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Original Contribution

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

Richard M. Nowak, MD [a], Joseph M. Parker, MD [b,*], Robert A. Silverman, MD [c], Brian H. Rowe, MD, MSc [d], Howard Smithline, MD [e], Faiz Khan, MD [f,1], Jon P. Fiening, MS [g], Keunpyo Kim, PhD [h], Nestor A. Molfino, MD, MSc [i,2]

[a] Clinical Trial Center, Henry Ford Health System, 2799 W Grand Blvd, Detroit, MI, USA
[b] Clinical Development, MedImmune, One MedImmune Way, Gaithersburg, MD, USA
[c] Department of Emergency Medicine, North Shore–Long Island Jewish Medical Center, 270-05 76th Ave New Hyde Park, NY, USA
[d] Department of Emergency Medicine and School of Public Health, University of Alberta, 1G1.42 Walter Mackenzie Centre, Edmonton, Alberta, Canada
[e] Department of Emergency Medicine, Baystate Emergency Medicine, 759 Chestnut St, Springfield, MA, USA
[f] Department of Emergency Medicine, Nassau University Medical Center, 2201 Hempstead Turnpike, Box 14, East Meadow, NY, USA
[g] Clinical Operations, MedImmune, One MedImmune Way, Gaithersburg, MD, USA
[h] Clinical Biostatistics, MedImmune, One MedImmune Way, Gaithersburg, MD, USA
[i] Clinical Research, MedImmune, One MedImmune Way, Gaithersburg, MD, USA

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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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* Corresponding author at: MedImmune, One MedImmune Way, Gaithersburg, MD, USA, 20878. Tel.: +1 301 398 4095; fax: +1 301 398 9095.
E-mail addresses: rnowak1@hfhs.org (R.M. Nowak), parkerj@medimmune.com (J.M. Parker), aresilv@aol.com (R.A. Silverman), brian.rowe@ualberta.ca (B.H. Rowe), howard.smithline@bhs.org (H. Smithline), faizkhan3@aol.com (F. Khan), fieningj@medimmune.com (J.P. Fiening), kimk@medimmune.com (K. Kim), nmolfino@kalobios.com (N.A. Molfino).
[1] Currently employed at City MD Urgent Care, New York, NY, USA.
[2] Currently employed at KaloBios, 260 East Grand Ave, South San Francisco, CA, USA.

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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).

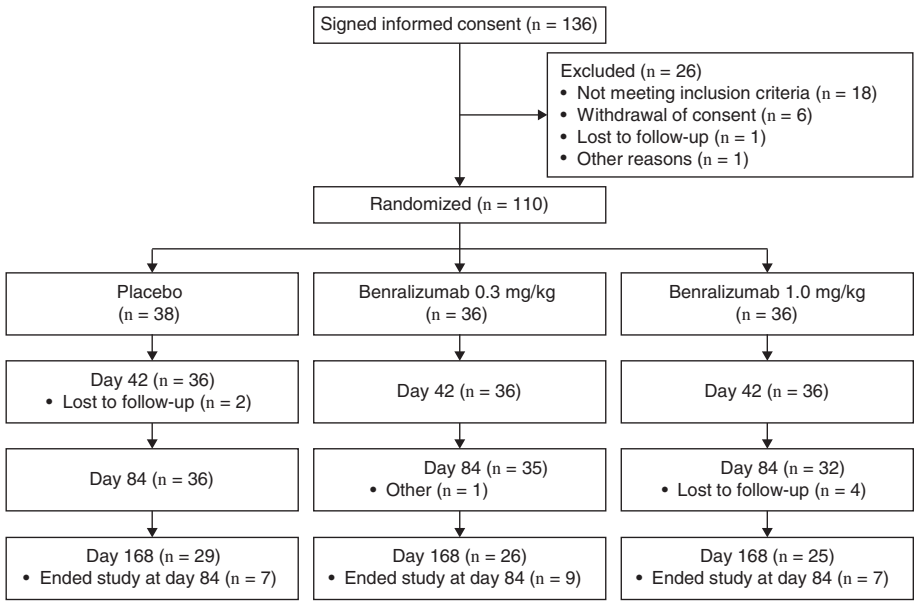

Fig. 1. Subject disposition. Analysis was performed on evaluable subjects on study days 84 and 168. Evaluable subjects were defined as those subjects followed up through at least study day 42.

