Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study

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Summary

Background Persistent eosinophilic airway inflammation in asthma increases the risk of exacerbations. In a phase 2b dose-ranging study, we aimed to assess the efficacy and safety of benralizumab, an anti-interleukin 5 receptor α monoclonal antibody that depletes blood and airway eosinophils, in adults with uncontrolled eosinophilic asthma.

Methods We did a randomised, controlled, double-blind, dose-ranging phase 2b study. Eligible participants were adults aged 18–75 years with uncontrolled asthma using medium-dose or high-dose inhaled corticosteroids and longacting β agonists, with two to six exacerbations in the past year. Current or former smokers were excluded. We used the ELEN index (an algorithm to predict elevated sputum eosinophils) or baseline fraction of exhaled nitric oxide to stratify patients by eosinophilic status, and with an interactive web–voice response system randomly assigned eosinophilic individuals in a 1:1:1:1 ratio to receive placebo, 2 mg benralizumab, 20 mg benralizumab, or 100 mg benralizumab, and non-eosinophilic individuals in a 1:1 ratio to receive placebo or 100 mg benralizumab. Study drugs were given as two subcutaneous injections every 4 weeks for the first three doses, then every 8 weeks, for 1 year. Patients, treating physicians, and study investigators were masked to treatment allocation. The primary endpoint was annual exacerbation rate in eosinophilic individuals after 1 year of follow-up. Analysis was by modified intention to treat. This study was designed with a two-sided α of 0·2 and powered at 78% for the primary outcome in the eosinophilic population. This study is registered with ClinicalTrials.gov, number NCT01238861.

Findings Between Jan 3, 2011, and March 6, 2012, we randomly assigned 324 eosinophilic individuals to placebo (n=80) or benralizumab 2 mg dose (n=81), 20 mg dose, (n=81), or 100 mg dose (n=82), and 285 non-eosinophilic individuals to 100 mg benralizumab (n=142, 140 included in analysis) or placebo (n=143, 142 included in analysis). In eosinophilic individuals, benralizumab reduced exacerbation rates compared with placebo in the 100 mg group (0·34 *vs* 0·57, reduction 41%, 80% CI 11 to 60, p=0·096) but not in the 2 mg group (0·65 *vs* 0·57, difference –9%, 80% CI –59 to 26, p=0·781) or the 20 mg group (0·37 *vs* 0·57, reduction 36%, 80% CI 3 to 58, p=0·173). In patients with a baseline blood eosinophil cutoff of at least 300 cells per μL, exacerbation rates in the benralizumab 20 mg group (n=70) and 100 mg group (n=97) were lower than in the placebo group (n=83; 0·30 *vs* 0·68, reduction 57%, 80% CI 33 to 72, p=0·015 for 20 mg dose; 0·38 *vs* 0·68, difference 43%, 80% CI 18 to 60, p=0·049 for 100 mg dose). Our findings suggested that benralizumab 20 mg and 100 mg resided at the dose–response plateau. Treatment-emergent adverse events occurred in 277 (72%) of 385 participants receiving any benralizumab dose compared with 143 (65%) of 221 receiving placebo. Nasopharyngitis (44 [11%] patients receiving benralizumab *vs* 13 [6%] patients receiving placebo) and injection site reactions (60 [16%] *vs* eight [4%]) occurred more frequently with benralizumab than with placebo.

Interpretation Benralizumab at 20 mg and 100 mg doses seemed to reduce asthma exacerbations in adults with uncontrolled eosinophilic asthma and baseline blood eosinophils of at least 300 cells per μL, possibly due to targeting of the interleukin 5 receptor rather than interleukin 5 ligand. Further investigation of benralizumab treatment in phase 3 studies is warranted.

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See Online for podcast interview with Leonardo M Fabbri

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Introduction

Persistent eosinophilic airway inflammation in asthma increases the risk of subsequent exacerbations.[1–3] Monoclonal antibodies against interleukin 5 (eg, mepolizumab and reslizumab) reduce blood and sputum eosinophils in patients with asthma.[4,5] However, findings from an early study of mepolizumab in an unselected population of patients with asthma did not show clinical benefit,[5] suggesting that anti-interleukin 5 therapy might be effective only in a targeted subgroup with an eosinophilic phenotype.[6] In three randomised, placebo-controlled studies, mepolizumab significantly reduced exacerbations in participants with asthma and evidence of eosinophilic inflammation.[7–9] Thus, selection of patients with asthma and an eosinophilic phenotype might be a more useful approach to

investigate the efficacy of anti-interleukin 5 therapies. Benralizumab (MedImmune, Gaithersburg, MD, USA) is a humanised, afucosylated IgG-1κ monoclonal antibody that targets human interleukin 5 receptor α (IL5Rα)[10] expressed on eosinophils and basophils.[11–13] In vitro, benralizumab exhibits enhanced antibody-dependent cell-mediated cytotoxicity and induces apoptosis of target cells.[10] Findings from two studies in participants with atopic or eosinophilic asthma have shown that benralizumab depletes eosinophils in blood,[14,15] airway mucosa, and sputum.[15]

In a phase 2b randomised dose-ranging study, we aimed to assess the efficacy and safety of repeated doses of subcutaneous benralizumab in adults with uncontrolled asthma to determine whether this biological product should undergo further phase 3 development.

Methods

Study design and participants

We did a phase 2b, randomised, double-blind, placebo-controlled, dose-ranging study at 33 sites in the USA, Canada, Bulgaria, Brazil, Peru, Mexico, Poland, Russia, Argentina, and Colombia.

We enrolled adults aged 18–75 years who had asthma and were treated with medium-dose to high-dose inhaled corticosteroids in combination with longacting β agonist therapy[16] for at least 1 year; criteria for medium and high daily doses of inhaled corticosteroids are provided in the appendix (p 5). Eligible participants had a documented history of two to six exacerbations needing treatment with systemic corticosteroids in the past year, a morning prebronchodilator forced expiratory volume in 1 s (FEV_1) of 40% or higher but less than 90% predicted, and an Asthma Control Questionnaire (ACQ-6) score of 1·5 or higher[17–19] on at least two occasions during screening. Participants had to demonstrate post-bronchodilator FEV_1 reversibility of at least 12% and 200 mL, or a positive response to a methacholine challenge (provoking concentration of methacholine to cause a 20% fall in FEV_1 [PC_{20}] ≤8 mg/mL).[20] Individuals with a history of cigarette smoking, or current smokers, were excluded. We studied this selective population to reduce variability. Full inclusion and exclusion criteria are provided in the appendix (pp 3–5).

The protocol was approved by the institutional review board at each study site. All participants provided written informed consent before participating in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. This study is registered with ClinicalTrials.gov, number NCT01238861.

Randomisation and masking

After enrolment we classified each participant as having an eosinophilic or non-eosinophilic phenotype, using elevated baseline fraction of exhaled nitric oxide (Fe_{NO}) and a mathematical algorithm[21] to predict elevated sputum eosinophils (the eosinophil/lymphocyte and eosinophil/neutrophil [ELEN] index). Each participant's eosinophilic or non-eosinophilic status was transferred to a central interactive web–voice response system for random assignment into the appropriate stratum.

See Online for appendix

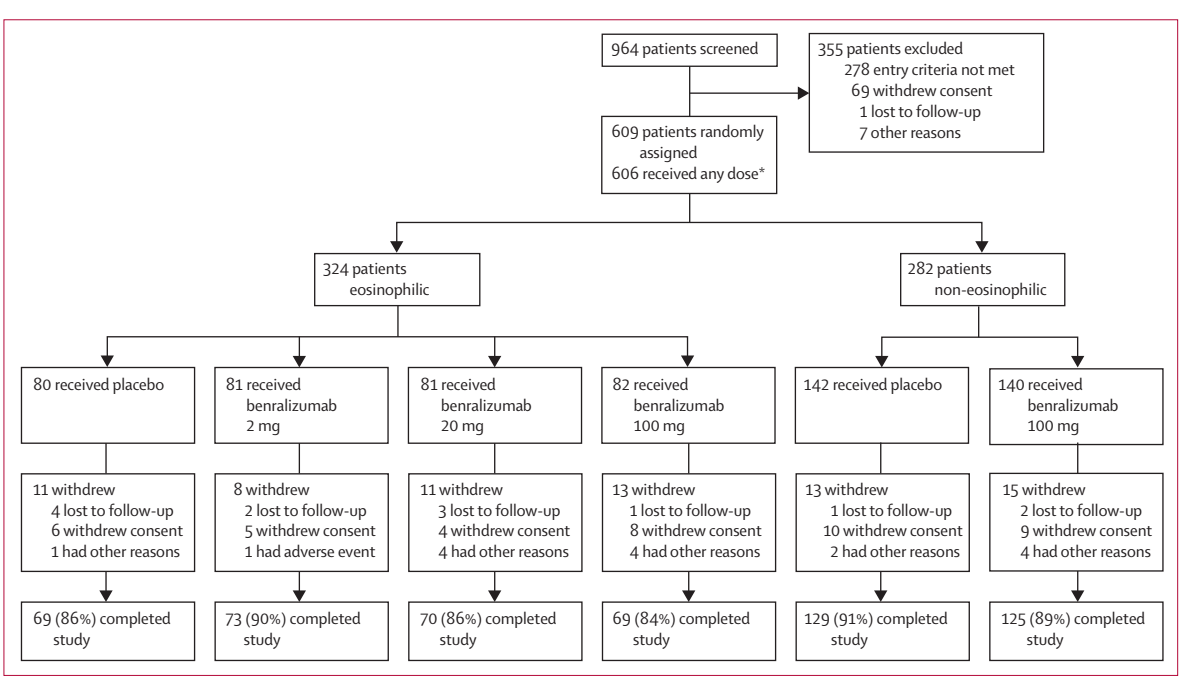

Figure 1: **Trial profile**
*Three non-eosinophilic patients (two in the benralizumab 100 mg group and one in the placebo group) were randomly assigned incorrectly and were excluded before receiving any dose of study drug.

	Eosinophilic*				Non-eosinophilic*	
	Placebo (n=80)	Benralizumab 2 mg (n=81)	Benralizumab 20 mg (n=81)	Benralizumab 100 mg (n=82)	Placebo (n=142)	Benralizumab 100 mg (n=140)
Demographics						
Age, years	45·6 (11·7)	47·1 (12·8)	46·6 (13·2)	47·8 (12·9)	50·0 (12·3)	50·0 (11·5)
Female	53 (66%)	58 (72%)	48 (59%)	60 (73%)	100 (70%)	98 (70%)
White	53 (66%)	59 (73%)	50 (62%)	62 (76%)	106 (75%)	99 (71%)
BMI, kg/m^2	28·8 (6·0)	29·2 (6·5)	28·0 (5·2)	28·0 (6·1)	29·6 (5·0)	29·5 (6·0)
Asthma characteristics						
ACQ-6 score†	2·7 (1·0)	2·6 (1·0)	2·5 (0·9)	2·5 (1·0)	2·5 (0·8)	2·6 (0·8)
Symptom score‡	1·6 (0·7)	1·6 (0·6)	1·6 (0·6)	1·6 (0·7)	1·6 (0·5)	1·6 (0·6)
AQLQ score†	3·6 (1·2)	3·7 (1·2)	3·8 (1·1)	3·7 (1·0)	3·8 (1·0)	3·7 (1·0)
Childhood asthma	31 (39%)	31 (38%)	33 (41%)	29 (35%)	46 (32·4)	48 (34·3)
Nasal polyps	15 (19%)	13 (16%)	21 (26%)	17 (21%)	12 (8%)	12 (9%)
Exacerbations in past year	2·2 (0·5)	2·3 (0·7)	2·5 (0·7)	2·3 (0·6)	2·2 (0·5)	2·3 (0·7)
Fe_{NO}, ppb	37·9 (31·9)	39·5 (32·7)	40·8 (31·0)	37·8 (31·7)	20·7 (13·9)	20·2 (12·1)
Airway function						
FEV_1, % predicted	65·0% (15·3)	65·1% (15·2)	64·8% (14·8)	66·1% (15·9)	69·1% (14·5)	66·8% (15·1)
FEV_1:FVC ratio, %	62·1% (11·3)	64·9% (11·0)	63·3% (10·9)	63·9% (11·5)	66·9% (11·4)	65·1% (11·4)
FEV_1 reversibility, %§	18·3% (15·1)	18·7% (22·0)	19·8% (20·3)	18·0% (13·3)	12·8% (13·0)	15·3% (15·3)
Blood eosinophil count, 10^3 per µL (local lab)	0·53 (0·30)	0·53 (0·33)	0·54 (0·28)	0·56 (0·36)	0·16 (0·09)	0·19 (0·12)
Baseline inhaled corticosteroid dose, µg/day¶	739·1	691·0	724·9	697·0	673·7	705·2
Medium-dose corticosteroids						
Number of patients	40 (50%)	39 (48%)	40 (49%)	41 (50%)	82 (58%)	76 (54%)
Dose, µg/day¶	450·0	444·1	426·0	433·7	435·4	437·8
High-dose corticosteroids‖						
Number of patients	40 (50%)	42 (52%)	41 (51%)	40 (49%)	60 (42%)	64 (46%)
Dose, µg/day¶	1028·3	920·2	1016·6	967·0	999·3	1022·8
Chronic use of oral corticosteroid	4 (5%)	9 (11%)	5 (6%)	3 (4%)	3 (2%)	6 (4%)

