

# Reslizumab for Poorly Controlled, Eosinophilic Asthma

## A Randomized, Placebo-controlled Study

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**Rationale:** Eosinophilic asthma is a phenotype of asthma characterized by the persistence of eosinophils in the airways. IL-5 is involved in the activation and survival of eosinophils.

**Objectives:** To evaluate the effect of the antibody to IL-5, reslizumab, in patients with eosinophilic asthma that is poorly controlled with high-dose inhaled corticosteroid.

**Methods:** Patients were randomly assigned to receive infusions of reslizumab at 3.0 mg/kg (n = 53) or placebo (n = 53) at baseline and at Weeks 4, 8, and 12, with stratification by baseline Asthma Control Questionnaire (ACQ) score less than or equal to 2 or greater than 2. The primary efficacy measure was the difference between the reslizumab and placebo groups in the change in ACQ score from baseline to end of therapy (Week 15 or early withdrawal).

**Measurements and Main Results:** Mean changes from baseline to end of therapy in ACQ score were -0.7 in the reslizumab group and -0.3 in the placebo group (P = 0.054) and in FEV<sub>1</sub> were 0.18 and -0.08 L, respectively (P = 0.002). In those patients with nasal polyps, the changes in ACQ score were -1.0 and -0.1, respectively (P = 0.012). Median percentage reductions from baseline in sputum eosinophils were 95.4 and 38.7%, respectively (P = 0.007). Eight percent of patients in the reslizumab group and 19% of patients in the placebo group had an asthma exacerbation (P = 0.083). The most common adverse events with reslizumab were nasopharyngitis, fatigue, and pharyngolaryngeal pain.

**Conclusions:** Patients receiving reslizumab showed significantly greater reductions in sputum eosinophils, improvements in airway function, and a trend toward greater asthma control than those receiving placebo. Reslizumab was generally well tolerated.

**Keywords:** eosinophils; asthma; interleukin-5; reslizumab

Asthma is a chronic disease of the airways of the lungs characterized by airflow obstruction and airway hyperresponsiveness and inflammation. Although most patients with asthma are able to control their symptoms with bronchodilators and low to moderate doses of inhaled corticosteroids, some remain uncontrolled

### AT A GLANCE COMMENTARY

#### Scientific Knowledge on the Subject

Inhibition of IL-5 has been shown to reduce blood and sputum eosinophils; however, it has not been effective at reducing the signs and symptoms of asthma in studies of patients who were not selected according to their asthma phenotype.

#### What This Study Adds to the Field

Anti-IL-5 therapy with reslizumab for the treatment of patients with severe, refractory, eosinophilic asthma was effective in improving lung function and trended toward greater asthma control, especially in patients with nasal polyps.

on high doses, which can result in time off from work or hospitalization (1, 2).

Eosinophilic asthma is a phenotype of asthma that is characterized by the persistence of eosinophils in the lung and sputum. The numbers of eosinophils in the blood and bronchial fluid can correlate with asthma severity (3). Eosinophils are involved in lung tissue remodeling, including airway thickening and fibrosis, and angiogenesis, which promotes further tissue growth and remodeling (4). Treatment strategies that aim to reduce the level of eosinophils in the sputum have resulted in improved control of asthma symptoms and fewer exacerbations (5, 6).

The proinflammatory cytokine IL-5 is a key mediator in the maturation, recruitment, and activation of eosinophils (7). Inhibition of IL-5 has been shown to reduce blood and sputum eosinophils in patients with asthma (8, 9). However, anti-IL-5 therapy was not effective at reducing the signs and symptoms of asthma in studies of patients who were not selected according to their asthma phenotype (8–10). In contrast, inhibition of IL-5 was effective as a prednisone-sparing therapy in patients with severe prednisone-dependent asthma and increased eosinophils in their sputum (11).

Reslizumab is an IgG4/κ humanized monoclonal antibody composed of the complementarity-determining regions of a murine antibody to human IL-5 that has been grafted onto human frameworks (12). Reslizumab neutralizes circulating IL-5 by preventing it from binding to eosinophils. The objective of this study was to evaluate the effect of reslizumab on patients with eosinophilic asthma that was poorly controlled with inhaled corticosteroids. Some of the results herein had previously been presented at scientific meetings (13, 14).

### METHODS

#### Patients

Patients aged 18 to 75 years with asthma (1) confirmed by airway hyperreactivity (a 20% reduction in FEV<sub>1</sub> after administration of