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

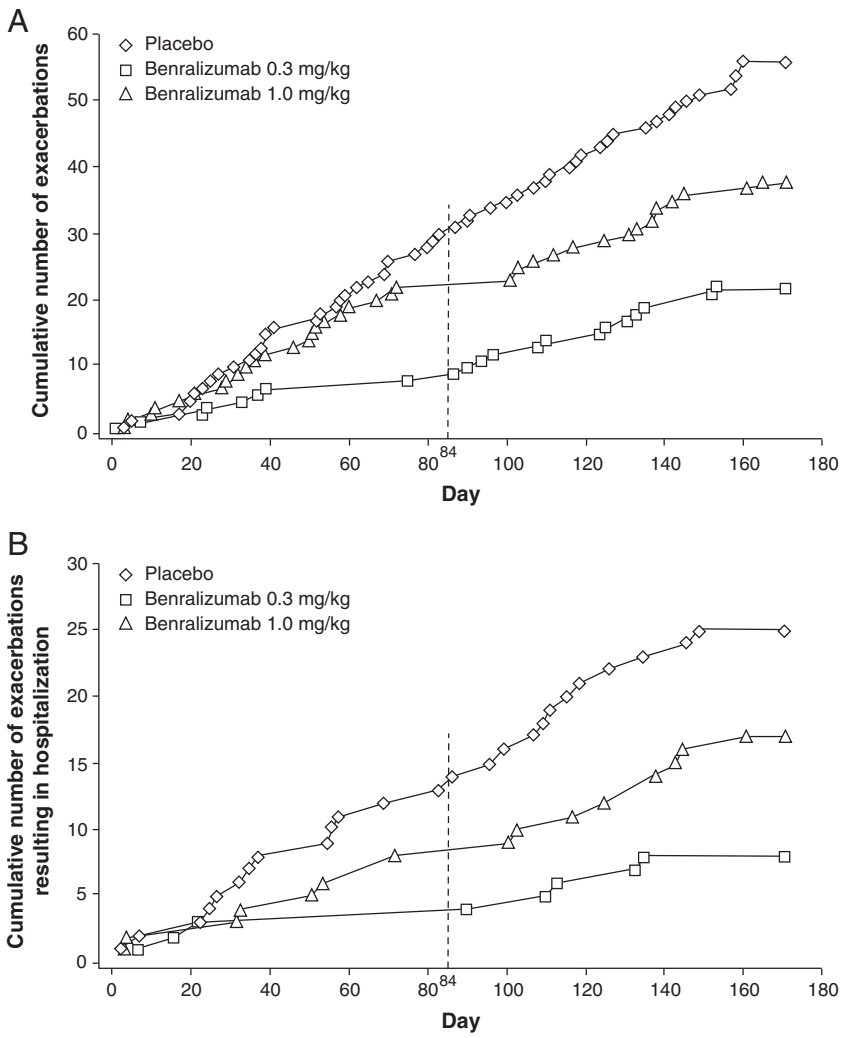

Fig. 2. Cumulative number of adjudicated asthma exacerbations. Analysis was performed on evaluable subjects. A, All exacerbations. B, Exacerbations requiring hospitalization.

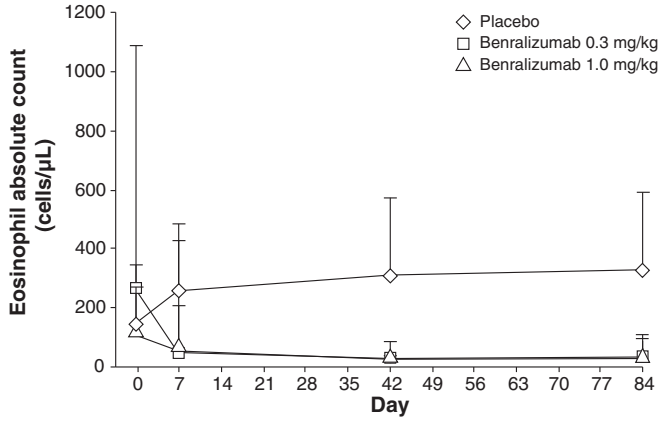

Fig. 3. Absolute eosinophil count by treatment group.