Data are n (%) or mean (SD). Protocol-defined eosinophilic phenotype classification based on ELEN index and Fe_{NO}. BMI=body-mass index. ACQ-6=Asthma Control Questionnaire, six-question version. AQLQ=Asthma Quality of Life Questionnaire, standard version. Fe_{NO}=fraction of exhaled nitric oxide. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. ppb=parts per billion. *Eosinophilic refers to ELEN index positive or Fe_{NO} ≥50 ppb; non-eosinophilic refers to ELEN index negative and Fe_{NO} <50 ppb. †Scores on the ACQ-6 range from 0 to 6, with lower scores indicating better control of asthma; scores on the AQLQ range from 1 to 7, with higher scores indicating better quality of life. ‡Overall symptom scores range from 0 to 4, with lower scores indicating less frequent or severe symptoms. §Percent reversibility refers to the increase in FEV_1 in response to salbutamol (maximum dose 720 µg per Severe Asthma Research Program) or equivalent relative to pre-bronchodilator FEV_1. ¶Fluticasone equivalent, mean dose. ||Not including one patient receiving high-dose corticosteroids for whom this information was missing at baseline.

Table 1: **Baseline demographic and clinical characteristics for protocol-defined eosinophilic and non-eosinophilic participants (modified intention-to-treat population)**

Participants were stratified by eosinophilic status (eosinophilic or non-eosinophilic) and baseline inhaled corticosteroid dose (medium or high; appendix),[16] with a target enrolment of at least 40% of participants on high-dose inhaled corticosteroids. We randomly assigned participants within each stratum using random permuted blocks of fixed size (eight for eosinophilic individuals and four for non-eosinophilic individuals). Eosinophilic participants were randomly assigned in a 1:1:1:1 ratio to receive placebo or 2 mg, 20 mg, or 100 mg benralizumab; non-eosinophilic participants were randomly assigned in a 1:1 ratio to receive placebo or 100 mg benralizumab. Study drugs were given as two subcutaneous injections every 4 weeks for the first three doses (weeks 1, 4, and 8), then every 8 weeks (weeks 16, 24, 32, and 40). Participants maintained the same dose of inhaled corticosteroid and longacting β agonist from the start of the screening period until week 52 (appendix p 20).

Patients, treating physicians, study investigators, and study statisticians were masked to treatment allocation. Allocation concealment was ensured by the vendor systems and no study personnel or site had access to the system.

Procedures

During screening we classified participants as having either an eosinophilic phenotype, defined as ELEN index positive or Fe_{NO} of at least 50 parts per billion (ppb), or a non-eosinophilic phenotype, defined as both ELEN index negative and Fe_{NO} less than 50 ppb. Complete blood count was measured locally. These data were automatically entered into a validated computer program to calculate the ELEN index for each participant.

	Eosinophilic phenotype				Non-eosinophilic phenotype	
	Placebo (n=80)	Benralizumab 2 mg (n=81)	Benralizumab 20 mg (n=81)	Benralizumab 100 mg (n=82)	Placebo (n=142)	Benralizumab 100 mg (n=140)
Primary efficacy endpoint*						
Annual exacerbation rate	0·57 (0·75)	0·65 (0·81)	0·37 (0·61)	0·34 (0·58)	0·56 (0·75)	0·43 (0·66)
Rate reduction compared with placebo (80% CI)	..	−9% (−59 to 26)	36% (3 to 58)	41% (11 to 60)	..	22% (−5 to 42)
p value for comparison with placebo	..	0·781	0·173	0·096	..	0·284
Key secondary efficacy endpoints†						
FEV_1						
Number of patients with data available	51	51	58	59	99	101
Baseline, L	2·03 (0·69)	1·98 (0·70)	2·08 (0·75)	1·99 (0·66)	2·04 (0·66)	2·02 (0·68)
Change from baseline, L	0·04 (0·46)	0·16 (0·47)	0·19 (0·52)	0·17 (0·39)	−0·01 (0·30)	0·06 (0·33)
Treatment difference (80% CI)	..	0·13 (0·02 to 0·24)	0·17 (0·05 to 0·29)	0·15 (0·05 to 0·25)	..	0·06 (0·01 to 0·12)
p value for comparison with placebo	..	0·140	0·069	0·063	..	0·155
ACQ-6 score‡						
Number of patients with data available	34	42	40	39	64	73
Change from baseline	−0·89 (1·20)	−1·10 (1·12)	−1·25 (1·22)	−1·12 (1·29)	−0·82 (1·11)	−1·13 (1·05)
Treatment difference (80% CI)	..	−0·36 (−0·65 to −0·06)	−0·45 (−0·77 to −0·13)	−0·47 (−0·79 to −0·16)	..	−0·34 (−0·57 to −0·12)
p value for comparison with placebo	..	0·125	0·074	0·057	..	0·053

Data are mean (SD) or difference (80% CI). ACQ-6=Asthma Control Questionnaire, six-question version. FEV_1=forced expiratory volume in 1 s. *Primary efficacy endpoint was annual exacerbation rate for eosinophilic population. Exacerbation rate reductions, CIs, and p values are calculated by using Poisson regression. Statistically significant result is a two-sided p<0·169. †p values, treatment differences, and the CIs of the differences are calculated by using ANCOVA (analysis of covariance); a statistically significant result is a two-sided p<0·169. ‡Scores on the ACQ-6 range from 0 to 6, with lower scores indicating better control of asthma and with 0·5 as the minimal clinically important change for an individual participant.

***Table 2*: Primary and key secondary efficacy endpoints for protocol-defined eosinophilic and non-eosinophilic participants (modified intention-to-treat population)**

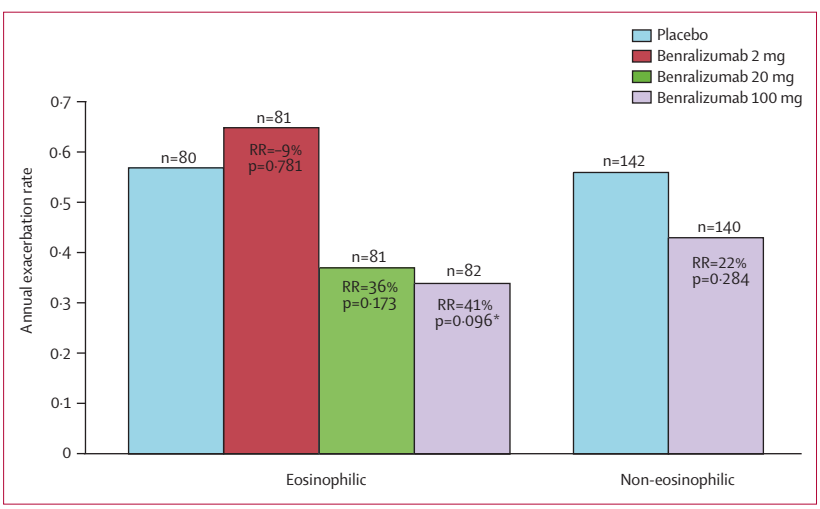

***Figure 2*: Annual exacerbation rate for protocol-defined eosinophilic and non-eosinophilic participants (modified intention-to-treat population)**
RR=rate reduction. *Statistically significant result is a two-sided p<0·169.

We developed the ELEN index as a surrogate marker of sputum eosinophils of at least 2% using multivariate statistical modelling of baseline sputum and blood data from a phase 2a clinical study (NCT00394654),[22] validated with two independent datasets (appendix).[23] The ELEN index uses two predictor variables (the ratio of blood eosinophils to lymphocytes, and the ratio of blood eosinophils to neutrophils) to classify participants as having either less than 2% or at least 2% sputum eosinophils, without the need to collect sputum. Derived ratios of eosinophils to lymphocytes and eosinophils to neutrophils measured in peripheral blood have been reported to have high efficiency to predict sputum eosinophilia.[24]

On the basis of American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines,[25] we defined asthma exacerbation as an increase in asthma symptoms that did not resolve after rescue medication and needed treatment with systemic steroids for at least 3 days. Other assessments included lung function; asthma control assessed with the ACQ-6[17,18] and symptom diary; health-related quality of life assessed with the Asthma Quality of Life Questionnaire (AQLQ);[26] Fe_{NO}; and peripheral blood eosinophil count. We did spirometry using centrally provided equipment according to ATS/ERS guidelines.[27] We tested maximum reversibility using a salbutamol metered-dose inhaler with an AeroChamber (Trudell Medical International, Canada) 15 min after four, six, or a maximum of eight total puffs (720 µg).[28] After four puffs, if the FEV_1 changed by 5% or more, then an additional two puffs were given; after six puffs, if the FEV_1 changed by 5% or more again, a further two additional puffs were given. We monitored safety and tolerability by recording adverse events. Efficacy assessments were made until week 52 (appendix p 6), after which participants were followed up for another 14 weeks to monitor safety.

Outcomes

The primary efficacy endpoint was the asthma annual exacerbation rate in eosinophilic individuals, calculated as

the total number of reported exacerbations in each group up to week 52 divided by the total duration of person-year follow-up in each group. Secondary efficacy endpoints, in eosinophilic individuals, were the change from baseline in FEV_1, mean ACQ-6 score, overall symptom score, and mean AQLQ score at week 52. Exploratory endpoints included change in Fe_{NO}, and blood eosinophil counts; all analyses in non-eosinophilic individuals were exploratory.

To further investigate benralizumab response, we did a prespecified subgroup analysis based on baseline blood eosinophil count (cutoffs of 200, 300, and 400 cells per µL). We dichotomised all participants according to an eosinophil cutoff of 300 cells per µL (<300 cells per µL *vs* ≥300 cells per µL). This approach is consistent with a recently published study of mepolizumab in which measurement of blood eosinophils was reported to be predictive of response to anti-interleukin 5 therapy.[29]

Statistical analysis

We did efficacy analyses using a modified intention-to-treat population, defined as all randomly assigned participants who received any dose of investigational product. The safety population included all participants who received any investigational product and had safety data. We planned to enrol 280 eosinophilic participants (70 per treatment group), giving roughly 78% power for each dose to detect a 40% reduction in annual exacerbation rate compared with placebo. We planned to enrol 242 non-eosinophilic participants (141 per treatment group), giving roughly 63% power to detect a 25% reduction in annual exacerbation rate compared with placebo. These calculations used a two-sided significance level of 0·2 and assumed annual exacerbation rates of 0·66 for individuals receiving medium-dose inhaled corticosteroids and 1·03 for those receiving high-dose inhaled corticosteroids. The two-sided significance level of 0·2 represents a 10% chance of declaring a positive study when there is no treatment effect (risk of going to phase 3 with an ineffective drug). The power of 78% presents a 22% chance of declaring a negative study when there is a positive treatment effect (risk of discontinuing drug development). We chose this selection of statistical risks to balance the continuation and discontinuation risks while maintaining a feasible phase 2b study.[30] Positive results in this study would need to be replicated in confirmatory phase 3 studies. To ensure appropriate power (reasonable type II error), α adjustment for multiple doses and subgroup analyses was not planned.

We planned and did an interim analysis after the last randomly assigned participant had completed the visit at week 24 to expedite planning for phase 3 studies.