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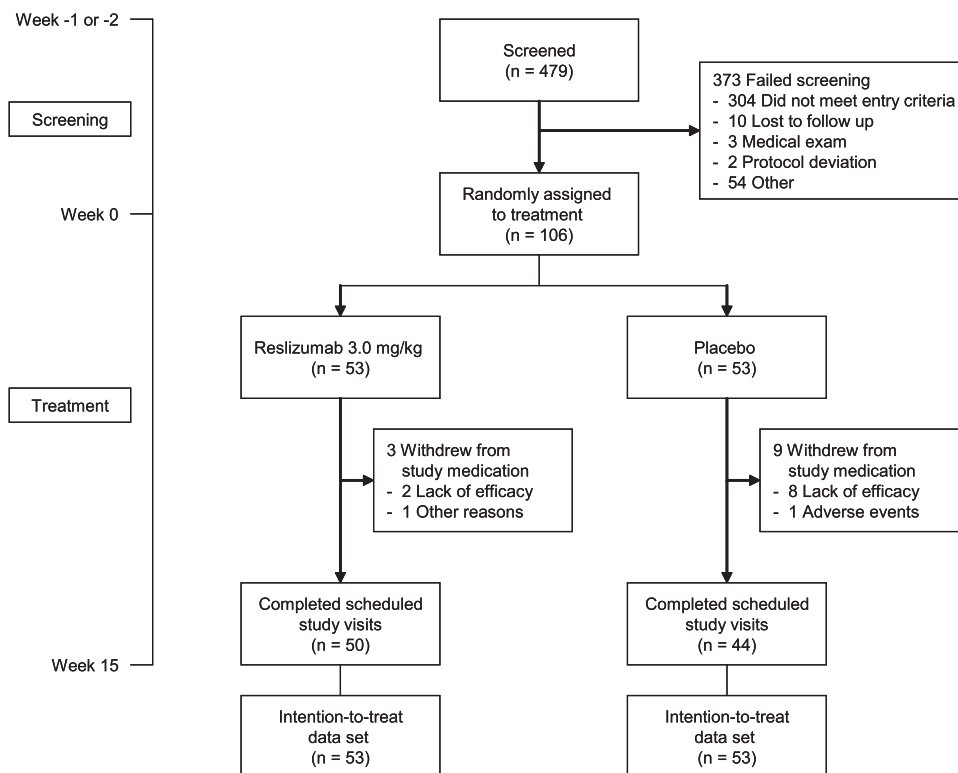


Figure 1. Study design and patient disposition.

methacholine up to 16 mg/ml) or by airway reversibility (a  $\geq 12\%$  improvement in FEV<sub>1</sub> after administration of a  $\beta$ -agonist), (2) treated with high-dose inhaled corticosteroids ( $\geq 440$   $\mu$ g of fluticasone twice

per day) in combination with at least one other agent (including short- or long-acting  $\beta$ -agonists, leukotriene antagonists, and cromolyn sodium), (3) that was poorly controlled as indicated by an Asthma

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

| Characteristic                                                                | Reslizumab, 3.0 mg/kg (n = 53) | Placebo (n = 53) |
|-------------------------------------------------------------------------------|--------------------------------|------------------|
| <b>Demographics</b>                                                           |                                |                  |
| Age, yr                                                                       | 44.9 (13.94)                   | 45.8 (11.74)     |
| Women, n (%)                                                                  | 34 (64)                        | 29 (55)          |
| <b>Asthma characteristics</b>                                                 |                                |                  |
| Years since asthma diagnosis                                                  | 23.3 (11.38)                   | 26.1 (16.06)     |
| ACQ score                                                                     | 2.8 (0.79)                     | 2.5 (0.73)       |
| ACQ randomization strata, n (%)                                               |                                |                  |
| Score $\leq 2$                                                                | 11 (21)                        | 14 (26)          |
| Score $> 2$                                                                   | 42 (79)                        | 39 (74)          |
| Aspirin sensitivity, n (%)                                                    | 3 (6)                          | 5 (9)            |
| Nasal polyps, n (%)                                                           | 22 (42)                        | 16 (30)          |
| Chronic sinusitis, n (%)                                                      | 19 (36)                        | 12 (23)          |
| Atopic dermatitis, n (%)                                                      | 9 (17)                         | 6 (11)           |
| Allergic rhinitis, n (%)                                                      | 41 (77)                        | 44 (83)          |
| <b>Airway function</b>                                                        |                                |                  |
| FEV <sub>1</sub> , L/s                                                        | 2.1 (0.60)                     | 2.3 (0.75)       |
| % of predicted FEV <sub>1</sub>                                               | 66.0 (15.16)                   | 69.3 (16.40)     |
| FEV <sub>1</sub> :FVC ratio                                                   | 0.67 (0.098)                   | 0.66 (0.110)     |
| Improvement in FEV <sub>1</sub> after bronchodilator use                      | n = 39                         | n = 37           |
| Percentage improvement                                                        | 23.1 (10.07)                   | 29.5 (21.30)     |
| <b>Eosinophil levels</b>                                                      |                                |                  |
| Induced sputum, median (min, max) %                                           | 10.7 (1.7, 94.5)               | 9.4 (3.0, 90.0)  |
| In patients with nasal polyps, median (min, max) %                            | 15.9 (1.7, 57.7)               | 17.7 (3.5, 83.3) |
| In patients without nasal polyps, median (min, max) %                         | 7.5 (3.3, 94.5)                | 6.6 (3.0, 90)    |
| Blood, median (min, max) 10 <sup>3</sup> / $\mu$ l                            | 0.50 (0.1, 1.5)                | 0.50 (0.0, 1.2)  |
| In patients with nasal polyps, median (min, max) 10 <sup>3</sup> / $\mu$ l    | 0.60 (0.2, 1.5)                | 0.60 (0.0, 1.2)  |
| In patients without nasal polyps, median (min, max) 10 <sup>3</sup> / $\mu$ l | 0.40 (0.0, 1.2)                | 0.40 (0.1, 1.5)  |
| <b>Concomitant medications*</b>                                               |                                |                  |
| Long-acting $\beta$ -agonists                                                 | 50 (94%)                       | 51 (96%)         |
| Leukotriene antagonists                                                       | 9 (17.0%)                      | 17 (32.1%)       |
| Cromolyn sodium                                                               | 1 (1.9%)                       | 1 (1.9%)         |

