow meter) was dispensed to the patient on visit 2 after respiratory inclusion criteria had been confirmed.
- Home PEF testing was performed by the patient in the morning upon awakening (and prior to taking their morning asthma controller) and in the evening at bedtime (and prior to taking their evening asthma controller).
- Home PEF data were captured in the Asthma Daily Diary.

Patient-reported outcomes (PROs)

- Patients were supplied with an electronic patient-reported outcomes (ePRO) device and hand-held spirometer at visit 2 after respiratory inclusion criteria had been confirmed.
- The study centre staff were trained on how to use both devices and were responsible for instructing patients on how to use both devices.

Asthma Daily Diary

- The Asthma Daily Diary included the following daily recordings: home PEF data (obtained from the home peak flow meter), asthma symptoms (including, but not limited to, shortness of breath, wheezing, coughing, and/or chest tightness), inhalations of rescue medication (number of puffs and number of times a nebuliser was used), nights with awakenings due to asthma symptoms, and background medication compliance.
- The Asthma Daily Diary was completed twice daily (morning upon waking and evening prior to going to bed) from the evening of visit 2 to the morning of visit 19.
- The morning assessment included one item pertaining to asthma symptoms that occurred in the night.
 - Patients were asked to score each of the questions on a 4-point scale (0 – No asthma symptoms to 3 – You were unable to sleep because of your asthma)
 - The morning diary also captured night-time awakenings (yes/no) and the use of rescue medication during these awakenings (yes/no).
- The evening diary contained a single item.
 - The patients were asked to score the question on a 4-point response scale (0 – No asthma symptoms to 3 – You were unable to do your normal activities because of your asthma).
- The total daily symptom score was the sum of the morning and evening responses.
 - The total daily symptom score was calculated only when both morning and evening scores were available, otherwise it was set to missing.

Asthma Control Questionnaire with 6 questions (ACQ-6)

- The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing), and SABA use while omitting the FEV₁ measurement from the original ACQ score.
- The ACQ-6 was completed using the ePRO device.
- Patients were asked to recall their experiences during the previous week and to score each of the questions on a 7-point scale ranging from 0 (totally controlled) to 6 (severely uncontrolled).
 - The overall score was calculated as the mean response to all questions.
- Individual ACQ-6 total score changes of ≥ 0.5 were considered to be clinically meaningful.
- An ACQ-5 score can be calculated from the ACQ-6 data by omitting the SABA item when scoring the instrument.

- Following visit 4 (randomisation), patients were asked to complete the ACQ-6 once every 2 weeks (± 1 day) throughout the treatment period.

Asthma Quality of Life Questionnaire (standardized) for 12 years and older (AQLQ[S]+12)

- The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by patients aged ≥ 12 years with asthma.
 - The questionnaire comprises four separate domains: symptoms, activity limitations, emotional function and environmental stimuli.
 - The questionnaire was completed using the ePRO device.
- Patients were asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment).
 - The overall score was calculated as the mean response to all questions.
 - The four individual domain scores were the means of the responses to the questions in each of the domains.
- Individual AQLQ(S)+12 total or domain score changes of ≥ 0.5 were considered to be clinically meaningful.
- Following visit 4 (randomisation), patients were asked to complete the AQLQ(S)+12 once every 4 weeks (± 1 day) throughout the treatment period.

Appendix 5. Definition of asthma worsening

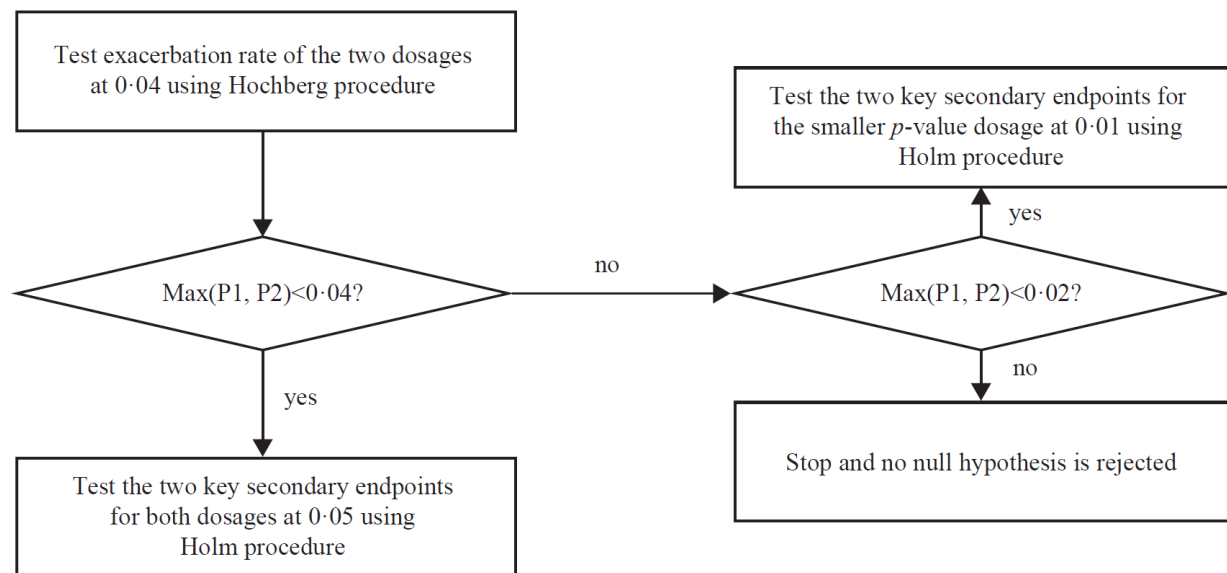
- Worsening of asthma was defined as new or increased symptoms and/or signs (examination or lung function) that could be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven).
- Asthma Daily diary alerts were considered to be one or a combination of: 1) a decrease in morning peak flow $\geq 30\%$ on at least 2 of 3 consecutive days compared with baseline, 2) $\geq 50\%$ increase in rescue medication and/or use of one new or additional nebulised LABA on at least 2 of 3 consecutive days compared with the average use for the previous week, 3) nocturnal awakening due to asthma, requiring rescue medication use for at least 2 of 3 consecutive nights, or 4) an increase in total asthma symptom score of at least 2 units above the run-in average (last 10 days of run-in), or a score of 6 (maximum possible score) on at least 2 of 3 consecutive days or a worsening of signs or symptoms as identified by physician assessment.