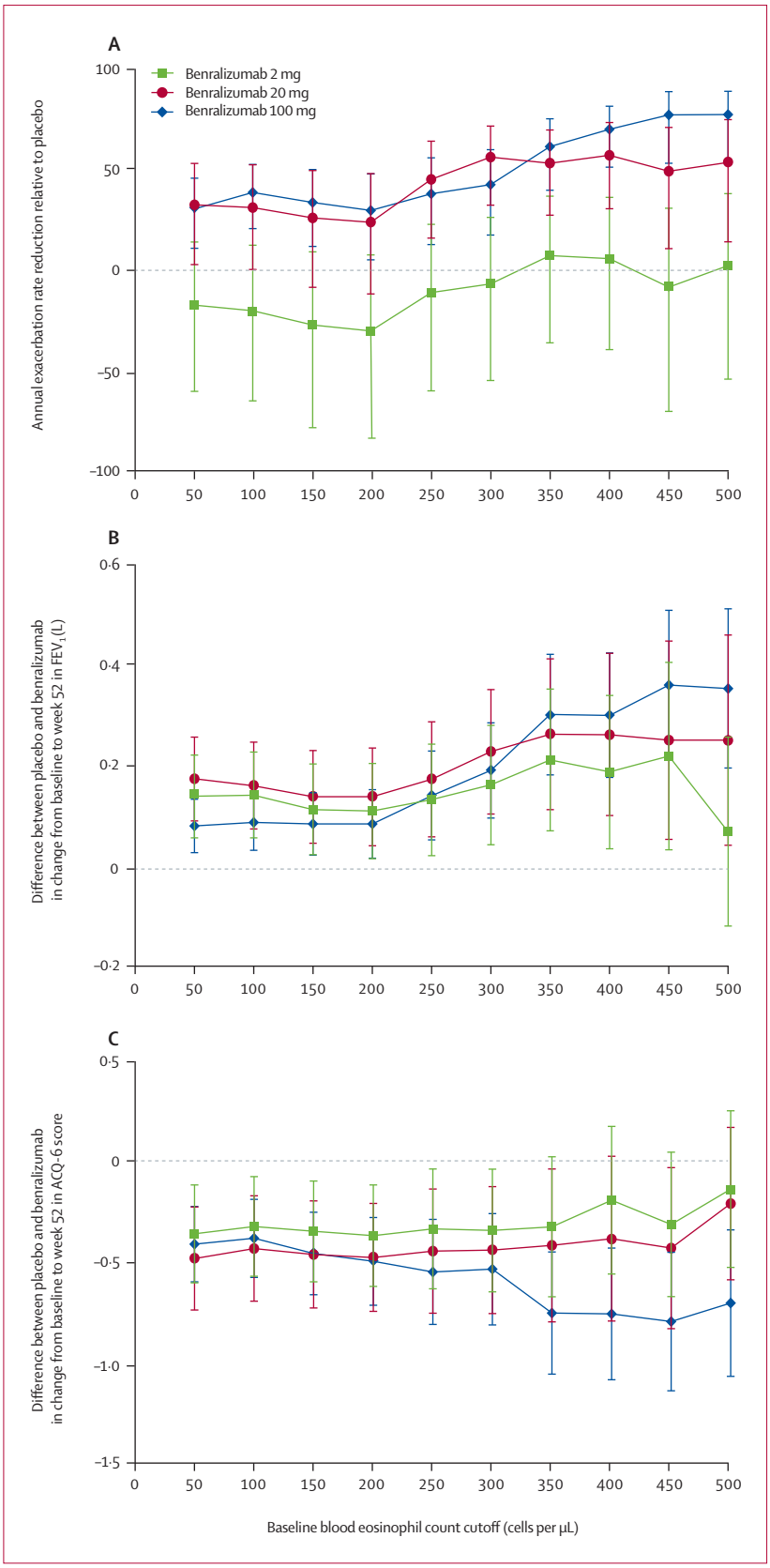

Figure 3: **Annual exacerbation rate reduction, FEV_1, and ACQ-6 score in eosinophilic participants (modified intention-to-treat population)**
(A) Mean (80% CI) difference in annual exacerbation rate compared with placebo. (B) Mean difference (80% CI) in FEV_1 compared with placebo. (C) Mean difference (80% CI) in ACQ-6 score compared with placebo. FEV_1=forced expiratory volume in 1 s. ACQ-6=Asthma Control Questionnaire, six-question version.

	Baseline blood eosinophil count ≥300 cells per μL				Baseline blood eosinophil count <300 cells per μL			
	Placebo (n=83)	Benralizumab 2 mg (n=65)	Benralizumab 20 mg (n=70)	Benralizumab 100 mg (n=97)	Placebo (n=139)	Benralizumab 2 mg (n=16)*	Benralizumab 20 mg (n=11)*	Benralizumab 100 mg (n=124)
Annual exacerbation rate†	0·68 (0·82)	0·75 (0·87)	0·30 (0·55)	0·38 (0·62)	0·49 (0·70)	0·21 (0·46)	0·82 (0·91)	0·42 (0·65)
Rate reduction (80% CI)	..	–7% (–55 to 26)	57% (33 to 72)	43% (18 to 60)	..	57% (NR)	–70% (NR)	16% (–15 to 39)
p value compared with placebo	..	0·822	0·015	0·049	..	0·271	0·265	0·479
FEV_1‡								
Number of patients with data available	53	41	48	68	97	10	10	91
Baseline, L	2·03 (0·72)	1·96 (0·64)	2·13 (0·78)	2·06 (0·63)	2·03 (0·64)	2·03 (0·94)	1·74 (0·38)	1·97 (0·70)
Change from baseline, L	–0·01 (0·45)	0·16 (0·50)	0·20 (0·55)	0·19 (0·40)	0·02 (0·30)	0·17 (0·31)	0·11 (0·40)	0·04 (0·31)
Treatment difference (80% CI)	..	0·17 (0·05 to 0·29)	0·23 (0·11 to 0·36)	0·20 (0·10 to 0·29)	..	..	..	0·02 (–0·04 to 0·08)
p value compared with placebo	..	0·079	0·019	0·010	..	..	..	0·637
ACQ-6 score‡§								
Number of patients with data available	38	35	35	52	60	7	5	60
Baseline, mean (SD)	2·63 (0·96)	2·67 (0·90)	2·43 (0·92)	2·67 (0·94)	2·54 (0·86)	2·57 (1·34)	2·77 (0·84)	2·54 (0·83)
Change from baseline, mean (SD)	–0·76 (1·20)	–1·00 (1·14)	–1·14 (1·19)	–1·26 (1·28)	–0·89 (1·10)	–1·62 (0·91)	–2·00 (1·30)	–1·02 (0·98)
Treatment difference (80% CI)	..	–0·34 (–0·65 to –0·03)	–0·44 (–0·75 to –0·12)	–0·53 (–0·81 to –0·26)	..	..	..	–0·22 (–0·46 to 0·02)
p value compared with placebo	..	0·156	0·079	0·015	..	..	..	0·233
Overall symptom score‡¶								
Number of patients with data available	39	31	32	44	72	5	7	67
Baseline, mean (SD)	1·51 (0·67)	1·60 (0·63)	1·53 (0·58)	1·63 (0·66)	1·62 (0·56)	1·85 (0·69)	2·06 (0·66)	1·57 (0·59)
Change from baseline, mean (SD)	–0·45 (0·64)	–0·51 (0·73)	–0·51 (0·59)	–0·62 (0·77)	–0·33 (0·59)	–0·88 (0·95)	–0·80 (1·07)	–0·47 (0·61)
Treatment difference (80% CI)	..	–0·02 (–0·21 to 0·18)	–0·05 (–0·23 to 0·13)	–0·07 (–0·26 to 0·11)	..	..	..	–0·15 (–0·28 to –0·02)
p value compared with placebo	..	0·901	0·718	0·619	..	..	..	0·147
AQLQ score‡§								
Number of patients with data available	37	32	34	47	51	7	4	58
Baseline, mean (SD)	3·72 (1·19)	3·78 (1·15)	3·82 (1·08)	3·62 (1·04)	3·72 (0·95)	3·47 (1·26)	3·58 (1·01)	3·81 (0·99)
Change from baseline, mean (SD)	0·98 (1·44)	1·08 (1·15)	1·41 (1·46)	1·12 (1·23)	0·95 (1·26)	2·11 (1·17)	1·80 (1·22)	1·13 (1·30)
Treatment difference (80% CI)	..	0·26 (–0·09 to 0·62)	0·44 (0·06 to 0·81)	0·15 (–0·18 to 0·49)	..	..	..	0·31 (0 to 0·61)
p value compared with placebo	..	0·335	0·134	0·552	..	..	..	0·195

Data are mean (SD) or difference (80% CI) unless otherwise stated. ACQ-6=Asthma Control Questionnaire, six-question version. AQLQ=Asthma Quality of Life Questionnaire, standard version. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. NR=not reported due to small sample size. *Number of participants too small to draw valid conclusions. †Exacerbation rate reductions, CIs and p values are calculated by using Poisson regression. Statistically significant result is a two-sided p<0·169. ‡p values, treatment differences, and the CIs of the difference are calculated by using analysis of covariance (ANCOVA). Statistically significant result is a two-sided p<0·169. §Scores on the ACQ-6 range from 0 to 6, with lower scores indicating better control of asthma and with 0·5 as the minimal clinically important change for an individual participant. Scores on the AQLQ range from 1 to 7, with higher scores indicating better quality of life. ¶Overall symptom scores range from 0 to 4, with lower scores indicating less frequent or severe symptoms.

***Table 3*: Efficacy endpoints according to baseline blood eosinophil count (modified intention-to-treat population)**

Although the interim analysis was not undertaken to stop the trial early for efficacy or futility (as in phase 3 studies), to be conservative we applied O'Brien-Fleming α spending function to control the type I error at 0·2 (two-sided), which reduced the α for final analysis to 0·169. Thus, a p value less than 0·169 would be classified as statistically significant for the final analysis. Interim analysis provides an additional chance to declare a positive study based on interim results; therefore, the overall chance of declaring a positive trial when there is no treatment effect is increased. To reduce this chance, the type error for the final analysis was adjusted. We report 80% CIs, rather than 83·1% CIs, for simplicity.

Before the interim analysis, we revised the statistical analysis plan to prespecify exploratory subgroup analyses on the basis of baseline blood eosinophil count and baseline inhaled corticosteroid status (medium *vs* high dose). We did an ad-hoc subgroup analysis on the subgroup of non-eosinophilic participants who had a baseline blood eosinophil count less than 300 cells per μL

because we noted a treatment effect in the non-eosinophilic group (appendix).

The primary efficacy endpoint was analysed by Poisson regression, with baseline inhaled corticosteroid dose status (medium *vs* high dose) as a covariate. We corrected for overdispersion with Pearson χ^2. We did sensitivity analyses using negative binomial regression and van Elteren test. The changes from baseline in FEV_1, ACQ-6, and AQLQ were analysed by ANCOVA, with baseline values and baseline inhaled corticosteroid status as covariates. We did an ad-hoc analysis for annual exacerbation rate using baseline inhaled corticosteroid status and historical exacerbations as covariates. We did not prespecify any imputation for missing data. We used mixed model repeated measures for FEV_1 and ACQ-6 as ad-hoc sensitivity analyses. All analyses were done with SAS software (version 9.3).

This trial is registered with ClinicalTrials.gov, number NCT01238861.

Role of the funding source

The study protocol was developed by MedImmune and the corresponding author. The investigators collected and had full access to all study data, which were analysed by the funding source. The analysis was done solely by MedImmune; however, the authors helped determine which analyses were done and could request further ad-hoc analyses. The report was written by the authors with a medical writer funded by the funding source. The corresponding author had final responsibility for the decision to submit for publication.

Results

We screened 964 patients and randomly assigned 609 between Jan 3, 2011 and March 6, 2012. The trial started screening in December 2010 (first participant enrolled Jan 3, 2011) and the first participant was dosed on Jan 3, 2011. The study was completed in August 2013 after the last protocol-specified visit or assessment was done (including telephone contact) for the last participant in the study.