Definition of abbreviation: ACQ = Asthma Control Questionnaire.

Data are expressed as means (SD) unless otherwise specified.

\* All patients were receiving high-dose inhaled corticosteroids equivalent to at least 440  $\mu$ g of fluticasone twice daily.

Control Questionnaire (ACQ) (15) score of 1.5 or more, and (4) associated with induced sputum eosinophils of 3% or more were eligible for the study. Patients were excluded from the study if they were using systemic corticosteroids (including oral corticosteroids), had a clinically significant comorbidity, or had hypereosinophilic syndrome. Detailed methods are available in the online supplement.

## Study Design

This randomized, double-blind, placebo-controlled study was conducted at 25 sites in the United States and Canada between February 2008 and January 2010. Eligible patients were randomly assigned to infusions of reslizumab (3.0 mg/kg) or placebo (0.9% saline) at a 1:1 ratio at baseline and at Weeks 4, 8, and 12. Reslizumab was infused at a rate no faster than 2 ml/minute. All doses were administered in the same total volume for patients of the same weight to maintain the study blind. Patients continued the doses of inhaled corticosteroids that they were receiving at the beginning of the study.

Study site visits occurred at screening and at Weeks 4, 8, 12, and 15. End-of-therapy assessments were conducted at Week 15 (i.e., 3 wk after the last dose of study medication) or early withdrawal. For the purposes of randomization, patients were stratified by baseline ACQ score ( $\leq 2$  or  $> 2$ ). Each site's institutional review board approved the protocol. All patients provided written informed consent before participating in the study.

## Assessments

The primary study end point was the difference between the reslizumab and placebo groups in the change from baseline to end of therapy (Week 15 or early withdrawal) in the ACQ score (seven-question instrument) (15). Other efficacy measures included spirometry, blood and induced sputum eosinophil counts, and the percentage of patients with clinical asthma exacerbations. A clinical asthma exacerbation was defined as (1) a 20% or more decrease from baseline in FEV<sub>1</sub>; or (2) worsening of asthma requiring emergency treatment, hospital admission, or three or more days of oral corticosteroid treatment. Patients with exacerbations were treated according to the investigator's discretion. The presence of nasal polyps was determined (at baseline only) through medical history, computed tomography (at selected sites), and/or physical examination.

## Statistical Analysis

Assuming a difference of 0.5 between the reslizumab and placebo groups in the change in ACQ score from baseline to end of therapy, a standard

deviation of 0.76, and a significance level of 0.05, we expected that a sample size of 120 patients (60 per treatment group) would provide more than 90% power to detect a difference between the treatment groups.

Changes from baseline to end of therapy in continuous variables (ACQ score, FEV<sub>1</sub>, percentage of the predicted value for FEV<sub>1</sub>, and sputum eosinophils) were analyzed by analysis of covariance, adjusting for the stratification factor (ACQ  $\leq 2$  or ACQ  $> 2$ ) and the baseline values for the variable being analyzed. Least-square means were used to determine the mean differences between reslizumab and placebo. Changes from baseline to multiple time points in ACQ score and FEV<sub>1</sub> were analyzed using a mixed-effects model, repeated-measures analysis of covariance, adjusting for the stratification factor and the baseline values for the variable being analyzed. For the primary efficacy analysis, if a patient had a missing ACQ score at the end of therapy visit, the last observation was carried forward and used as the end-of-therapy value. The incidence of clinical asthma exacerbations was analyzed by logistic regression, adjusting for the stratification factor. A subgroup analysis of patients with nasal polyps was prespecified. Subgroup analyses of disease duration and baseline sputum and blood eosinophil levels were performed *post hoc*. All analyses were tested using two-sided hypotheses at the  $\alpha = 0.05$  level and were conducted with SAS version 9.1 (Cary, NC).

## Role of Funding Source

The study was sponsored by Ception Therapeutics, Inc., which has since been acquired by Cephalon, Inc. Cephalon employees were involved in the study design and data interpretation. Data analysis was conducted by United BioSource, Inc., employees, with funding from Ception, and Cephalon employees. Former Ception employees and current Cephalon and United BioSource employees contributed to the preparation of the manuscript and are listed as authors, as appropriate. S.M., F.H., L.P., and P.N. had unrestricted opportunity to examine and interpret the data and prepare the manuscript. M.C. had full access to the study data and had final responsibility for the decision to submit the manuscript for publication.