Appendix 6. Patient subgroups for analysis of exacerbation rates

- We conducted pre-specified subgroup analyses to assess the exacerbation rate in the following patient subgroups of clinical relevance:
 - Baseline OCS use (yes/no).
 - Sex (male/female).
 - Age (<18, 18–<65, or ≥65 years).
 - Geographic region (Asia, Eastern Europe, Europe [excluding Eastern Europe]), North America, or rest of the world [i.e., Africa, South America]).
 - Body mass index (≤ 35 / >35 kg/m²).
 - Number of exacerbations in the previous year (2, 3, or ≥4).
 - Race (white, black or African-American, Asian, or other).
 - Nasal polyps at baseline (yes/no).
 - Immunoglobulin E at baseline (≤ 30 , >30 – ≤ 700 IU/L).
 - Atopic asthma at baseline (yes/no).
 - Prior treatment with omalizumab (yes/no).

Appendix 7. Testing strategy to account for multiplicity testing

- To account for multiplicity to test the primary endpoint (annual asthma exacerbation rate) and two key secondary endpoints (the change in FEV₁ and total asthma symptom score from baseline to week 48, respectively) for each of the two dosing regimens (for patients with baseline blood eosinophils $\geq 300/\mu\text{L}$) a testing strategy was followed to control the overall type-1 error rate.
- We conducted the testing strategy according to the following gatekeeping procedure:
 - Step 1: Perform the two tests of annual asthma exacerbation rate (one test for each dosing regimen vs placebo) at the familywise error rate (FWER) of 0.04 using a Hochberg Procedure.¹ If both p -values are less than 0.04, then proceed to Step 2; if the smaller p -value is less than 0.02, then proceed to Step 2a; otherwise, no null hypothesis was rejected.
 - Step 2: Test the two key secondary endpoints for both dosing regimens as one family at the FWER of 0.05 using a Holm procedure.²
 - Step 2a: Test the two secondary endpoints for the smaller p -value dosage at the FWER of 0.01 using a Holm procedure.
- The gatekeeping procedure is also shown in the diagram below:



1 Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1988; **75**:800–2.

2 Holm S. A simple sequentially rejective multiple test procedure. *Scand J Statist* 1979; **6**:65–70.

Appendix 8. Data safety monitoring board and adjudication committees

- A data safety monitoring board and two adjudication committees were involved with this study:
 - The data safety monitoring board was responsible for evaluating cumulative safety and other clinical trial data from patients at regular intervals and making appropriate recommendations based on the available data independently from the study investigators and sponsor.
 - An independent asthma-associated ED visits and/or hospitalisations adjudication committee reviewed all ED visits and/or hospitalisations to determine whether the reason for health care utilisation was specifically the result of an asthma-related worsening and not another health-related issue.
 - An independent major adverse cardiovascular events/malignancies adjudication committee for major adverse cardiovascular events and malignancies provided unbiased assessments of blinded data to confirm diagnoses of 1) investigator-reported non-fatal myocardial infarction, non-fatal stroke (haemorrhagic, ischaemic, and embolic), as well as cardiovascular deaths; and 2) investigator-reported malignancies during the trial.

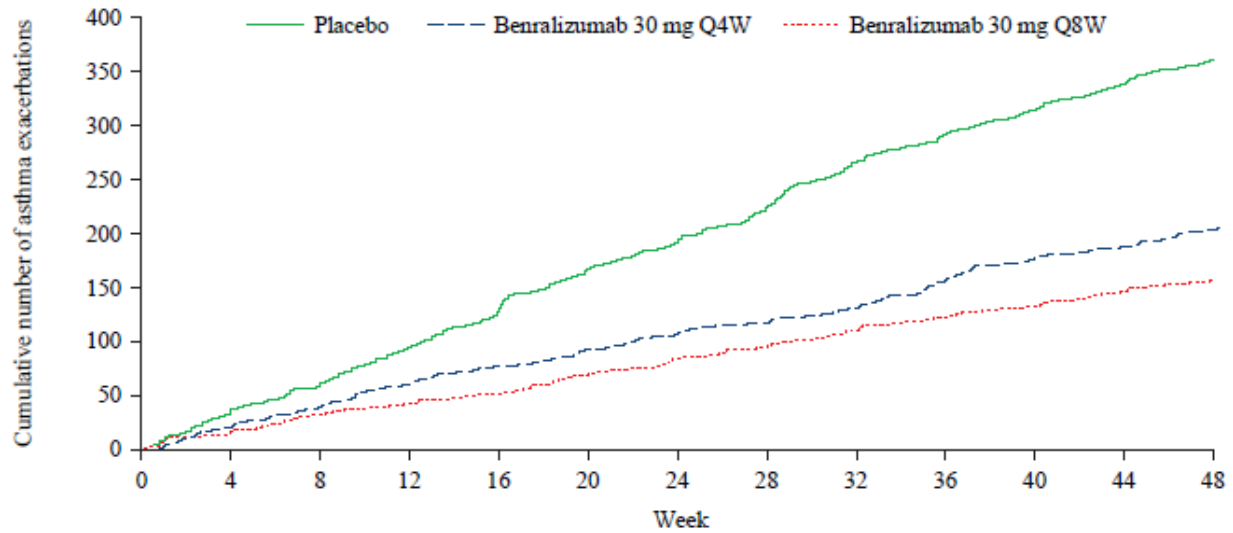
Appendix 9: Table 1: Concomitant maintenance asthma medications at baseline (full analysis set)