We randomly assigned 324 patients in the eosinophilic cohort (81 in the 2 mg benralizumab group, 81 in the 20 mg benralizumab group, 82 in the 100 mg benralizumab group, and 80 in the placebo group) and 285 in the non-eosinophilic cohort (142 in the 100 mg benralizumab group and 143 in the placebo group). Three patients in the non-eosinophilic group (two in the benralizumab group and one in the placebo group) were erroneously randomly assigned and did not receive any dose of study drug; these participants were excluded from the modified intention-to-treat and safety analyses (figure 1; appendix p 2). In the modified intention-to-treat population, 324 participants were characterised by the protocol as eosinophilic and 282 were classified as non-eosinophilic. In the eosinophilic cohort, 237 (73%) participants were ELEN index positive, with Fe_{NO} less than 50 ppb; 25 (8%) were ELEN index negative, with Fe_{NO} of 50 ppb or higher; and 62 (19%) were ELEN index positive and had Fe_{NO} of 50 ppb or higher. Across all participants, 315 had baseline eosinophil counts of at least 300 cells per µL and 290 participants had counts of less than 300 cells per µL (appendix p 13); one patient did not have data for baseline eosinophil count.

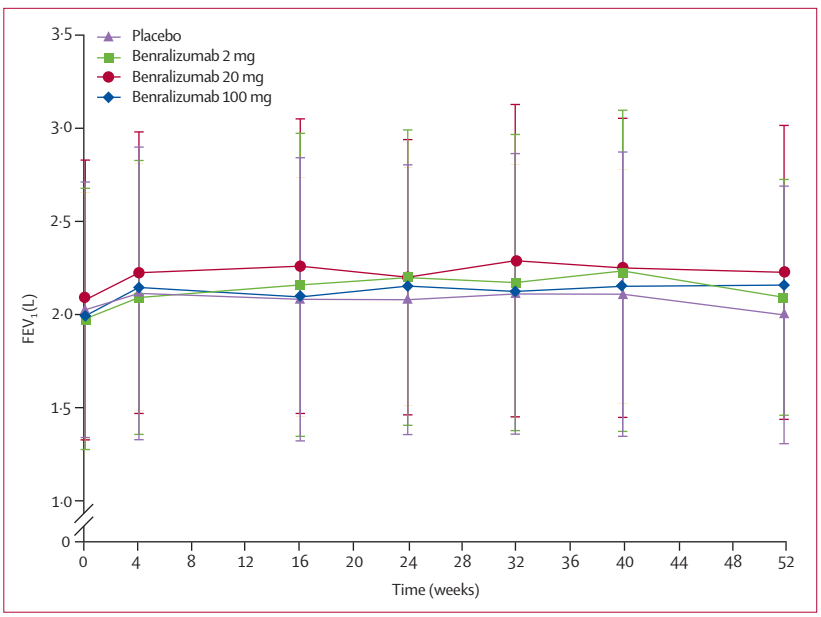

Figure 4: **Mean (SD) FEV_1 for protocol-defined eosinophilic participants (modified intention-to-treat population)**
FEV_1=forced expiratory volume in 1 s.

Table 1 shows participants' demographic and clinical characteristics. We noted a higher baseline frequency of nasal polyps, a higher exacerbation rate, and greater Fe_{NO} measurement in the eosinophilic benralizumab 20 mg group than in the other dose groups. At baseline, 288 (48%) participants overall were taking high-dose inhaled corticosteroids.

In the eosinophilic cohort, the annual exacerbation rate at week 52 was lower in the benralizumab 100 mg group than in the placebo group (p=0·096; table 2, figure 2). Exacerbation rates did not significantly differ between the placebo group and the eosinophilic 2 mg and 20 mg groups (p=0·781 and p=0·173, respectively; table 2, figure 2). Sensitivity analysis results were similar to the primary analysis (appendix), with the strongest effects noted with the negative binomial regression in which the primary endpoint p value was 0·035 for the benralizumab 100 mg dose.

Benralizumab showed a greater numerical reduction in annual exacerbation rate in subgroups with higher baseline blood eosinophil counts (figure 3), although the significance of this association was not tested. In the subgroup with eosinophil counts of 300 cells per µL or higher, benralizumab 20 mg and benralizumab 100 mg reduced exacerbations compared with placebo, but had no significant effect in the subgroup with eosinophil

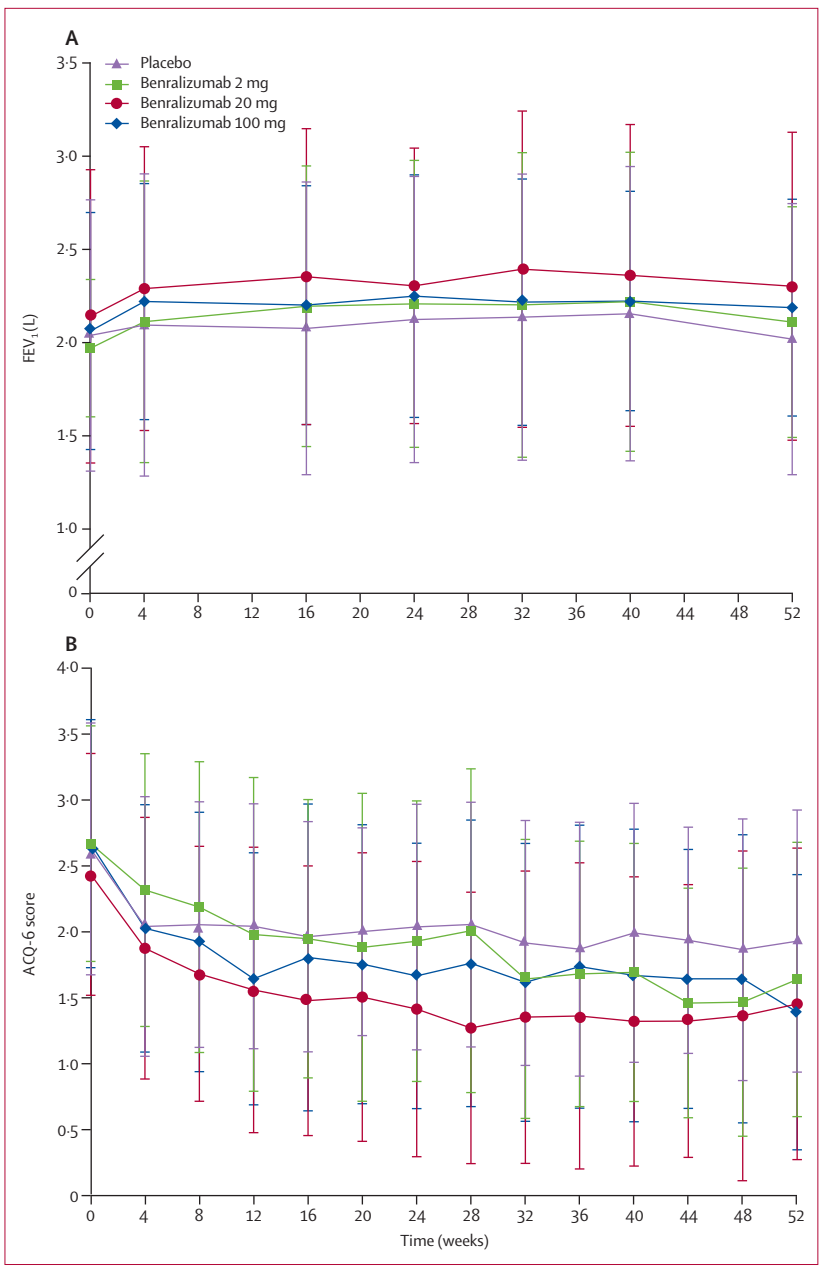

Figure 5: **FEV_1 (A) and ACQ-6 score (B) for participants with baseline blood eosinophil count ≥300 cells per µL**
Figure shows mean (SD). FEV_1=forced expiratory volume in 1 s; ACQ-6=Asthma Control Questionnaire, six-question version.

counts less than 300 cells per µL (table 3). We did an ad-hoc analysis including the historical number of exacerbations as a covariate; the results were similar to those for analysis without this covariate (appendix p 7). We also tested the interaction between the historical number of exacerbations and treatment for the combined placebo and combined benralizumab 100 mg groups (p=0·0473); covariates included corticosteroid status, historical exacerbation number, treatment group, and the interaction item of historical exacerbation number and treatment group.

In eosinophilic individuals, benralizumab 20 mg and 100 mg reduced exacerbations more in participants who were receiving high-dose inhaled corticosteroids compared with those receiving medium-dose corticosteroids; however, these differences were not significant (appendix p 16). A test of the interaction between baseline inhaled corticosteroid status and treatment showed that the noted differences in exacerbation rate were not statistically significant (p=0·570 for 2 mg dose, 0·456 for 20 mg dose, and 0·186 for 100 mg dose; all compared with placebo). Time to first exacerbation seemed to be longer in both the 20 mg (p=0·126) and 100 mg (p=0·121) benralizumab groups than in the placebo group (appendix p 22).

We designed this study to detect a dose–response relationship; however, in view of the overlapping CIs, there is no clear difference between the 20 mg and 100 mg doses, suggesting that the doses might be on the plateau of the dose–response curve.

In the eosinophilic cohort, patients receiving all benralizumab doses had improvements from baseline at week 52 in mean FEV_1 and mean ACQ-6 score compared with placebo (table 2, figure 4, appendix p 25). These results were based only on data from patients with complete information available. We used mixed model repeated measures for FEV_1 and ACQ as sensitivity analyses. In the eosinophilic cohort, mean differences in change from baseline at week 52 based on mixed model repeated measures for benralizumab 100 mg *vs* placebo were 0·10 L for FEV_1 (p=0·144) and −0·26 for ACQ-6 score (p=0·113). Similar to the results based on the complete data only, data from mixed model repeated measures showed significant reduction in ACQ-6 score.

In eosinophilic participants, we noted that benralizumab's effect on FEV_1 tended to be greater in participants who were receiving high-dose inhaled corticosteroids at baseline compared with those receiving medium-dose corticosteroids (appendix p 18). Ad hoc, we tested the effect of the interaction between baseline inhaled corticosteroid status and treatment on FEV_1 (p=0·345 for 2 mg dose, p=0·209 for 20 mg dose, and p=0·057 for 100 mg dose, compared with placebo).

All doses of benralizumab produced improvements in mean FEV_1 and mean ACQ-6 score compared with placebo in the subgroup with baseline blood eosinophil count ≥300 cells per µL; improvements were also seen in the <300 cells per µL group with 2 mg and 20 mg benralizumab, however the sample sizes for these groups were too small to draw conclusions (table 3, figures 3, 5, appendix p 28).

We noted improvement in mean AQLQ score compared with placebo (p=0·134) in participants with at least 300 cells per µL for the benralizumab 20 mg dose only (table 3, appendix p 26). Benralizumab had no consistent effect on overall symptom score (table 3, appendix p 26) or Fe_{NO} (appendix p 29). There were also

	Placebo (n=221)	Benralizumab 2 mg (n=81)	Benralizumab 20 mg (n=81)	Benralizumab 100 mg (n=223)	Benralizumab combined (n=385)
Any treatment-emergent adverse event	143 (65%)	56 (69%)	58 (72%)	163 (73%)	277 (72%)
Any serious treatment-emergent adverse event	23 (10%)	10 (12%)	6 (7%)	24 (11%)	40 (10%)
Discontinuation of study drug due to an adverse event	3 (1%)	4 (5%)	2 (2%)	6 (3%)	12 (3%)
Treatment-emergent adverse events by system organ class that occurred in ≥3% of participants in combined benralizumab group					
Infections and infestations	81 (37%)	38 (47%)	33 (41%)	99 (44%)	170 (44%)
Respiratory, thoracic, and mediastinal disorders	87 (39%)	34 (42%)	34 (42%)	89 (40%)	157 (41%)
General disorders and administrative-site conditions	20 (9%)	18 (22%)	18 (22%)	51 (23%)	87 (23%)
Nervous system disorders	28 (13%)	19 (23%)	9 (11%)	38 (17%)	66 (17%)
Musculoskeletal and connective tissue disorders	18 (8%)	13 (16%)	16 (20%)	28 (13%)	57 (15%)
Gastrointestinal disorders	24 (11%)	13 (16%)	15 (19%)	28 (13%)	56 (15%)
Skin and subcutaneous tissue disorders	16 (7%)	5 (6%)	10 (12%)	21 (9%)	36 (9%)
Vascular disorders	8 (4%)	3 (4%)	3 (4%)	20 (9%)	26 (7%)
Injury, poisoning, and procedural complications	13 (6%)	6 (7%)	4 (5%)	14 (6%)	24 (6%)
Investigations	13 (6%)	4 (5%)	1 (1%)	15 (7%)	20 (5%)
Cardiac disorders	6 (3%)	1 (1%)	6 (7%)	8 (4%)	15 (4%)
Metabolism and nutrition disorders	4 (2%)	3 (4%)	2 (2%)	10 (4%)	15 (4%)
Psychiatric disorders	6 (3%)	5 (6%)	2 (2%)	6 (3%)	13 (3%)

Data are n (%). Treatment-emergent adverse event refers any adverse event occurring after dosing. General disorders refers to all disorders coded as general but not at the site of injection. Administrative site conditions refers to all adverse events that occurred at the site of administration of benralizumab or placebo. *Adverse events summarised for eosinophilic and non-eosinophilic participants combined; since an initial review of the data provided no clinically relevant differences in adverse event rates between these groups.