## RESULTS

A total of 479 patients were screened, and 106 patients were randomized (Figure 1). Three patients in the reslizumab group and 9 in the placebo group withdrew from treatment; 10 of the 12 withdrawals were attributable to a lack of efficacy. The mean age was 45.4 years, the mean time since asthma diagnosis was

TABLE 2. EFFICACY OUTCOMES FOR ASTHMA SYMPTOMS AND AIRWAY FUNCTION

|                                                       | Reslizumab |                  |                       | Placebo |                  |                      | Least-square Mean Difference (95% CI)* | P Value* |
|-------------------------------------------------------|------------|------------------|-----------------------|---------|------------------|----------------------|----------------------------------------|----------|
|                                                       | n          | Baseline         | Change from Baseline  | n       | Baseline         | Change from Baseline |                                        |          |
| Asthma control                                        |            |                  |                       |         |                  |                      |                                        |          |
| ACQ score                                             | 53         | 2.8 (0.79)       | −0.7 (1.02)           | 53      | 2.5 (0.73)       | −0.3 (1.01)          | −0.38 (−0.76, 0.01)                    | 0.0541   |
| $\leq 2$ at baseline                                  | 11         | 1.8 (0.15)       | −0.2 (0.93)           | 14      | 1.8 (0.15)       | 0.0 (0.96)           | −0.15 (−0.96, 0.66)                    | 0.7028   |
| $> 2$ at baseline                                     | 42         | 3.0 (0.66)       | −0.9 (1.00)           | 39      | 2.8 (0.65)       | −0.4 (1.03)          | −0.45 (−0.90, 0.00)                    | 0.0505   |
| Airway function, prebronchodilator                    |            |                  |                       |         |                  |                      |                                        |          |
| FEV <sub>1</sub> , L/s                                | 52         | 2.08 (0.609)     | 0.18 (0.372)          | 52      | 2.26 (0.746)     | −0.08 (0.413)        | 0.240 (0.088, 0.392)                   | 0.0023   |
| % predicted FEV <sub>1</sub>                          | 52         | 66.31 (15.134)   | 6.19 (11.757)         | 52      | 68.90 (16.325)   | −2.44 (12.927)       | 7.978 (3.304, 12.652)                  | 0.0010   |
| FVC, L                                                | 52         | 3.13 (0.830)     | 0.18 (0.460)          | 52      | 3.43 (1.020)     | −0.13 (0.521)        | 0.271 (0.082, 0.460)                   | 0.0054   |
| Eosinophils†                                          |            |                  |                       |         |                  |                      |                                        |          |
| Induced sputum, median (min, max) percentage          | 38‡        | 10.7 (1.7, 67.6) | −95.4 (−100.0, 315.9) | 36‡     | 8.5 (3.0, 77.0)  | −38.7 (−96.0, 1,480) | −125.29 (−214.81, −35.77)              | 0.0068   |
| Blood, median (min, max) $\times 10^3$ cells/ $\mu$ L | 52         | 0.5 (0.10, 1.50) | −0.40 (−1.50, 0.00)   | 50      | 0.5 (0.00, 1.20) | 0.00 (−0.80, 0.80)   | −0.42 (−0.49, −0.35)                   | <0.0001  |

Definition of abbreviations: ACQ = Asthma Control Questionnaire; CI = confidence interval.

Data are expressed as mean (SD) unless otherwise specified.

\*Analysis of covariance, adjusting for the stratification factor (ACQ score  $\leq 2$  or ACQ  $> 2$ ) and the baseline values for the variable being analyzed, was used to compare reslizumab and placebo. Least-square means were used to calculate the difference and 95% confidence interval between treatment groups.

†Changes in eosinophils in the induced sputum are expressed as median (range) percentage change from baseline in the percentage of eosinophils in the induced sputum. Changes in eosinophils in the blood are expressed as median (range) change in eosinophil count.

‡Although all patients provided sputum for eosinophil counts at baseline, some patients did not provide sputum at the end-of-therapy visit.

24.7 years, and the mean baseline ACQ score was 2.7 (range, 1.6 to 5.1). The median percentage of eosinophils in the induced sputum sample was 10.0% and was significantly greater in those patients with nasal polyps. The treatment groups were generally well balanced regarding baseline demographics (Table 1). Imbalances in disease characteristics were the result of chance because all patients were randomly assigned to treatment groups.

### Efficacy

We compared the efficacy of reslizumab with placebo for the primary outcome measure of asthma control (Table 2 and Figure 2A). The mean change from baseline to end of therapy in ACQ score was  $-0.7$  in the reslizumab group and  $-0.3$  in the placebo group ( $P = 0.0541$ ). Significant improvements in ACQ scores were observed in the reslizumab group versus placebo in the stratum of patients with baseline ACQ scores greater than 2 ( $P = 0.0505$ ) and in those with nasal polyps ( $P = 0.0119$ ) (Table 3). Overall, 59% of patients in the reslizumab group and 40% of patients in the placebo group achieved an improvement of at least 0.5 in ACQ score (odds ratio [95% confidence interval], 2.06 [0.88 to 4.86];  $P = 0.0973$ ), which is considered to be the minimal clinically significant change (16).