	All patients (N=1,204)			High-dosage ICS/LABA + baseline blood eosinophils ≥300 cells/μL (n=809)			High-dosage ICS/LABA + baseline blood eosinophils <300 cells/μL (n=395)		
	Placebo (n=407)	Benralizumab 30 mg Q4W (n=399)	Benralizumab 30 mg Q8W (n=398)	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=124)	Benralizumab 30 mg Q8W (n=131)
ICS	407 (100%)	399 (100%)	398 (100%)	267 (100%)	275 (100%)	267 (100%)	140 (100%)	124 (100%)	131 (100%)
Total daily dose (μg)	896 (125–3000)	899 (250–3000)	903 (500–2500)	902 (125–3000)	894 (417–3000)	913 (500–2500)	886 (500–2250)	909 (250–2292)	881 (500–2000)
LABA	407 (100%)	399 (100%)	398 (100%)	267 (100%)	275 (100%)	267 (100%)	140 (100%)	124 (100%)	131 (100%)
ICS/LABA	378 (93%)	382 (96%)	378 (95%)	250 (94%)	261 (95%)	251 (94%)	128 (91%)	121 (98%)	127 (97%)
OCS	68 (17%)	57 (14%)	71 (18%)	37 (14%)	38 (14%)	52 (19%)	31 (22%)	19 (15%)	19 (15%)
Total daily dose (mg)	15.3 (5.0–40.0)	14.4 (2.5–60.0)	15.2 (1.3–60.0)	13.9 (5.0–30.0)	15.3 (5.0–60.0)	15.5 (2.5–60.0)	16.9 (5.0–40.0)	12.5 (2.5–30.0)	14.3 (1.3–40.0)
LAMA	34 (8%)	34 (9%)	33 (8%)	22 (8%)	23 (8%)	25 (9%)	12 (9%)	11 (9%)	8 (6%)
LTRA	153 (38%)	128 (32%)	150 (38%)	102 (38%)	92 (33%)	103 (39%)	51 (36%)	36 (29%)	47 (36%)
Xanthine derivatives	65 (16%)	49 (12%)	60 (15%)	41 (15%)	30 (11%)	46 (17%)	24 (17%)	19 (15%)	14 (11%)
Other	5 (1%)	6 (2%)	3 (1%)	4 (1%)	3 (1%)	3 (1%)	1 (1%)	3 (2%)	0

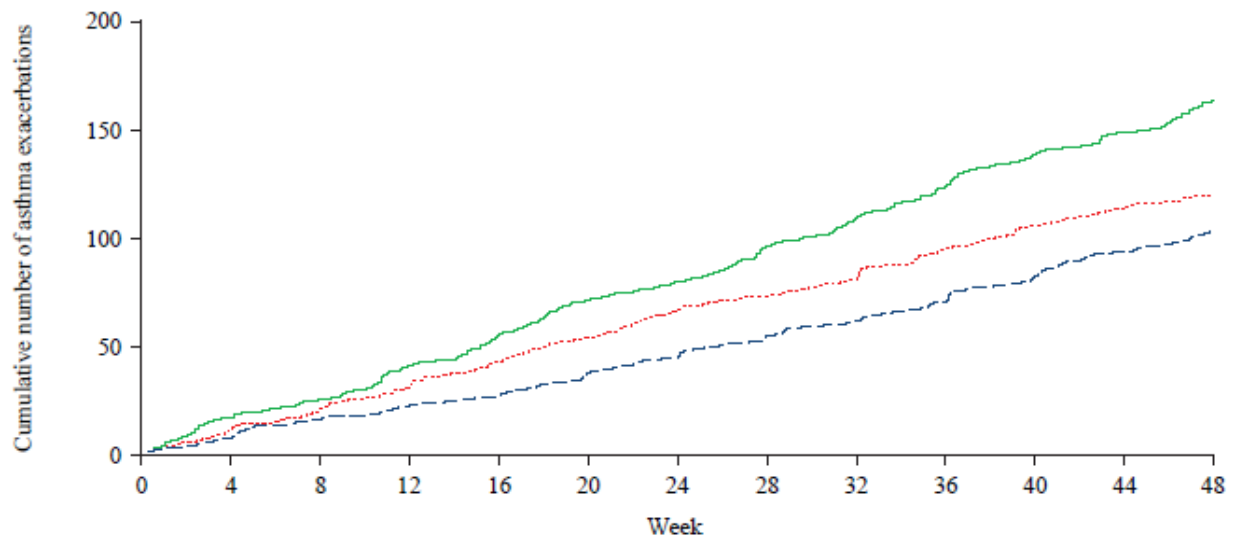
Data are number of patients (%) or mean (range). ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonist. LAMA=long-acting muscarinic receptor antagonist. LTRA= leukotriene receptor antagonists. OCS=oral corticosteroids. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).

Appendix 10: Figure 1. Cumulative number of asthma exacerbations over 48 weeks for patients receiving high-dosage ICS/LABA with baseline blood eosinophils (A) ≥ 300 cells/ μ L and (B) < 300 cells/ μ L (full analysis set)