Table 4*: Adverse events (irrespective of causality) reported by week 66 (safety population)

no statistically significant differences in total daily rescue medication use between any of the benralizumab groups versus placebo (data not shown).

The annual exacerbation rate did not differ between benralizumab 100 mg and placebo for the non-eosinophilic participants (p=0·284; table 2, figure 2), and ad-hoc subgroup analysis showed that benralizumab 100 mg had no effect on annual exacerbation rate in non-eosinophilic participants with a baseline blood eosinophil concentration less than 300 cells per µL (appendix p 15). However, we noted improvements in FEV_1 and ACQ-6 score in the non-eosinophilic group receiving benralizumab 100 mg (table 2).

All doses of benralizumab decreased blood eosinophil counts after the first dose, with mean values of 46–56 cells per µL on day 6 in participants with baseline values of at least 300 cells per µL (appendix p 28). Eosinophil counts recovered to near baseline levels by week 66, after the last injection at week 40 (appendix).

Treatment-emergent adverse events were reported by a higher proportion of participants in the combined benralizumab groups (277 of 385, 72%) than in the placebo groups (143 of 221, 65%) to week 66 (table 4). Adverse events were summarised for eosinophilic and non-eosinophilic participants combined, because an initial review of the data showed that there were no clinically relevant differences between these groups. Most adverse events were mild to moderate in severity. Adverse events irrespective of causality with more than 5% higher occurrence in the benralizumab groups than in the placebo groups were nasopharyngitis (44 [11%] cases in benralizumab groups *vs* 13 [6%] cases in placebo groups) and injection-site reactions (60 [16%] *vs* eight [4%]). Treatment-emergent adverse events resulted in discontinuation of the study drug in 12 participants (3%) receiving benralizumab and three participants (1%) receiving placebo.

Serious adverse events were reported by the same proportion of participants receiving benralizumab (40 [10%]) as for placebo (23 [10%]). Five participants (1%) receiving benralizumab had serious adverse events that we thought were treatment related, four in the 100 mg group (acute cholecystitis, herpes zoster, polyarteritis nodosa, and uterine leiomyoma) and one in the 20 mg group (erythema nodosum), compared with two participants (1%) in the placebo group (anaphylactic reaction and pneumonia). The acute cholecystitis was assessed by the funder and deemed to be unrelated. The other suspected related serious adverse events were assessed and thought to be related but confounded by pre-existing disorders or concomitant drugs. All serious adverse events resolved and were reported to regulatory authorities as per the requirement for safety reporting. There were no deaths.

Discussion

In this phase 2 dose-ranging study in participants with uncontrolled eosinophilic asthma, benralizumab

Panel: Research in context

Systematic review

A systematic review of PubMed was carried out using the terms "asthma", "eosinophil", and "anti-interleukin-5" and limited to papers published in English. This search yielded 26 results, which included a review article discussing the main clinical studies investigating new anti-interleukin 5 therapies in asthma.[31] References within the aforementioned review article indicate that, whilst these therapies consistently reduce sputum and blood eosinophils, their degree of clinical benefit can vary. According to our systematic review of the literature, benralizumab seems to be the only monoclonal antibody targeted against the receptor of interleukin 5, currently being evaluated in asthma. Persistent eosinophilic airway inflammation in asthma increases the risk of subsequent exacerbations. As it is difficult to measure sputum eosinophils in practice, the ELEN index was developed to predict sputum eosinophils ≥2%. At the time of study start, the evidence pointed to sputum eosinophils as a predictor of response. Subsequently more data have been published which demonstrate the value of blood eosinophil count in predicting response to anti-interleukin 5 therapy.[29]

Interpretation

This trial provides supporting evidence that participants with asthma and raised eosinophils respond to interventions that decrease eosinophils such as the anti-IL5Rα antibody, benralizumab, and corroborates the evidence that blood eosinophils are a predictor of response to anti-interleukin 5 therapies. Benralizumab (20 and 100 mg doses) may show improvement in lung function and reduce exacerbations in participants with asthma with elevated peripheral eosinophils counts. The optimal dosing regimen identified by such exposure–response analysis is being evaluated in phase 3 studies. Clinicians should await confirmation from ongoing phase 3 studies.

100 mg seemed to reduce exacerbations and improve lung function and quality of life in participants with a protocol-defined eosinophilic phenotype (and also in a prespecified subgroup analysis in participants with baseline blood eosinophils ≥300 cells per μL), with a predetermined α of 0·169. These potentially promising results are important in the early development of a drug but are not definitive until prospectively replicated in larger studies with appropriate statistical endpoints (ie, α=0·05) and more generalised populations (panel). We designed this study on the basis of the hypothesis that benralizumab would show efficacy in participants with asthma and at least 2% sputum eosinophils. We used the ELEN index (a surrogate blood-based marker of sputum eosinophilia) and Fe_{NO} to stratify participants. These assessments are more practical for large clinical trials than are measurement of sputum eosinophils. However, we noted significant improvements in exacerbation rate, FEV_1, and ACQ-6, for participants with increased baseline blood eosinophil concentrations, suggesting that blood eosinophil count might be a useful biomarker to predict efficacy of benralizumab in asthma (figure 3). Similar to findings from previous studies with benralizumab,[14,15] blood eosinophil counts were substantially decreased after the first dose and remained below baseline values up to the last dose. Outcomes from this dose-ranging study suggested that 20 mg and 100 mg doses of benralizumab resided at the dose–response plateau. We used the data from this trial in an exposure–response analysis to identify the optimum benralizumab dosing regimens to be studied in a phase 3 study of 30 mg benralizumab subcutaneously every 4 weeks, and 30 mg benralizumab subcutaneously every 4 weeks for the first three doses followed by 30 mg benralizumab subcutaneously every 8 weeks.[32] As projected, the 2 mg dose was ineffective, probably because of inadequate drug distribution into the lung. Overall, these results provide evidence to support pursuit of benralizumab in participants with eosinophil-driven, uncontrolled asthma in larger phase 3 studies.

In previous studies, participants with uncontrolled asthma and eosinophilia who were treated for 1 year with an anti-interleukin 5 monoclonal antibody (mepolizumab) had a significant reduction in exacerbations but little effect on lung function or symptoms.[7,9] However, FEV_1 and asthma control were significantly improved in a small 12-week study of mepolizumab in patients with prednisone-dependent asthma and persistent sputum eosinophilia.[8] A significant improvement in lung function and modest improvement in asthma control was also shown with another anti-interleukin 5 monoclonal antibody, reslizumab, in participants with eosinophilic asthma.[4] In this study, benralizumab seemed to reduce exacerbations similar to the effect reported with mepolizumab,[7,9] in addition to improving lung function and asthma control after 1 year. These differential effects could be related to the fact that benralizumab targets the interleukin 5 receptor and subsequently reduces eosinophils[15] more efficiently via antibody-dependent cell-mediated cytotoxicity. An alternative explanation could be differences between studies in baseline FEV_1 reversibility. In studies where FEV_1 improved during active treatment, baseline FEV_1 reversibility was higher (18–28%; table 1)[4,8] than in those studies that did not demonstrate an effect on FEV_1.[7,9]

Interestingly, in participants who were characterised as having a non-eosinophilic phenotype, benralizumab 100 mg seemed to improve lung function and asthma control but did not seem to affect exacerbations. By contrast, findings from previous studies have shown that inhibition of interleukin 5 in a population unselected for eosinophilia had no effect on lung function or asthma control.[5,33,34] Blood eosinophils might be a better predictor of response than the ELEN index–Fe_{NO} classification, a

surrogate for at least 2% sputum eosinophils; 46 (16%) of 281 patients in the non-eosinophilic group had baseline blood eosinophils of more than 300 cells per μL. In a retrospective post-hoc analysis of the DREAM mepolizumab asthma study,[29] comparing baseline sputum eosinophil percentages with blood eosinophil counts, we noted that the blood eosinophil count seemed to more accurately predict response to anti-interleukin 5 monoclonal antibody therapy. Sputum eosinophil levels could fluctuate more than blood eosinophil levels,[35,36] and thus eosinophils in the blood compartment might be a better predictive biomarker. Alternatively, our findings in non-eosinophilic participants could be accounted for by the effect of benralizumab on other IL5Rα-expressing cells contributing to airway inflammation, such as basophils.[13,15]

Benralizumab had an acceptable safety profile at all doses, with few serious treatment-related adverse events. The overall incidence of adverse events irrespective of causality was slightly higher in the benralizumab treatment groups than in the placebo groups. Adverse events were mild to moderate in severity, with nasopharyngitis and injection-site reactions being the most frequent.

This study has several limitations. The study was powered assuming placebo annual exacerbation rate of 0·66 and 1·03 for participants on medium-dose and high-dose inhaled corticosteroids, respectively, on the basis of findings from two studies, COMPASS[37] and AHEAD.[38] We estimated a relative rate reduction of 40% for annual exacerbation rate in the power calculation, which was similar to the rate reduction (41%) noted for benralizumab 100 mg. However, the annual exacerbation rate for participants receiving medium-dose and high-dose inhaled corticosteroids in the placebo group was lower than estimated. A lower placebo rate increases the variance estimate in the Poisson regression model and, consequently, reduces the overall power of the study.

In addition to the study not being powered for the subgroup analyses, some participants with high baseline blood eosinophil counts were classified as having a non-eosinophilic phenotype, and vice versa. Consequently, in a prespecified subgroup analysis that was not randomised or stratified, participants were grouped according to a baseline blood eosinophil cutoff point of at least 300 cells per μL. The clinical usefulness of blood eosinophil cutoff points as predictive biomarkers for anti-interleukin 5 and anti-IL5Rα therapies for asthma needs prospective validation in phase 3 studies, which are underway. Other limitations include that no adjustment was made for multiplicity and loss of follow-up data from participants, possibly resulting in over-interpretation of FEV_1 and ACQ data.

In conclusion, the results at the prespecified statistical significance level ($p<0·169$) from this dose-ranging study suggest that benralizumab 20 mg and 100 mg could have a positive effect on exacerbations, lung function, and asthma control compared with placebo in participants with uncontrolled eosinophilic asthma. These preliminary findings support further clinical development of benralizumab in asthma. Phase 3 studies are underway in patients with moderate or severe asthma with peripheral eosinophils count of at least 300 cells per μL with two dosing regimens based on exposure–response analysis of this study,[32] 30 mg benralizumab subcutaneously every 4 weeks, and 30 mg benralizumab subcutaneously every 4 weeks for the first three doses followed by 30 mg subcutaneously every 8 weeks (NCT01914757, NCT02075255, and NCT01928771).

Contributors

MC contributed to study design, and data collection, analysis, and interpretation. SEW and PK contributed to data collection, analysis, and interpretation. EP contributed to data collection and interpretation. WWB contributed to collection of data for the ELEN index and data interpretation. DLG contributed to study design, conduct, data interpretation, and development of the ELEN index. ERB, CKW, YW, and BW contributed to study design, data analysis, and interpretation. DBK contributed to development of the ELEN index, study design, and data interpretation. RvdM contributed to data analysis and interpretation. RK contributed to study design and data interpretation. NAM contributed to study design and data interpretation. DGR contributed to study design, conduct, data analysis, and interpretation. All authors contributed to writing and critical review of the report.