We then examined the effect of reslizumab in comparison with placebo on airway function (Table 2). Patients in the reslizumab group showed statistically significant improvements from baseline in FEV<sub>1</sub> ( $P = 0.0023$ ), percentage of predicted FEV<sub>1</sub> ( $P = 0.0010$ ), and FVC ( $P = 0.0054$ ) than those in the placebo group (Table 2 and Figure 2B).

We then evaluated the effect of reslizumab in comparison with placebo on sputum and blood eosinophils. Patients in the reslizumab group showed significantly greater reductions from baseline in eosinophils in the induced sputum (Table 2 and Figure 3A) and in blood eosinophil counts (Table 2 and Figure 3B) than those in the placebo group. Reductions in the reslizumab group were observed as early as the first assessment at Week 4. By the end of therapy, the median percentage reduction in the percentage of eosinophils in the induced sputum was 95.4% in the reslizumab group and 38.7% in the placebo group ( $P = 0.0068$ ) (Table 2). Actual sputum and blood eosinophil data at each visit are shown in the online supplement.

One patient in the reslizumab group and one patient in the placebo group had sputum eosinophil values at end of therapy that were outliers in the data set. The patient in the placebo group had a clinical asthma exacerbation during the study, but the patient in the reslizumab group did not have an exacerbation.

**TABLE 3. SUBGROUP ANALYSIS OF ASTHMA CONTROL QUESTIONNAIRE SCORES AND FEV<sub>1</sub> VALUES**

|                                                           | Reslizumab |              |                      | Placebo |              |                      | Least-square Mean Difference (95% CI)* | P Value* |
|-----------------------------------------------------------|------------|--------------|----------------------|---------|--------------|----------------------|----------------------------------------|----------|
|                                                           | n          | Baseline     | Change from Baseline | n       | Baseline     | Change from Baseline |                                        |          |
| ACQ                                                       |            |              |                      |         |              |                      |                                        |          |
| Nasal polyps                                              |            |              |                      |         |              |                      |                                        |          |
| Yes                                                       | 22         | 2.6 (0.85)   | −1.0 (1.17)          | 16      | 2.6 (0.76)   | −0.1 (1.11)          | −0.94 (−1.65, −0.22)                   | 0.0119   |
| No                                                        | 31         | 2.9 (0.74)   | −0.5 (0.85)          | 37      | 2.5 (0.72)   | −0.4 (0.96)          | −0.08 (−0.54, 0.37)                    | 0.7176   |
| Disease duration                                          |            |              |                      |         |              |                      |                                        |          |
| <23 yr                                                    | 28         | 2.6 (0.71)   | −0.6 (0.94)          | 24      | 2.4 (0.62)   | −0.3 (0.82)          | −0.35 (−0.83, 0.14)                    | 0.1595   |
| ≥23 yr                                                    | 25         | 3.0 (0.82)   | −0.9 (1.09)          | 29      | 2.6 (0.81)   | −0.3 (1.16)          | −0.49 (−1.10, 0.12)                    | 0.1114   |
| Baseline sputum eosinophil level, %                       |            |              |                      |         |              |                      |                                        |          |
| <10%                                                      | 25         | 3.0 (0.80)   | −0.7 (1.24)          | 27      | 2.6 (0.80)   | −0.3 (1.01)          | −0.28 (−0.90, 0.35)                    | 0.3795   |
| ≥10%                                                      | 28         | 2.6 (0.74)   | −0.8 (0.79)          | 25      | 2.5 (0.63)   | −0.3 (1.04)          | −0.42 (−0.92, 0.07)                    | 0.0933   |
| Baseline blood eosinophil level (10 <sup>9</sup> cells/L) |            |              |                      |         |              |                      |                                        |          |
| <0.5 × 10 <sup>9</sup> cells/L                            | 25         | 2.7 (0.61)   | −0.6 (0.87)          | 26      | 2.6 (0.84)   | −0.4 (0.88)          | −0.06 (−0.55, 0.43)                    | 0.8039   |
| ≥0.5 × 10 <sup>9</sup> cells/L                            | 28         | 2.9 (0.92)   | −0.9 (1.13)          | 27      | 2.5 (0.61)   | −0.1 (1.12)          | −0.57 (−1.19, 0.05)                    | 0.0720   |
| FEV <sub>1</sub> , L/s                                    |            |              |                      |         |              |                      |                                        |          |
| Nasal polyps                                              |            |              |                      |         |              |                      |                                        |          |
| Yes                                                       | 22         | 2.14 (0.578) | 0.18 (0.341)         | 16      | 2.14 (0.446) | −0.04 (0.270)        | 0.199 (−0.011, 0.409)                  | 0.0625   |
| No                                                        | 30         | 2.03 (0.637) | 0.18 (0.399)         | 36      | 2.31 (0.846) | −0.10 (0.465)        | 0.249 (0.031, 0.466)                   | 0.0257   |
| Disease duration                                          |            |              |                      |         |              |                      |                                        |          |
| <23 yr                                                    | 28         | 2.07 (0.557) | 0.19 (0.368)         | 23      | 2.27 (0.657) | 0.02 (0.386)         | 0.16 (−0.06, 0.38)                     | 0.1456   |
| ≥23 yr                                                    | 24         | 2.09 (0.676) | 0.17 (0.385)         | 29      | 2.25 (0.821) | −0.17 (0.421)        | 0.30 (0.08, 0.53)                      | 0.0084   |
| Baseline sputum eosinophil level, %                       |            |              |                      |         |              |                      |                                        |          |
| <10%                                                      | 24         | 2.01 (0.707) | 0.11 (0.277)         | 26      | 2.33 (0.824) | −0.18 (0.438)        | 0.25 (0.04, 0.47)                      | 0.0211   |
| ≥10%                                                      | 28         | 2.13 (0.517) | 0.24 (0.433)         | 25      | 2.18 (0.678) | 0.01 (0.378)         | 0.22 (0.00, 0.44)                      | 0.0525   |
| Baseline blood eosinophil level (10 <sup>9</sup> cells/L) |            |              |                      |         |              |                      |                                        |          |
| <0.5 × 10 <sup>9</sup> cells/L                            | 24         | 2.21 (0.667) | 0.08 (0.359)         | 25      | 2.05 (0.604) | −0.12 (0.336)        | 0.19 (−0.02, 0.39)                     | 0.0737   |
| ≥0.5 × 10 <sup>9</sup> cells/L                            | 28         | 1.97 (0.542) | 0.27 (0.367)         | 27      | 2.46 (0.819) | −0.05 (0.478)        | 0.25 (0.01, 0.50)                      | 0.0419   |