A. Eosinophils ≥ 300 cells/ μ L



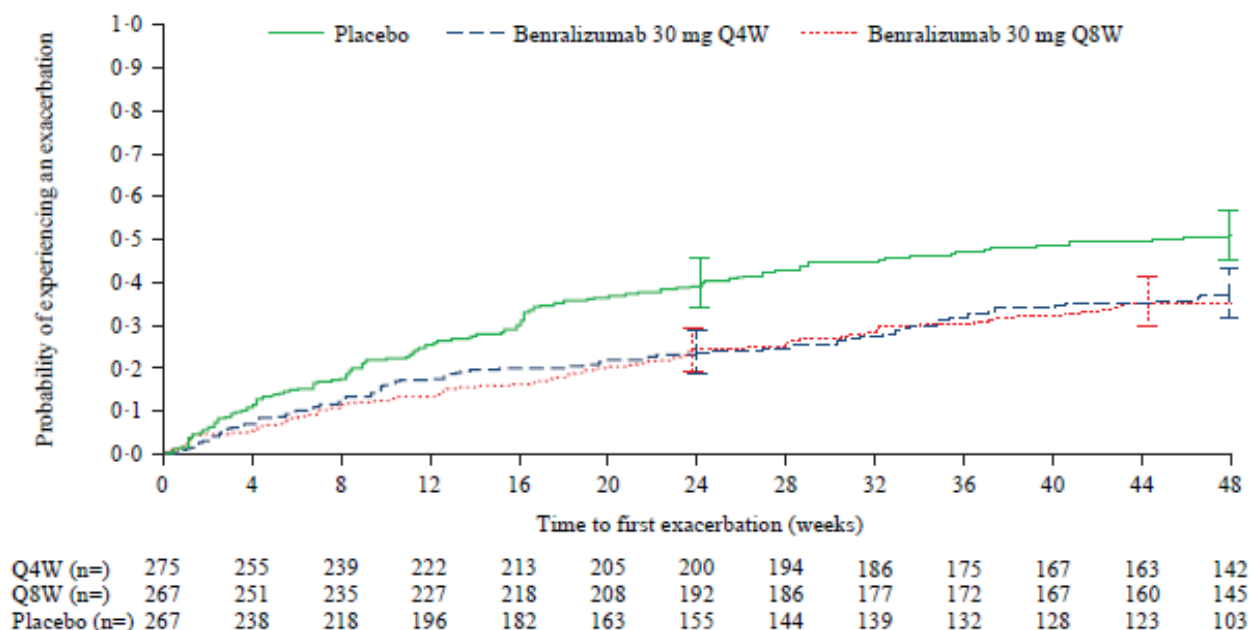
B. Eosinophils < 300 cells/ μ L



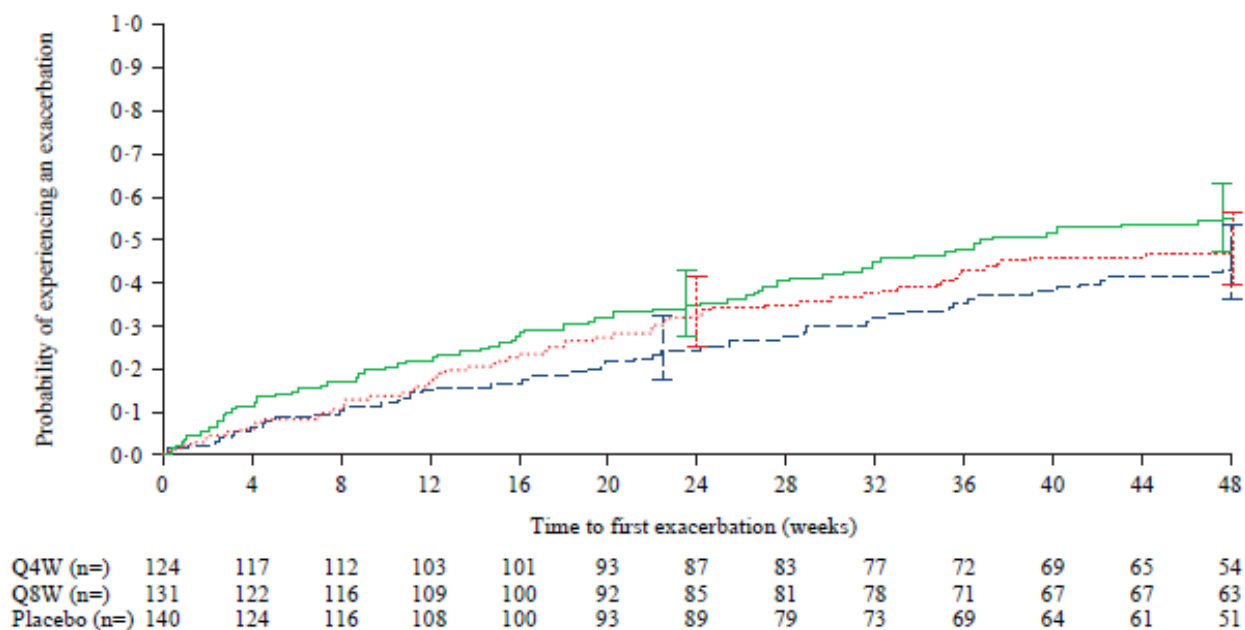
ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonist. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

Appendix 11: Figure 2. Time to first asthma exacerbation for patients receiving high-dosage ICS/LABA with baseline blood eosinophils (A) ≥ 300 cells/ μ L and (B) < 300 cells/ μ L (full analysis set)

A. Eosinophils ≥ 300 cells/ μ L



B. Eosinophils < 300 cells/ μ L



Error bars represent 95% confidence intervals. ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonist. Q4W=every 4 weeks. Q8W=every 8 weeks (first three doses Q4W).

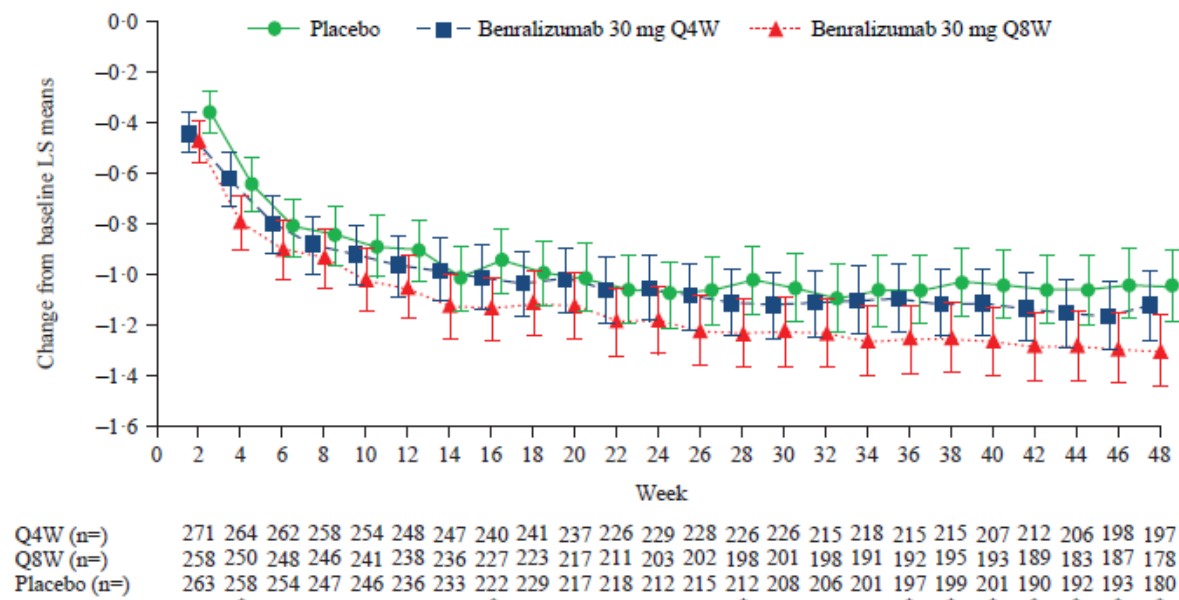
Appendix 12: Table 2: Post-bronchodilator FEV₁ change from baseline at week 48 (full analysis set)