Declaration of interests

MC has received grants from the National Institutes of Health (NIH), Boston Scientific, Amgen, Ception/Cephalon/Teva, Genentech, MedImmune, Merck, Novartis, GlaxoSmithKline (GSK), Sanofi-Aventis, Vectura, NexBio, and Kalabios; and personal fees from GSK, Genentech, Innovative Pulmonary Solutions/Holaira, Neostem, Asthmatx/Boston Scientific, Boehringer Ingelheim, and Teva; has stock options in Sparo; and receives royalties from Elsevier. SEW has received grants from Amgen, Array, AstraZeneca, GSK, Merck, and Sanofi-Aventis; and personal fees from Amgen, AstraZeneca, GSK, Merck, Novartis, Up to Date, and Icon. ERB has acted as a consultant for Amgen, AstraZeneca, MedImmune, GSK, Boehringer Ingelheim, Pfizer, Forest, Genentech, Johnson & Johnson (Janssen), Merck, Novartis, Regeneron, Roche, Sanofi-Aventis, and Teva; has been involved in conducting clinical trials for Amgen, AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, Johnson & Johnson (Janssen), Cephalon/Teva, Forest, Genentech, GSK, Novartis, and Sanofi-Aventis; and has received research grants from the National Heart, Lung and Blood Institute and NIH. EP has declared no competing interests. PK reports grants and personal fees from AstraZeneca, GSK, Novartis, Boehringer Ingelheim, Teva, Chiesi, Almirall, Polpharma, Adamed, Celon Pharma, Polfarmex, Sandoz, MSD, and FAES Farma. WWB reports personal fees from Merck, Novartis, GSK, Genentech, Boston Scientific, Circassia, Icon, and Elsevier. DLG is a former employee of MedImmune; a current employee of Gilead Sciences and holds Gilead Sciences stock; and has a patent pending relevant to this work. CKW is an employee of MedImmune, owns AstraZeneca stock, and has patents pending relevant to this work. BW is an employee of MedImmune. DBK is an employee of MedImmune, owns AstraZeneca company stock or stock options, and has a patent pending relevant to this work. YW, RvdM, and RK are employees of MedImmune and own AstraZeneca company stock. NAM is a former employee of MedImmune and has a patent pending relevant to this work. DGR is a former employee of MedImmune.

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Original Contribution

A randomized trial of benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, after acute asthma☆,☆☆,★,★★,☆☆☆

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ABSTRACT

Background: Patients with frequent asthma exacerbations resulting in emergency department (ED) visits are at increased risk for future exacerbations. We examined the ability of 1 dose of benralizumab, an investigational antiinterleukin 5 receptor α monoclonal antibody, to reduce recurrence after acute asthma exacerbations.
Methods: In this randomized, double-blind, placebo-controlled study, eligible subjects presented to the ED with an asthma exacerbation, had partial response to treatment, and greater than or equal to 1 additional exacerbation within the previous year. Subjects received 1 intravenous infusion of placebo (n = 38) or benralizumab (0.3 mg/kg, n = 36 or 1.0 mg/kg, n = 36) added to outpatient management. The primary outcome was the proportion of subjects with greater than or equal to 1 exacerbation at 12 weeks in placebo vs the combined benralizumab groups. Other outcomes included the time-weighted rate of exacerbations at week 12, adverse events, blood eosinophil counts, asthma symptom changes, and health care resource utilization.
Results: The proportion of subjects with greater than or equal to 1 asthma exacerbation at 12 weeks was not different between placebo and the combined benralizumab groups (38.9% vs 33.3%; $P = .67$). However, compared with placebo, benralizumab reduced asthma exacerbation rates by 49% (3.59 vs 1.82; $P = .01$) and exacerbations resulting in hospitalization by 60% (1.62 vs 0.65; $P = .02$) in the combined groups. Benralizumab reduced blood eosinophil counts but did not affect other outcomes, while demonstrating an acceptable safety profile.
Conclusions: When added to usual care, 1 dose of benralizumab reduced the rate and severity of exacerbations experienced over 12 weeks by subjects who presented to the ED with acute asthma.

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★★ Author contributions: N Molfino proposed the concept. R Nowak, R Silverman, J Parker, and N Molfino designed the study. N Molfino, J Parker, and K Kim contributed to protocol development, interpreted results, and drafted and approved the final manuscript. JP Fiening contributed to protocol development, monitored the study, and drafted and approved the final manuscript. R Nowak and R Silverman contributed to the study design and protocol development. R Nowak, F Khan, RA Silverman, BH Rowe, and H Smithline recruited 80% of subjects and critically revised and approved the manuscript for important intellectual content.
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1. Introduction

More than 300 million people worldwide have asthma [1]. Despite decades of improvements in asthma treatment, unscheduled visits to doctor's offices and emergency departments (ED) and hospitalizations due to asthma exacerbations continue to occur. These visits account for a significant proportion of health care costs attributable to asthma [1,2].

Relapse at 12 weeks after an acute asthma exacerbation has been reported to range from 41% to 52% despite the use of systemic corticosteroids upon discharge [3]. Management of these patients has proven problematic due to severe refractory disease or inability and/or unwillingness to comply with medical treatment. In 1 study of patients admitted to the hospital, some with near fatal asthma, 50% were noncompliant with systemic corticosteroids at 7 days after discharge [4]. Many factors may contribute to patient noncompliance including poor access to routine quality health care (particularly in the inner city), lack of education or understanding of their disease, unwillingness to accept the chronic nature of their disease, or inability to obtain medications.

Many lines of evidence implicate eosinophils as one of the main causative cells of asthma airway inflammation [5,6]. Peripheral blood eosinophilia is a risk factor for relapse of acute asthma [7]. In subjects with eosinophilia, the risk of dying of asthma was 7.4 times greater than in those without eosinophilia [8]. Necropsy results have identified 2 distinct pathogenic inflammatory mechanisms of fatal asthma [9]. A neutrophilic airway infiltrate is more prominent in those dying suddenly (within approximately 2 hours of symptom onset), whereas an eosinophilic airway infiltrate is more common in those dying from more protracted asthma crises. Sputum and blood eosinophils can also be increased in patients presenting to the ED with rapid onset of asthma symptoms [10]. Treatment strategies focusing on reducing sputum eosinophils have led to a reduction in the number and severity of asthma exacerbations [6,11,12].

Benralizumab is an investigational humanized monoclonal antibody (mAb) that binds to the α chain of the interleukin 5 (IL-5) receptor, which is expressed on eosinophils and basophils and produces apoptosis via antibody-dependent cellular cytotoxicity. A single intravenous (IV) dose of benralizumab administered to adults with mild asthma provoked prolonged peripheral blood eosinopenia, likely due to the effects on eosinophil/basophil bone marrow progenitors that express the target [13]. Benralizumab does not affect other cell lineages in the bone marrow or periphery [14].

This study evaluated how 1 IV dose of benralizumab added to current standard of care medication affected recurrence (asthma exacerbations and/or hospitalization for acute asthma) after an ED visit for asthma exacerbations. To our knowledge, no reports exist on the therapeutic effects of a single IV dose of any antieosinophilic therapy on asthma exacerbations in a relatively unselected patient population after experiencing an asthma exacerbation.

2. Methods

2.1. Subjects

Subjects who were eligible for enrollment presented to the study EDs with an asthma exacerbation that had been ongoing for greater than or equal to 2 hours, had received greater than or equal to 2 treatments with inhaled bronchodilators either prehospital or in the ED with an incomplete clinical response (defined as a posttreatment forced expiratory volume in 1 second (FEV_1) or predicted peak expiratory flow of less than or equal to 70%), and had at least to 1 previous asthma exacerbation requiring an urgent care visit in the past 12 months. Subjects were aged 18 to 60 years with a physician diagnosis of asthma for greater than or equal to 2 years and met National Heart Lung and Blood Institute guidelines [15] for persistent asthma in the previous 3 months. Active tobacco smoking with a total exposure of less than or equal to 20 pack years was permitted. Subjects with a physician diagnosis of chronic obstructive pulmonary disease, another acute illness at study entry, fever greater than 38.6°C, aspirin-induced asthma attack, anaphylactic/anaphylactoid reaction presenting with bronchospasm, symptoms of or exposure to parasitic infections, and immunodeficiency were excluded. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidance for Good Clinical Practice. The protocol was approved by a local institutional review board or ethics committee, and written informed consent was obtained from each subject before study entry or any study-related procedure.

2.2. Study design

This was a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group study conducted at 15 sites across the United States and Canada between February 2009 and March 2011 (ClinicalTrials.gov no.: NCT00768079). Subjects were stratified by baseline blood eosinophil count of less than or equal to 450 or greater than 450 cells/μL and randomized 2:1 to benralizumab (0.3 mg/kg or 1.0 mg/kg) or placebo with an interactive voice response system. Dose selection was based upon the expected duration of eosinopenia, which was approximately 84 days for 0.3 mg/kg and greater than 84 days for 1.0 mg/kg. Placebo and benralizumab doses were identical in appearance (Supplementary Appendix Fig. 1).

The initial qualifying asthma exacerbation was managed by the treating health care provider in accordance with published guidelines [15]. Upon discharge from the ED or hospital, all subjects received a 7-day supply of greater than or equal to 40 mg/day prednisone or equivalent and a prescription for inhaled corticosteroids (ICS). Subjects were required to be clinically stabilized and demonstrate an FEV_1 greater than or equal to 30% of predicted normal before dosing. Subjects were dosed up to 7 days after their qualifying asthma exacerbation with either placebo or benralizumab administered as a single IV infusion over at least 30 minutes.

Subjects were followed up for a total of 168 days after dosing. Scheduled clinic visits occurred on days 7, 42, and 84 and telephone calls on days 28, 63, 112, 140, and 168. Measurements included FEV_1; Asthma Control Questionnaire (ACQ) [16]; Asthma Quality of Life Questionnaire (AQLQ) [17]; and use of rescue medications, physician assessment of health status, health care resource utilization, safety assessments, pharmacokinetics, and immunogenicity.

2.3. Primary and secondary outcomes

The primary efficacy outcome was the proportion of subjects with greater than or equal to 1 exacerbation at week 12. Secondary outcomes included the proportion of subjects with an exacerbation at weeks 4 and 24, eosinophil counts and eosinophil-derived protein levels, lung function, asthma symptom changes, health-related quality of life, health care resource utilization, and safety assessments. The time-weighted rate of exacerbations at week 12 was added as an efficacy end point before unblinding the study and data analysis. Asthma exacerbations were defined as either (1) an increase of asthma symptoms that did not resolve within 2 hours after the use of rescue albuterol or corticosteroids and required an unscheduled medical visit; or (2) during a scheduled study visit, the subject had acute asthma symptoms and a reduction of greater than or equal to 20% in predicted peak expiratory flow or FEV_1, which in the opinion of the investigator required treatment. For each exacerbation, the dates of onset and health care provider or ED visit, treatment received, and resolution date were collected. A period of 7 days of stability after the resolution of an exacerbation was required between exacerbations.

2.4. Safety assessments

Adverse events (AEs) were monitored after administration of placebo or benralizumab through week 24. Other assessments

included physical examination, vital sign monitoring, and laboratory measurements.

2.5. Statistical analysis

Sample size was calculated for the proportion of subjects with greater than or equal to 1 asthma exacerbation using Fisher exact test with a 2-sided α level of .05 for testing the difference between the combined benralizumab groups and the placebo group. With 108 subjects (36 in the placebo group and 72 in the combined benralizumab group), the study had an 80% power to detect a 50% difference in exacerbation rate. Assumptions included a 60% asthma exacerbation rate for the placebo group at week 12 and an α level of .05.

Reported asthma exacerbations were adjudicated in a blinded fashion to determine whether they met the protocol definition. Exacerbations that occurred within 7 days of the previous exacerbation were counted as a single exacerbation.

The weighted asthma exacerbation/hospitalization rate over a given period equaled (total no. of exacerbations/hospitalizations)/(total duration of person-year follow-up). Person-year follow-up for each subject equaled (no. of days between first dose and last contact or cut-off, whichever came first)/365.25 days. The Poisson model with an offset option compared the weighted asthma exacerbation/hospitalization rate between the combined benralizumab and placebo groups. The reduction in rate was calculated by taking exponentiation of the coefficient for the combined benralizumab group in the Poisson regression model. Additional statistical analyses are described in the Supplementary Appendix.