Definition of abbreviations: ACQ = Asthma Control Questionnaire; CI = confidence interval.

Analysis of subgroups with or without nasal polyps was prespecified. Analyses of subgroups of disease duration and baseline sputum and blood eosinophil levels were conducted *post hoc*.

Data are expressed as means (SD).

\*Analysis of covariance, adjusting for the stratification factor (ACQ score ≤ 2 or ACQ > 2) and the baseline values for the variable being analyzed, was used to compare reslizumab and placebo. Least-square means were used to calculate the difference and 95% confidence interval between treatment groups.

Sputum and blood eosinophil levels at baseline and end of therapy for these patients are provided in the online supplement.

Among patients with asthma with nasal polyps, we observed a statistically significantly greater improvement from baseline to end of therapy in ACQ score in the reslizumab group compared with the placebo group (Table 3), whereas no such decrease was observed among patients without nasal polyps. Differences between the treatment groups were observed in the changes from baseline to end of therapy in FEV<sub>1</sub> values for both patients with nasal polyps and patients without nasal polyps. Results of *post hoc* analyses of subgroups of disease duration and baseline sputum or blood eosinophils are also shown in Table 3.

Exacerbations occurred in 4 patients (8%) in the reslizumab group and in 10 patients (19%) in the placebo group (odds ratio [95% confidence interval], 0.33 [0.10, 1.15];  $P = 0.0833$ ). Two of the four exacerbations in the reslizumab group occurred before the second dose of study medication. Of the patients in the reslizumab group with exacerbations, one had a 20% decrease from baseline in FEV<sub>1</sub>, three required emergency treatment for asthma, one was admitted to the hospital for asthma, and all four required at least 3 days of oral corticosteroid treatment for asthma worsening. Of the patients in the placebo group with exacerbations, five had a 20% decrease from baseline in FEV<sub>1</sub>, four required emergency treatment for asthma, and four required at least 3 days of oral corticosteroid treatment for asthma worsening. Additional information about the patients with exacerbations, including sputum and blood eosinophil data, is provided in the online supplement.

## Tolerability

The proportions of patients in the treatment groups with adverse events were similar (Table 4). Adverse events were generally mild or moderate in severity. The most common adverse event was nasopharyngitis, which occurred in 11 patients (21%) in the reslizumab group and in 5 patients (9%) in the placebo group. Of the patients with nasopharyngitis adverse events, eight patients in the reslizumab group and two patients in the placebo group also had nasal polyps at baseline. No clinically meaningful changes in laboratory values or vital signs were observed.

Serious adverse events occurred in two patients in the reslizumab group (pneumonia and worsening of asthma) and one patient in the placebo group (hypertension). The patient with worsening of asthma was the only patient in the reslizumab group who discontinued study treatment because of an adverse event. One patient in the placebo group also discontinued study treatment because of an adverse event (generalized pruritus).