	High-dosage ICS/LABA + baseline blood eosinophils ≥ 300 cells/μL		
	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)
Post-bronchodilator FEV ₁ (L)*			
N [†]	245	250	238
LS mean change	0·134; 228 [‡]	0·231; 231 [‡]	0·233; 225 [‡]
LS means difference vs placebo	—	0·097 (0·006 to 0·189)	0·099 (0·007 to 0·192)
p-value vs placebo	—	0·0369	0·0357

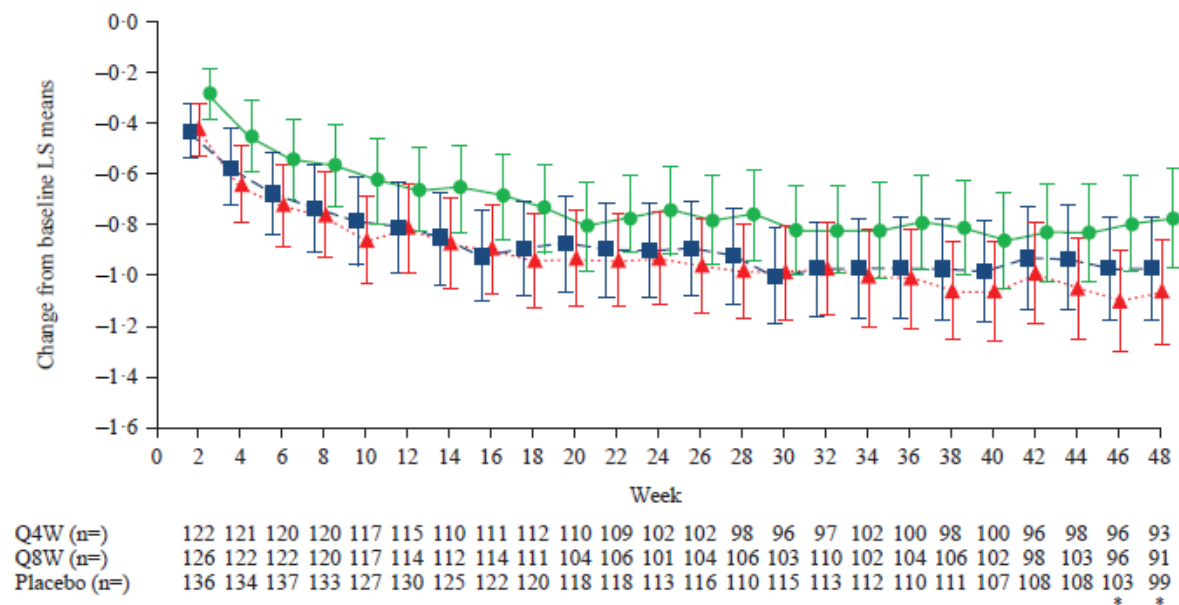
Data are mean change from baseline at week 48 or mean difference (95% CI). *Estimates calculated using a mixed-effects model for repeated measures analysis, with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit×treatment. [†]Number of patients with baseline and at least one post-baseline assessment (i.e., patients contributing to analysis). [‡]Number of patients with both baseline data and week 48 data available. CI=confidence interval. FEV₁=forced expiratory volume in 1 second. LS=least squares. Q4W=once every 4 weeks. Q8W=once every 8 week (first three doses Q4W).

Appendix 13: Figure 3. Change from baseline through week 48 in total asthma symptom score for patients receiving high-dosage ICS/LABA with blood eosinophils (A) ≥ 300 cells/ μ L and (B) < 300 cells/ μ L (full analysis set)

A. Eosinophils ≥ 300 cells/ μ L



B. Eosinophils < 300 cells/ μ L



Error bars represent 95% confidence intervals. * $P < 0.05$ for benralizumab 30 mg Q8W vs placebo. ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonist. LS=least squares. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).

Appendix 14: Table 3. Exacerbations resulting in adjudicated ED visit, urgent care visit, or hospitalisation for patients receiving high-dosage ICS/LABA with baseline blood eosinophil counts ≥ 300 cells/ μ L (full analysis set)*

	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)
Annual exacerbation rate associated with ED visit or hospitalisation over 48 weeks n (%)	37 (14%)	28 (10%)	18 (7%)
Annual exacerbation rate estimate	0.18 (0.13 to 0.25)	0.11 (0.07 to 0.16)	0.06 (0.04 to 0.11)
Absolute difference estimate	–	–0.07 (–0.14 to 0.00)	–0.11 (–0.18 to –0.05)
Rate ratio vs placebo	–	0.61 (0.37 to 1.01)	0.37 (0.20 to 0.67)
P-value vs placebo	–	0.0529	0.0010

Data are absolute difference or rate ratio (95% CI). *Estimates via negative binomial model adjusting for treatment, region, oral corticosteroid use at time of randomisation, and prior exacerbations associated with ER visits or hospitalisations. ED=emergency department. ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonist. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).

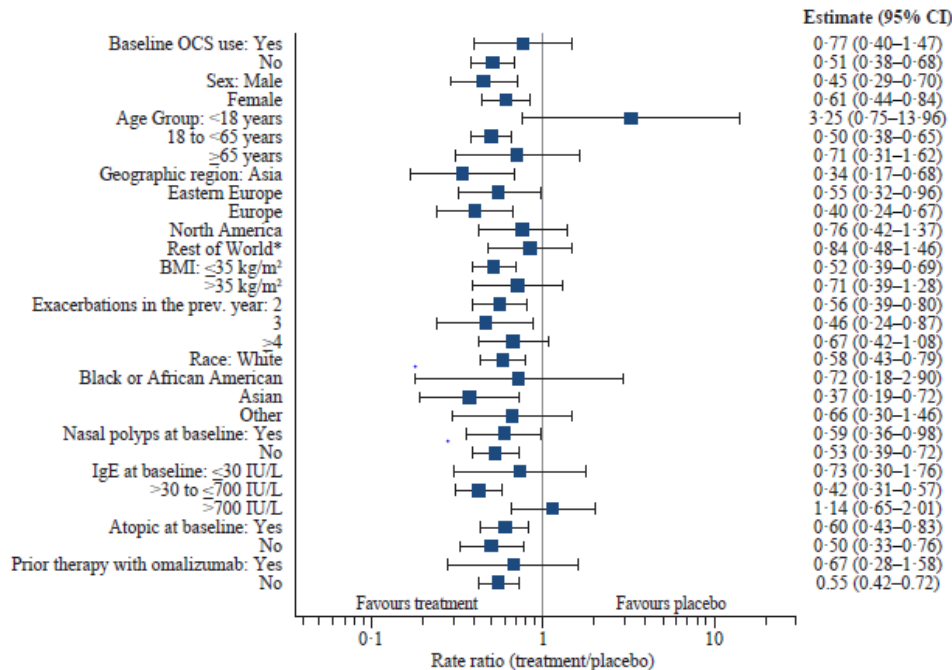
Appendix 15: Table 4: Post-hoc analysis of the treatment effect of exacerbation history on primary and secondary endpoints