3. Results

3.1. Enrollment and baseline characteristics

Of 136 subjects who signed informed consent, 110 were randomized into the study. Two subjects in the placebo group were lost to follow-up after dosing and not included in the evaluable population. One hundred eight subjects completed evaluations through day 42 and were considered evaluable at the primary end point of 84 days (Fig. 1). Overall, of the 110 randomized subjects, 80 (73%) were followed up for the entire 24 weeks.

Baseline demographic and clinical characteristics were similar between the groups except for body mass index and posttreatment FEV_1 at dosing date (Table 1). Systemic corticosteroid use for both the initial treatment and during the course of the study was comparable for all groups (Supplementary Appendix Table 1). Median (interquartile range) time between ED admission and administration of benralizumab was 0 (0-2) days.

3.2. Exacerbations

The proportion of subjects who experienced greater than or equal to 1 asthma exacerbation through week 12 was 14/36 (38.9%) vs 24/72 (33.3%; $P = .67$) for the placebo vs combined benralizumab groups, respectively. This measure was also not significantly different at weeks 4 and 24 (Table 2). The cumulative number of exacerbations through week 12 was 31 from 36 evaluable subjects in the placebo group and 31 from 72 evaluable subjects in the combined benralizumab groups (Fig. 2A). Compared with placebo, the asthma exacerbation rate was reduced by 49% ($P = .01$; Table 2). Systemic corticosteroids were not administered for 2 of 62 adjudicated asthma exacerbations (1 each in the placebo and 0.3 mg/kg groups).

The number of subjects with high (or low) eosinophil counts was similar between the 2 benralizumab dose groups (Table 1). Exacerbation rates (exacerbations/subject/year) in the combined benralizumab groups were similar for subjects who had eosinophil counts greater than 300 cells/μL at screening and those with counts less than or equal to 300 cells/μL (1.90; 95% confidence interval (CI), 1.24-2.78; Supplementary Appendix Table 2).

The number of subjects who experienced greater than or equal to 1 asthma exacerbation resulting in hospitalization through week 12 was 7/36 (19.4%) vs 8/72 (11.1%; $P = .25$) for the placebo vs combined benralizumab groups, respectively (Table 2). The number of exacerbations resulting in hospitalization through week 12 was 14 from 36 evaluable subjects in the placebo group and 11 from 72 evaluable subjects in the combined benralizumab group (Fig. 2B). Compared with placebo, the rate of exacerbations resulting in hospitalization in the combined benralizumab groups was reduced by 60% ($P = .02$; Table 2).

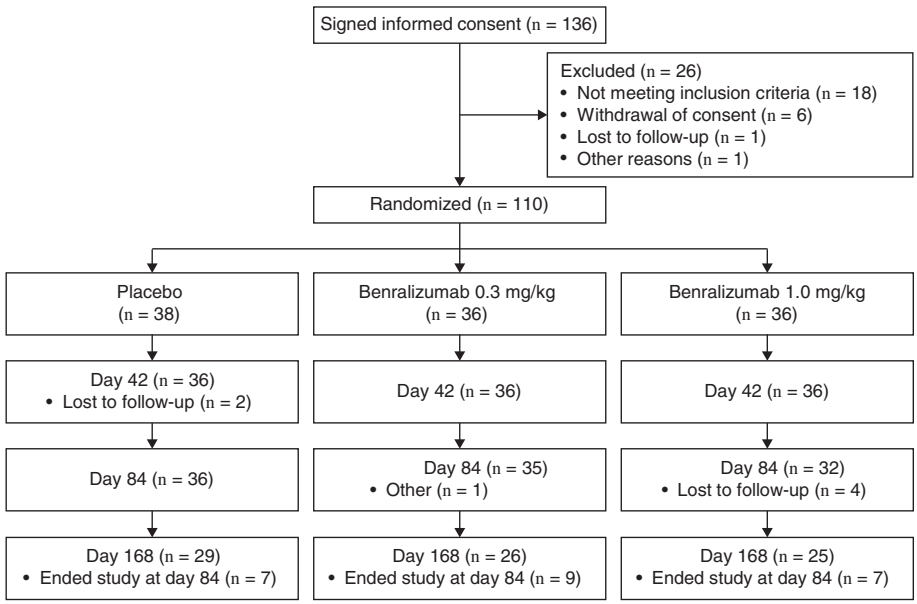

Fig. 1. Subject disposition. Analysis was performed on evaluable subjects on study days 84 and 168. Evaluable subjects were defined as those subjects followed up through at least study day 42.

Table 1
Baseline characteristics (intent-to-treat population)

Characteristic[a]	Placebo	Benralizumab		
	n = 38	0.3 mg/kg	1.0 mg/kg	Total
		n = 36	n = 36	n = 72
Age, y				
Mean	35.9	37.9	34.8	36.3
Range	22-55	20-60	19-54	19-60
Sex, n				
Male	8	12	13	25
Female	30	24	23	47
Race, n				
Black	26	19	19	38
White	11	14	16	30
Other	1	3	1	4
BMI, kilograms per square meter	34.7 (8.9)	30.1 (8.1)	30.8 (8.3)	30.5 (8.2)[b]
Smoking status, %				
Ever smoked	55.3	58.3	50.0	54.2
Current smoker	20.0	26.5	40.0	32.8
Marijuana smoker	13.2	16.7	33.3	25.0
FEV_1 on dosing date[c]				
L	1.68	1.69	2.07	1.88[b]
% Predicted	56.1	53.1	63.3	58.1
Eosinophil count, $10^3/\mu L$[d]	0.350 (0.525)	0.259 (0.511)	0.168 (0.220)	0.213 (0.393)
Eosinophil count $10^3/\mu L$, n (%)[d]				
0	12 (32)	17 (47)	13 (36)	30 (42)
>0 to ≤0.3	13 (35)	12 (33)	16 (44)	28 (39)
>0.3	12 (32)	7 (19)	7 (19)	14 (19)
Asthma controller use at entry, n (%)[e]				
ICS	8 (22)	9 (25)	6 (17)	15 (21)
ICS/LABA	22 (61)	20 (56)	19 (53)	39 (54)
LABA	4 (11)	5 (14)	2 (6)	7 (10)
LTRI	12 (33)	9 (25)	8 (22)	17 (24)
LAMA	0 (0)	2 (6)	1 (3)	3 (4)
Steroid bursts past 3 mo, n				
0	13	11	11	22
1	9	9	11	20
2	2	10	8	18
3	6	3	4	7
≥4	8	3	2	5
ED visits past 12 mo				
Mean	6.0	5.6	3.7	4.6
Median	3.0	2.0	2.0	2.0
Range	0-30	0-40	0-20	0-40
Hospital admissions past 12 mo				
Mean	2.6	1.9	1.3	1.6
Median	1.5	1.0	1.0	1.0
Range	0-20	0-13	0-8	0-13
ICU admissions ever				
Mean	2.5	3.2	3.0	3.1
Median	0.5	0.0	0.5	0.0
Range	0-50	0-80	0-30	0-80
ACQ	3.64 (0.83)	3.72 (1.18)	3.26 (1.27)	3.49 (1.24)
AQLQ	3.10 (0.90)	3.18 (0.95)	3.35 (1.11)	3.27 (1.03)

Abbreviations: *BMI*, body mass index; *ICU*, intensive care unit; *LABA*, long-acting β agonist; *LAMA*, long-acting muscarinic antagonist; *LTRI*, leukotriene modifier.
[a] Values are expressed as mean (SD) unless otherwise indicated.
[b] $P < .05$ for differences among 3 groups by analysis of variance.
[c] Patients were stable; before benralizumab dosing.
[d] Blood samples for eosinophil counts were collected at screening when a subject presented to the ED and analyzed at the local laboratory. Placebo group, n = 37.
[e] Placebo group is based on the evaluable population (n = 36). Controller use at entry includes an asthma medication with onset at study day 7 or earlier. Subjects may have taken more than one of these medications.

3.3. Secondary outcomes

Administration of benralizumab produced a significant, rapid, and sustained reduction in eosinophil counts at both dose levels up to week 12 (Fig. 3). Similar declines were produced by both dose levels in eosinophil-derived proteins: eosinophilic cationic protein (ECP) and eosinophil-derived neurotoxin (EDN). For the combined benralizumab groups, ECP declined from a baseline mean (SD) of 26.1 (30.3) μg/L to 8.6 (9.1) μg/L at day 84, and EDN declined from 25.67 (33.80) ng/mL to 4.79 (9.87) ng/mL.

Benralizumab demonstrated no significant effects on pulmonary function, ACQ, or AQLQ when compared with placebo. Baseline values were established during the initial asthma exacerbation, and these measurements recovered similarly during the following 12 weeks in all 3 groups (Supplementary Appendix Table 3).

Health care resource utilization is shown in Table 3. Visits to the ED at week 24 were lower in the combined benralizumab groups compared with placebo (weighted rate of 2.95 vs 4.32; $P = .02$).

3.4. Safety

Adverse events occurring in greater than or equal to 5% of subjects treated with benralizumab were asthma, headache, dizziness, cough, pyrexia, bronchitis, anxiety, muscle spasms, and hyperhidrosis. All AEs were mild to moderate in severity and self-limiting (Supplementary Appendix Table 4). The numbers of severe AEs were similar among groups. The number of subjects who experienced serious AEs considered related to benralizumab was: pyrexia (n = 2), tachycardia (n = 1), and anxiety (n = 1). Six subjects in the benralizumab group had antidrug antibodies at week 12 without any clinical sequelae.

4. Discussion

This study demonstrates that 1 dose of benralizumab significantly reduced the blood eosinophil count, the rate and severity of subsequent exacerbations, and health care utilization in subjects who presented to the ED with an asthma exacerbation. It did not, however, impact the proportion of subjects who experienced greater than or equal to 1 subsequent exacerbation or important indicators such as pulmonary function and self-reported quality of life.

Patients with acute asthma who are discharged from a hospital or ED setting are at risk for relapse and future exacerbations. Subjects in this study had inadequately controlled asthma evidenced by a history of multiple ED visits, hospitalizations, and intensive care unit admissions. Comparable patient populations are among the most difficult in which to achieve acceptable asthma control [18]. Best evidence indicates treatment with systemic [19] and inhaled [20] corticosteroids is required to regain and maintain control after discharge. Previous studies have also demonstrated that an outpatient monitoring strategy focused on reducing sputum eosinophils reduces the number of subsequent asthma exacerbations [6,21-23]. This study extends this line of reasoning to unstable patients who present to the ED with an asthma exacerbation that is poorly responsive to usual therapy with bronchodilators and systemic corticosteroids. Treatment of these subjects with a single dose of benralizumab after an asthma exacerbation resulted in a reduction in the cumulative number of exacerbations requiring an urgent care visit over the subsequent 12 weeks. Of note, the rate of asthma exacerbations resulting in hospital admission at 12 weeks due to asthma was reduced by 60% in the combined benralizumab groups compared with usual therapeutic regimens—particularly in subjects with multiple exacerbations. This result is comparable with that previously reported in a similar patient population [11].

This study also suggests that there is a persistent effect of a single dose of benralizumab on exacerbations beyond 12 weeks. These data are limited, however, because only 80 of 108 evaluable subjects were followed up from 12 through 24 weeks by telephone contact to inquire about asthma exacerbations and related AEs. Additional studies are needed to confirm this observation.