## DISCUSSION

In this multicenter study, we identified patients with an eosinophilic asthma phenotype *a priori* that was uncontrolled with high-dose inhaled corticosteroids and at least one other agent and then provided targeted therapy with a monoclonal antibody to IL-5, reslizumab. The results show that patients with this phenotype who received reslizumab had significantly greater improvement in airway function and reduction in sputum and blood eosinophil counts than those who received placebo.

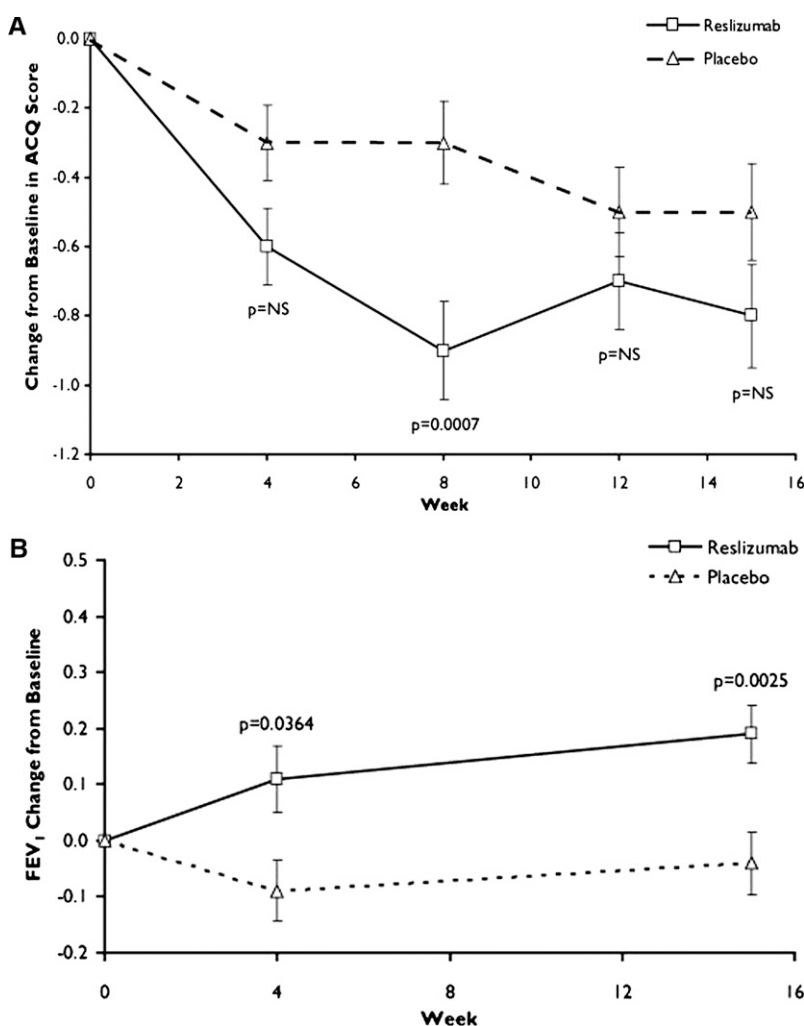


**Figure 2.** Changes in asthma control and airway function with reslizumab and placebo. Mean ( $\pm$  standard error of the mean) changes from baseline in (A) Asthma Control Questionnaire (ACQ) score and in (B) FEV<sub>1</sub> at each time point. Comparisons between reslizumab and placebo were made using a mixed-effects model, repeated-measures analysis of covariance, adjusting for the stratification factor and baseline values for the variable being analyzed. NS = not significant.