	High-dosage ICS/LABA + baseline blood eosinophils ≥ 300 cells/ μ L		
	Placebo (n=267)	Benralizumab 30 mg Q4W (n=275)	Benralizumab 30 mg Q8W (n=267)
Primary analysis population*			
N	267	275	267
Annual exacerbation rate			
Crude rate	1.53	0.85	0.66
Rate ratio vs placebo	–	0.55 (0.42 to 0.71)	0.49 (0.37 to 0.64)
p-value vs placebo	–	<0.0001	<0.0001
Patients who had two prior exacerbations†			
N	149	173	164
Annual exacerbation rate			
Crude rate	1.05	0.58	0.55
Rate ratio vs placebo	–	0.56 (0.38 to 0.81)	0.55 (0.37 to 0.80)
p-value vs placebo	–	0.0023	0.0020
Pre-bronchodilator FEV ₁ (L)			
LS mean change	0.230	0.340	0.343
LS means difference vs placebo	–	0.110 (–0.004 to 0.224)	0.113 (–0.002 to 0.228)
p-value vs placebo	–	0.0576	0.0548
Total asthma symptom score			
LS mean change	–1.04	–1.12	–1.26
LS means difference vs placebo	–	–0.08 (–0.34 to 0.18)	–0.22 (–0.49 to 0.04)
p-value vs placebo	–	0.5289	0.0948
ACQ-6 score			
LS mean change	–1.11	–1.34	–1.40
LS means difference vs placebo	–	–0.23 (–0.46 to 0.00)	–0.29 (–0.53 to –0.06)
p-value vs placebo	–	0.0506	0.0146
AQLQ(S)+12 score			
LS mean change	1.17	1.42	1.55
LS means difference vs placebo	–	0.25 (0.00 to 0.50)	0.38 (0.13 to 0.63)
p-value vs placebo	–	0.0488	0.0034
Patients who had three or more prior exacerbations†			
N	118	102	103
Annual exacerbation rate			
Crude rate	2.15	1.29	0.84
Rate ratio vs placebo	–	0.54 (0.38 to 0.78)	0.43 (0.29 to 0.63)
p-value vs placebo	–	0.0010	<0.0001
Pre-bronchodilator FEV ₁ (L)			
LS mean change	0.251	0.358	0.486
LS means difference vs placebo	–	0.108 (–0.040 to 0.255)	0.235 (0.088 to 0.382)
p-value vs placebo	–	0.1510	0.0018
Total asthma symptom score			
LS mean change	–1.05	–1.12	–1.36
LS means difference vs placebo	–	–0.07 (–0.37 to 0.23)	–0.32 (–0.62 to –0.01)
p-value vs placebo	–	0.6475	0.0420
ACQ-6 score			
LS mean change	–1.24	–1.25	–1.56
LS means difference vs placebo	–	–0.02 (–0.33 to 0.30)	–0.33 (–0.65 to –0.01)
p-value vs placebo	–	0.9105	0.0458
AQLQ(S)+12 score			
LS mean change	1.37	1.45	1.59
LS means difference vs placebo	–	0.07 (–0.26 to 0.40)	0.22 (–0.11 to 0.55)
p-value vs placebo	–	0.6722	0.1966

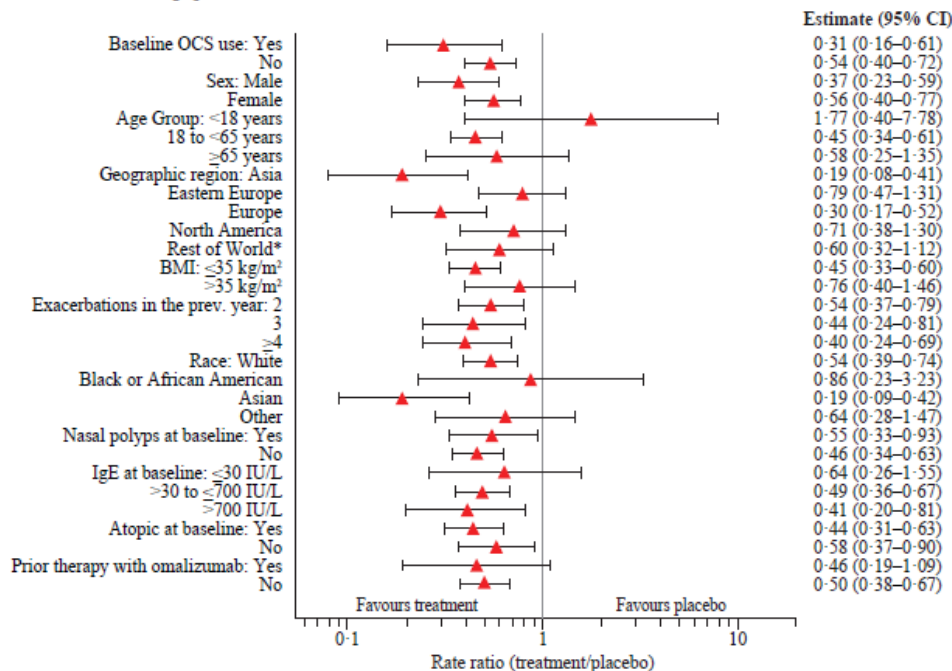
LS mean differences at week 48. Data are rate ratio or LS mean difference (95% CI). *Annual asthma exacerbation rate over 48 weeks. †In the previous year. ACQ-6=Asthma Control Questionnaire-6. AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 years and older. CI=confidence interval. FEV₁= forced expiratory volume in 1 second. ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonist. LS=least squares. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).