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

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References

[1] Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469–78.
[2] Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. J Allergy Clin Immunol 2011;127:145–52.
[3] Lederle FA, Pluhar RE, Joseph AM, Niewoehner DE. Tapering of corticosteroid therapy following exacerbation of asthma. A randomized, double-blind, placebo-controlled trial. Arch Intern Med 1987;147:2201–3.
[4] Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, et al. Corticosteroid use after hospital discharge among high-risk adults with asthma. Am J Respir Crit Care Med 2004;170:1281–5.
[5] James A. Airway remodeling in asthma. Curr Opin Pulm Med 2005;11:1–6.
[6] Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002;360:1715–21.
[7] Janson C, Herala M. Blood eosinophil count as risk factor for relapse in acute asthma. Respir Med 1992;86:101–4.
[8] Ulrik CS, Frederiksen J. Mortality and markers of risk of asthma death among 1,075 outpatients with asthma. Chest 1995;108:10–5.
[9] Restrepo RD, Peters J. Near-fatal asthma: recognition and management. Curr Opin Pulm Med 2008;14:13–23.
[10] Bellido-Casado J, Plaza V, Perpina M, Picado C, Bardagi S, Martinez-Bru C, et al. Inflammatory response of rapid onset asthma exacerbation. Arch Bronconeumol 2010;46:587–93.
[11] Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009;360:973–84.
[12] Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012;380:651–9.
[13] Busse WW, Katial R, Gossage D, Sari S, Wang B, Kolbeck R, et al. Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma. J Allergy Clin Immunol 2010;125:1237–44.
[14] Kolbeck R, Kozhich A, Koike M, Peng L, Andersson CK, Damschroder MM, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immunol 2010;125:1344–53.
[15] National Heart Lung and Blood Institute, National Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma: expert panel report 3. NIH Publication No. 08-4051; 2007 [Bethesda, MD].
[16] Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902–7.
[17] Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest 1999;115:1265–70.
[18] Moore WC, Peters SP. Severe asthma: an overview. J Allergy Clin Immunol 2006;117:487–94.
[19] Rowe BH, Villa-Roel C, Sivilotti ML, Lang E, Borgundvaag B, Worster A, et al. Relapse after emergency department discharge for acute asthma. Acad Emerg Med 2008;15:709–17.
[20] Rowe BH, Bota GW, Fabris L, Therrien SA, Milner RA, Jacono J. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department: a randomized controlled trial. JAMA 1999;281:2119–26.
[21] Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemiere C, Pizzichini E, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. Eur Respir J 2006;27:483–94.
[22] Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med 2009;360:985–93.
[23] Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 2011;184:1125–32.
[24] Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database of Systematic Reviews 2001(1):CD000195. http://dx.doi.org/10.1002/14651858.CD000195.
[25] Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol 2013;132:1086–96.
[26] Pavord ID, Haldar P, Bradding P, Wardlaw AJ. Mepolizumab in refractory eosinophilic asthma. Thorax 2010;65:370.
[27] Pizzichini E, Pizzichini MM, Efthimiadis A, Dolovich J, Hargreave FE. Measuring airway inflammation in asthma: eosinophils and eosinophilic cationic protein in induced sputum compared with peripheral blood. J Allergy Clin Immunol 1997;99:539–44.
[28] Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA. Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. Arch Intern Med 2007;167:221–8.
[29] Gaeta TJ, Hammock R, Spevack TA, Brown H, Rhoden K. Association between substance abuse and acute exacerbation of bronchial asthma. Acad Emerg Med 1996;3:1170–2.