There are 2 potential explanations for the response to benralizumab after an asthma exacerbation. Studies of near-fatal asthma [9] and

Table 2
Outcome measures (evaluable population)

Outcome measure	Placebo	Benralizumab			
	n = 36	0.3 mg/kg	1.0 mg/kg	Total	*P*
		n = 36	n = 36	n = 72	
Subjects with ≥1 asthma exacerbation, n (%)					
Wk 4	8 (22.2)	4 (11.1)	8 (22.2)	12 (16.7)	.60[b]
Wk 12[a]	14 (38.9)	9 (25.0)	15 (41.7)	24 (33.3)	.67[b]
Wk 24	17 (47.2)	13 (36.1)	18 (50.0)	31 (43.1)	.69[b]
Subjects with ≥1 exacerbation requiring hospitalization, n (%)					
Wk 4	4 (11.1)	3 (8.3)	2 (5.6)	5 (6.9)	.48[b]
Wk 12	7 (19.4)	3 (8.3)	5 (13.9)	8 (11.1)	.25[b]
Wk 24	10 (27.8)	6 (16.7)	7 (19.4)	13 (18.1)	.32[b]
Exacerbation rate through wk 12 (95% CI)[c]	3.59 (2.44, 5.10)	1.05 (0.48, 1.99)	2.61 (1.63, 3.95)	1.82 (1.24, 2.59)	.01[d]
Asthma hospitalization rate through wk 12 (95% CI)[c,e]	1.62 (0.89, 2.72)	0.35 (0.07, 1.02)	0.95 (0.41, 1.87)	0.65 (0.32, 1.16)	.02[f]

[a] Primary end point.
[b] *P* value by Fisher exact test comparing combined benralizumab groups with placebo.
[c] Time-weighted exacerbation rate = total number of exacerbations/total duration of person-year follow-up.
[d] *P* value by Poisson regression model without overdispersion comparing benralizumab combined group with placebo. *P* = .02 by Poisson regression model with overdispersion.
[e] Post hoc analysis.
[f] *P* value by Poisson regression model without overdispersion comparing benralizumab combined group with placebo. *P* = .02 by Poisson regression model with overdispersion.

sputum cell counts in patients presenting to the ED with an asthma exacerbation [10] suggest that most of these patients have an increase in airway eosinophils. A course of systemic corticosteroids given in the ED or hospital after discharge is effective in reducing asthma exacerbations over the subsequent 21 days [24]. Benralizumab achieves greater reductions in eosinophils and basophils to levels that cannot be achieved by systemic corticosteroids both in the blood [13,14] and in the airways [25] and for a sustained effect over a longer period. In addition to eosinopenia, other measures of eosinophil activity such as ECP and EDN achieved sustained reductions greater than 65% over baseline

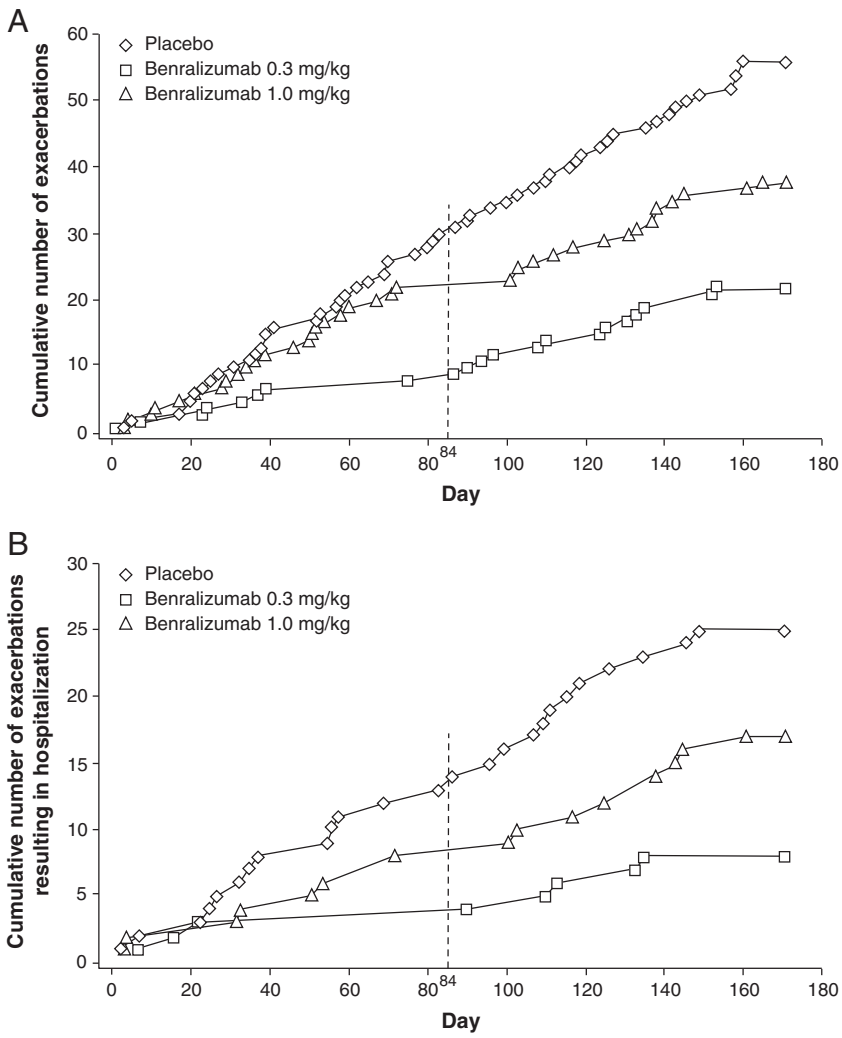

Fig. 2. Cumulative number of adjudicated asthma exacerbations. Analysis was performed on evaluable subjects. A, All exacerbations. B, Exacerbations requiring hospitalization.

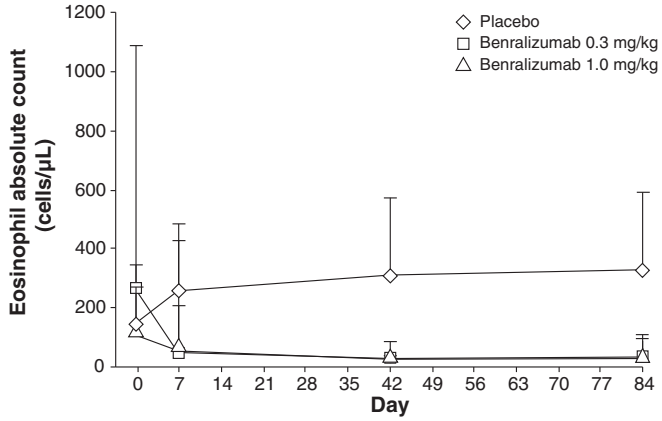

Fig. 3. Absolute eosinophil count by treatment group.

by 12 weeks. Thus, the incomplete therapeutic effect of usual controller therapy as compared with the effect of controller therapy plus benralizumab in this population may explain the difference in outcomes during the extended follow-up period.

Another possibility is that the prolonged depletion of eosinophils produced by benralizumab may have resulted in improved clinical outcomes independent of compliance with usual oral and/or inhaled asthma therapy in these subjects. Patients who repeatedly present to the ED with inadequately controlled asthma have incomplete adherence to post-ED controller medications. Compliance was measured by self-report, which is unreliable and poses a limitation of this study.

Previous studies targeting eosinophils with either an anti-IL-5 mAb or corticosteroids selected ambulatory patients with eosinophilic asthma as characterized by increased sputum eosinophils [6,11]. The current study did not select subjects based on elevated blood or sputum eosinophils; instead, an "all-comers" (with exacerbations likely to be eosinophilic) strategy was used. Subjects were stratified by baseline eosinophil count of less than or equal to 450 or greater than 450 cells/μL to ensure even distribution of patients at increased risk for early relapse [7]. Although subjects with increased sputum eosinophils were not specifically targeted, patients who present to the ED with an asthma exacerbation have demonstrated elevated sputum and blood eosinophils [10]. In addition, a poor response to bronchodilators has been associated with eosinophilic airway inflammation and a favorable response to antieosinophilic therapy [26]. These characteristics may explain the response to benralizumab in this particular population.

The best method for determining an eosinophilic exacerbation in the acute setting is not well established. Sputum analysis is not practical in the ED, and blood eosinophil counts are at best poor predictors of increased airway eosinophils [27]. Although one would expect benralizumab to demonstrate a greater clinical effect in subjects who experience predominantly eosinophilic exacerbations, subjects in this study demonstrated a clinical response to benralizumab regardless of whether they had a high or low baseline blood eosinophil count. However, a significant number of subjects had been exposed to systemic corticosteroids before measurement of baseline eosinophil counts that were low or not measurable, confounding this analysis. These data suggest that blood eosinophil measurements do not appear to be a particularly useful predictor of clinical response in this setting.

One aspect of this study that remains unexplained is the dose-response relationship: the benralizumab 0.3 mg/kg group fared better than the 1.0 mg/kg group. The 2 doses had essentially the same pharmacodynamic effect on EDN, ECP, and peripheral blood eosinophils over the 12-week observation period, suggesting that these dose levels are comparable and that the observed differences may be due instead to baseline differences in the study groups. The 1.0 mg/kg group had more active tobacco and marijuana smokers, which has been reported to result in more characteristics of chronic obstructive pulmonary disease [28] and a greater number of asthma exacerbations [29]. A post hoc multiple regression analysis demonstrated that marijuana use was associated with a poorer response to treatment. In addition, the 0.3 mg/kg group had higher baseline ECP and EDN suggesting that more subjects in this group experienced an initial eosinophilic exacerbation. This group may have been at increased risk for subsequent eosinophilic asthma exacerbations and more responsive to antieosinophilic treatment.

A patient's response to β-agonist therapy and corticosteroids may predict clinical response to an antieosinophil treatment. When treated with mepolizumab, an anti–IL-5 mAb, subjects with the least improvement in FEV_1 after β-agonist administration and best response to a course of oral corticosteroids had the greatest improvement in exacerbation rates. Conversely, those patients with a good response to bronchodilators and a poor response to corticosteroids had the least improvement in exacerbation rates [26]. In the current study, baseline percent-predicted FEV_1 may be used as a proxy for bronchodilator response because most of these measurements were taken after receiving bronchodilator treatment in the ED. The benralizumab 0.3 mg/kg group had the lowest baseline FEV_1, indicating a poor response to bronchodilators and the best response at day 7 after a week of corticosteroid treatment. In comparison, the benralizumab 1.0 mg/kg group had the highest baseline FEV_1 and least improvement after a week of corticosteroids, which may suggest that this group was generally less likely to respond to an antieosinophil medication (Supplementary Appendix Table 3).

Despite the reduction in the exacerbation rate, benralizumab had little impact on other dimensions of asthma care such as pulmonary function, asthma control, and asthma quality of life. No significant

Table 3
Health care resource utilization[a]

Health care resource	Placebo	Benralizumab		
	n = 36	0.3 mg/kg	1.0 mg/kg	Total
		n = 36	n = 36	n = 72
ED visits				
12 wk	4.40 (38)	3.73 (32)	2.96 (25)	3.35 (57)
24 wk	4.32 (65)	2.83 (42)	3.07 (44)	2.95 (86)[b]
Hospital admissions				
12 wk	1.51 (13)	0.82 (7)	0.95 (8)	0.88 (15)
24 wk	1.66 (25)	0.88 (13)	1.26 (18)	1.06 (31)
Total time spent in hospital at 24 wk, d	73	38	82	120
ICU admissions				
12 wk	0.12 (1)	0	0	0
24 wk	0.27 (4)	0.07 (1)	0.07 (1)	0.07 (2)
Total time spent in the ICU at 24 wk, d	14	2	8	10

[a] Values are expressed as rate (no. of events) for the evaluable population unless otherwise indicated. Rate for each group = total events/total duration of person-year follow-up.
[b] $P < .05$ between the combined treatment and placebo groups by Poisson regression.

safety issues with benralizumab were identified during this or a prior study [13].

Several limitations need to be considered when interpreting the results of this preliminary proof-of-concept study. Although in line with power requirements, the sample size was small, and the study enrolled predominantly female and African American subjects, which may limit the generalizability of the findings. Larger studies are required to confirm the efficacy and safety profile of benralizumab; the phase 3 program of benralizumab (multiple subcutaneous doses) in patients with asthma is ongoing.

5. Conclusions

Benralizumab, by merit of the sustained reduction in eosinophils, warrants further clinical investigation to mitigate the risk for subsequent asthma exacerbations in this population. The presence of an effective therapy in this setting may provide an impetus to identify these patients and to improve medical care in this underserved patient population. Additional studies are needed to confirm the observations in this study.

These phase 2 study results build on the literature describing the role of antieosinophil therapies in the management of asthma exacerbations. Administration of 1 dose of this anti-IL-5 receptor α mAb resulted in a long-lasting reduction of eosinophils and in the rate and severity of exacerbations in subjects who presented to the ED with an asthma exacerbation poorly responsive to initial therapy.

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Appendix. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ajem.2014.09.036.

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