Appendix 16: Figure 4. Annual asthma exacerbation rate ratio at 48 weeks by subgroup for (A) benralizumab Q4W versus placebo and (B) benralizumab Q8W versus placebo for patients receiving high-dosage ICS/LABA with blood eosinophils ≥ 300 cells/ μ L

A. Benralizumab 30 mg Q4W



B. Benralizumab 30 mg Q8W



*Africa, South America. BMI=body mass index. CI=confidence interval. ICS=inhaled corticosteroids. IgE=immunoglobulin E. LABA=long-acting β_2 agonist. OCS=oral corticosteroid. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).

Appendix 17: Table 5: Baseline demographics and clinical characteristics by geographic region for patients receiving high-dosage ICS/LABA with baseline blood eosinophils ≥ 300 cells/ μ L

	Asia (n=96)	Eastern Europe (n=250)	Europe (n=164)	North America (n=142)	Rest of World (Africa and South America) (n=157)
Age (years)	52.1 (11.1)	49.2 (14.1)	50.5 (12.1)	45.5 (16.1)	45.7 (15.2)
Sex					
Male	36 (37.5%)	94 (38%)	55 (34%)	53 (37%)	44 (28%)
Female	60 (62.5%)	156 (62%)	109 (66%)	89 (63%)	113 (72%)
Race					
White	0	250 (100%)	160 (98%)	107 (75%)	57 (36%)
Black or African-American	0	0	1 (<1%)	24 (17%)	6 (4%)
Asian	96 (100%)	0	1 (<1%)	3 (2%)	10 (6%)
Other*	0	0	2 (1%)	8 (6%)	84 (54%)
BMI (kg/m ²)	24.4 (4.3)	28.2 (5.7)	27.7 (6.0)	31.9 (8.5)	28.9 (6.6)
Local eosinophil count (cells/ μ L)	713.2 (468.2)	493.3 (229.6)	700.6 (461.6)	677.6 (450.0)	664.1 (350.7)
FEV ₁ pre-bronchodilator (% predicted normal)	58.8% (13.1)	56.3% (14.1)	51.6% (15.1)	57.9% (13.8)	57.2% (15.2)
FEV ₁ /FVC pre-bronchodilator (%)	61.6% (12.8)	61.3% (11.9)	56.1% (12.5)	65.2% (11.5)	61.5% (12.7)
Reversibility (%)	20.9% (22.1)	30.2% (26.5)	22.5% (20.0)	25.7% (21.0)	27.0% (25.0)
ACQ-6 score [†]	2.3 (0.7)	2.8 (0.9)	2.9 (1.0)	2.9 (1.1)	2.9 (0.8)
Smoking history					
Never	70 (73%)	212 (85%)	110 (67%)	120 (85%)	141 (90%)
Current	1 (1%)	0	0	1 (<1%)	0
Former	25 (26%)	38 (15%)	54 (33%)	21 (15%)	16 (10%)
Time since asthma diagnosis (years)	8.4 (1.1 to 43.1)	11.3 (1.2 to 62.6)	13.9 (1.1 to 66.9)	20.3 (1.3 to 64.0)	21.0 (1.2 to 65.2)
Number of exacerbations in the previous 12 months	3.4 (2.3)	2.4 (0.9)	3.5 (2.3)	3.1 (2.0)	2.9 (1.6)
2 exacerbations	50 (52%)	188 (75%)	80 (49%)	75 (53%)	93 (59%)
≥ 3 exacerbations	46 (48%)	62 (25%)	84 (51%)	67 (47%)	64 (41%)
Exacerbations leading to hospitalisation in the previous 12 months	16 (17%)	106 (42%)	30 (18%)	29 (20%)	23 (15%)
OCS use	17 (18%)	15 (6%)	61 (37%)	16 (11%)	18 (11%)
ICS total daily dose (μ g)	953.2 (327.1)	826.7 (345.0)	1079.4 (477.7)	772.9 (274.0)	927.5 (316.4)

Data are mean (SD), median (range), or n (%). *Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and Other. [†]The ACQ-6 is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β_2 -agonist use on a 0–6 scale (low numbers represent better control). ACQ-6=Asthma Control Questionnaire-6. BMI=body mass index. FEV₁= forced expiratory volume in 1 second. FVC=forced vital capacity. ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonist. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W). SD=standard deviation.

Appendix 18: Table 6. Blood eosinophil count changes with benralizumab treatment for patients receiving high-dosage ICS/LABA with baseline blood eosinophils ≥ 300 cells/ μ L and < 300 cells/ μ L*

	High-dosage ICS/LABA + ≥ 300 cells/ μ L baseline blood eosinophils			High-dosage ICS/LABA + < 300 cells/ μ L baseline blood eosinophils		
	Placebo	Benralizumab 30 mg Q4W	Benralizumab 30 mg Q8W	Placebo	Benralizumab 30 mg Q4W	Benralizumab 30 mg Q8W
Baseline blood eosinophil count (cells/ μ L)	460 (330, 760); 265	450 (300, 720); 275	440 (280, 690); 267	150 (80, 220); 139	160 (100, 220); 123	150 (80, 240); 129
Week 4 blood eosinophil count (cells/ μ L)	420 (255, 640); 244 [†]	0 (0, 10); 263	0 (0, 10); 247	160 (90, 250); 134 [†]	0 (0, 10); 118 [†]	0 (0, 10); 118 [†]
LS mean change	3.0%	-95.2%	-91.0%	81.6%	-87.5%	-89.2%
LS mean difference	—	-98.3% (-107.3 to -89.2)	-94.1% (-103.3 to -84.9)	—	-169.1% (-208.7 to -129.5)	-170.8% (-210.2 to -131.3)
P-value vs placebo	—	<0.0001	<0.0001	—	<0.0001	<0.0001
Week 48 blood eosinophil count (cells/ μ L)	375 (230, 580); 202 [†]	0 (0, 10); 202	0 (0, 10); 208	150 (80, 310); 97 [†]	0 (0, 10); 90 [†]	0 (0, 10); 99 [†]
LS mean change	6.9%	-95.3%	-92.7%	122.1%	-84.0%	-88.3%
LS mean difference	—	-102.2% (-116.2 to -88.2)	-99.6% (-113.6 to -85.6)	—	-206.1% (-292.0 to -120.3)	-210.5% (-294.9 to -126.0)
P-value vs placebo	—	<0.0001	<0.0001	—	<0.0001	<0.0001

Data are median (Q1, Q3); n, mean percent change from baseline or mean difference (95% CI). *Estimates via mixed-effects model for repeated measures analysis with adjustment for treatment, baseline value, region, oral corticosteroid use at time of randomisation, visit, and visit $\times$ treatment. [†]Not all patients evaluated for LS mean change and difference. CI=confidence interval. ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonist. LS=least squares. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).

Appendix 19: Table 7. Adverse events during on-treatment period categorised for blood eosinophil counts (safety population)

	High-dosage ICS/LABA + ≥300 cells/μL baseline blood eosinophils			High-dosage ICS/LABA + <300 cells/μL baseline blood eosinophils		
	Placebo (n=267)	Benralizumab 30 mg Q4W (n=277)*	Benralizumab 30 mg Q8W (n=265)	Placebo (n=140)	Benralizumab 30 mg Q4W (n=126)*	Benralizumab 30 mg Q8W (n=129)
Any AE	203 (76%)	205 (74%)	185 (70%)	108 (77%)	88 (70%)	96 (74%)
Any AE leading to treatment discontinuation [†]	2 (<1%)	3 (1%)	6 (2%)	1 (<1%)	6 (5%)	2 (2%)
Any SAE	36 (13%)	28 (10%)	33 (12%)	19 (14%)	19 (15%)	19 (15%)
Deaths	1 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)	1 (<1%)
AEs in >3% of patients [‡]						
Asthma	51 (19%)	38 (14%)	25 (9%)	27 (19%)	22 (17%)	20 (16%)
Nasopharyngitis	35 (13%)	35 (13%)	34 (13%)	12 (9%)	12 (10%)	12 (9%)
Upper respiratory tract infection	26 (10%)	31 (11%)	25 (9%)	10 (7%)	13 (10%)	7 (5%)
Headache	17 (6%)	16 (6%)	28 (11%)	4 (3%)	14 (11%)	9 (7%)
Bronchitis	22 (8%)	14 (5%)	12 (5%)	8 (6%)	10 (8%)	7 (5%)
Sinusitis	19 (7%)	10 (4%)	17 (6%)	9 (6%)	7 (6%)	5 (4%)
Influenza	16 (6%)	11 (4%)	15 (6%)	7 (5%)	6 (5%)	4 (3%)
Acute sinusitis	9 (3%)	8 (3%)	11 (4%)	1 (<1%)	2 (2%)	2 (2%)
Back pain	9 (3%)	8 (3%)	3 (1%)	6 (4%)	3 (2%)	5 (4%)
Cough	8 (3%)	8 (3%)	8 (3%)	2 (1%)	7 (6%)	5 (4%)
Hypertension	8 (3%)	7 (3%)	5 (2%)	4 (3%)	4 (3%)	5 (4%)
Pyrexia	8 (3%)	12 (4%)	9 (3%)	0	4 (3%)	3 (2%)
Nausea	7 (3%)	5 (2%)	10 (4%)	1 (<1%)	3 (2%)	2 (2%)
Rhinitis	7 (3%)	10 (4%)	6 (2%)	8 (6%)	6 (5%)	4 (3%)
Pharyngitis	6 (2%)	12 (4%)	14 (5%)	8 (6%)	5 (4%)	9 (7%)
Arthralgia	6 (2%)	9 (3%)	15 (6%)	4 (3%)	2 (2%)	3 (2%)
Rhinitis allergic	6 (2%)	9 (3%)	8 (3%)	2 (1%)	2 (2%)	4 (3%)
Viral infection	5 (2%)	9 (3%)	3 (1%)	3 (2%)	0	3 (2%)
Pain in extremity	4 (1%)	1 (<1%)	9 (3%)	1 (<1%)	2 (2%)	4 (3%)
Dyspnoea	3 (1%)	5 (2%)	8 (3%)	1 (<1%)	6 (5%)	2 (2%)
Gastroesophageal reflux disease	1 (<1%)	4 (1%)	5 (2%)	5 (4%)	1 (<1%)	3 (2%)
Asthenia	3 (1%)	4 (1%)	5 (2%)	0	5 (4%)	1 (<1%)
Dizziness	6 (2%)	3 (1%)	2 (<1%)	2 (1%)	5 (4%)	0
Gastroenteritis	3 (1%)	5 (2%)	6 (2%)	3 (2%)	4 (3%)	6 (5%)
Injection-site reactions	6 (2%)	11 (4%)	5 (2%)	2 (1%)	5 (4%)	4 (3%)
Hypersensitivity adverse events [§]	7 (3%)	9 (3%)	6 (2%)	4 (3%)	4 (3%)	5 (4%)
Causally related [¶]	1 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)	0	0
Urticaria	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	0
Allergic granulomatous angiitis	0	1 (<1%)	0	0	0	0

Data are n (%), where n is the number of patients. The on-treatment period was defined as the day of first dose of study treatment to the scheduled end of therapy visit. *Includes patients in the Q8W cohort who received extra doses of benralizumab. [†]One additional patient in the Q8W cohort discontinued treatment during the post-treatment period. [‡]Medical Dictionary for Regulatory Activities version 18.1. [§]High-level term. [¶]In the opinion of the investigator. AE=adverse event. ICS=inhaled corticosteroids. LABA=long-acting β_2 -agonist. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W). SAE=serious adverse event.

Appendix 20: Table 8. Immunogenicity of benralizumab in treated patients (safety population)

	Placebo (n=407)	Benralizumab 30 mg Q4W (n=403)	Benralizumab 30 mg Q8W (n=394)
Any anti-drug antibody–positive response*	21 (5%)	47 (12%)	58 (15%)
Anti-drug antibody–positive post-baseline, not positive/missing at baseline†	10 (3%)	39 (10%)	49 (13%)
Anti-drug antibody–persistent-positive†	16 (4%)	23 (6%)	39 (10%)
Anti-drug antibody–transient-positive†	4 (1%)	18 (5%)	13 (3%)
Anti-drug antibody–positive, neutralizing antibody–positive*	11 (3%)	31 (8%)	49 (13%)

Data expressed as n (%). *Denominator based on patients with any anti-drug antibody data available. †Denominator based on patients with ≥ 1 post-baseline result available. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W).