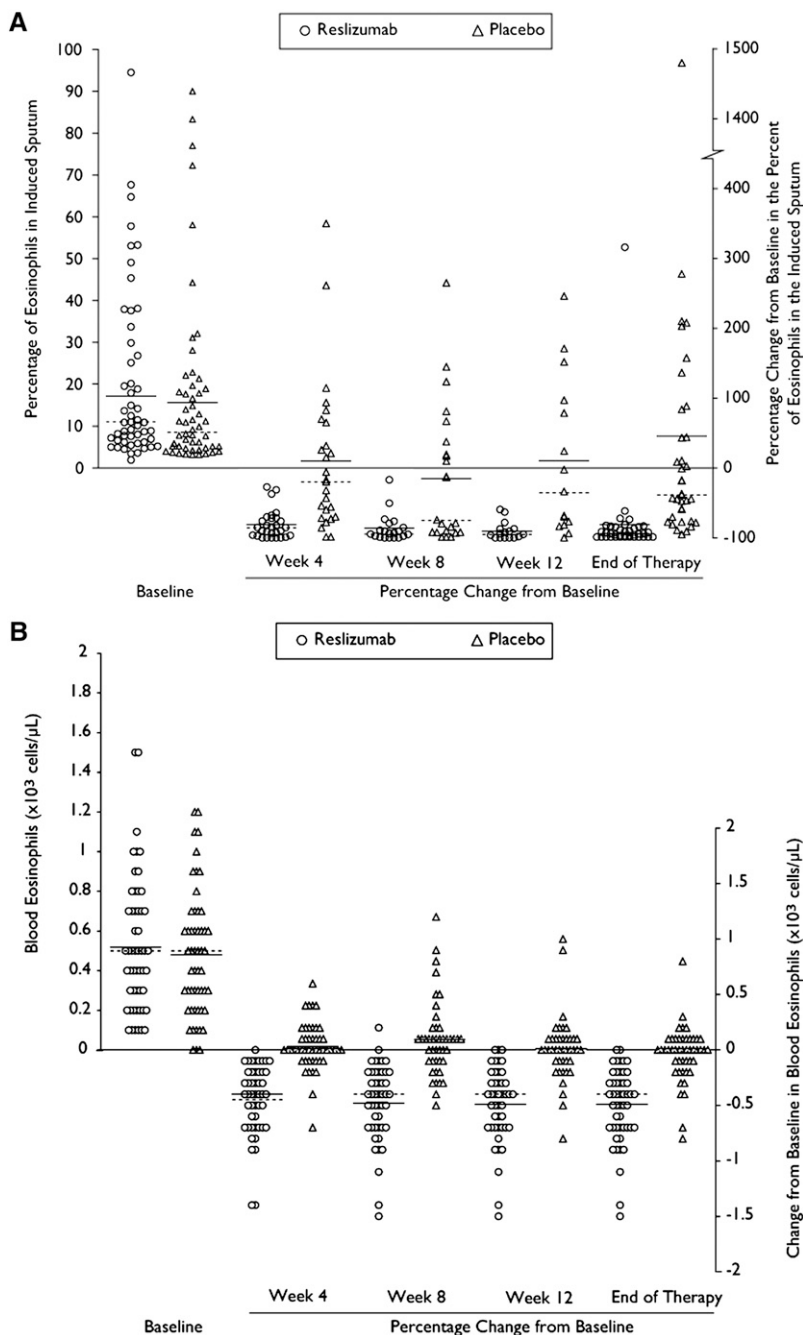


**Figure 3.** Changes in sputum and blood eosinophils with reslizumab and placebo. Individual patient data for eosinophils in the induced sputum and blood: (A) percentage of eosinophils in the induced sputum at baseline and the percentage changes from baseline to Weeks 4, 8, and 12 and end of therapy; (B) blood eosinophil counts at baseline and changes from baseline to Weeks 4, 8, and 12 and end of therapy. Thick horizontal lines indicate means. See text for more information regarding outliers.

Modest improvement in asthma control was also observed with reslizumab, but the difference between the treatment groups did not reach statistical significance. However, the improvements in asthma control were greater in patients with nasal polyposis, a hallmark of eosinophilic disease in patients with asthma (17, 18). These results provide evidence that inhibition of IL-5 in patients with the eosinophilic asthma on high-dose inhaled corticosteroids reduces airway eosinophilia and that such a reduction improves clinical outcomes in these patients.

Early studies of anti-IL-5 therapy in patients with severe asthma did not include consideration of the pathophysiological asthma phenotype to determine which patients should be selected for such therapy (8–10). The reduction of eosinophils in the blood and sputum of patients who received anti-IL-5 therapy in these studies was not associated with improvement in airway function. In our study, sputum eosinophilia was a requirement for study

entry, and patients who received reslizumab showed statistically significant improvements in airway function and a trend toward improved asthma control versus placebo.

Two studies demonstrated that when patients were selected with eosinophilic asthma there was clinical improvement. In one of these, involving 61 patients with refractory eosinophilic asthma, Haldar and colleagues (19) demonstrated that inhibition of IL-5 reduced asthma exacerbations over 1 year although there was no significant effect on FEV<sub>1</sub>. In this study, demonstration of eosinophilia was only required at some point in the previous 2 years. In contrast, our study required persistent airway eosinophilia at randomization. Establishing a persistent eosinophilic phenotype appears critical in determining the optimal response to anti-IL-5 therapy (20). In the other study, of nine patients with severe prednisone-dependent asthma with persistent airway eosinophilia, Nair and colleagues (11) demonstrated

TABLE 4. ADVERSE EVENTS

|                                                                | Reslizumab, 3.0 mg/kg<br>(n = 53) | Placebo<br>(n = 53) |
|----------------------------------------------------------------|-----------------------------------|---------------------|
| Patients with at least one adverse event                       | 38 (71.7)                         | 42 (79.2)           |
| Patients with at least one serious adverse event               | 2 (3.8)                           | 1 (1.9)             |
| Patients who discontinued because of an adverse event          | 1 (1.9)                           | 1 (1.9)             |
| Adverse events that occurred in $\geq 3\%$ of reslizumab group |                                   |                     |
| Upper respiratory adverse events                               | 15 (28.3)                         | 12 (22.6)           |
| Nasopharyngitis                                                | 11 (20.8)                         | 5 (9.4)             |
| Sinusitis                                                      | 2 (3.8)                           | 2 (3.8)             |
| Upper respiratory tract infection                              | 2 (3.8)                           | 5 (9.4)             |
| Fatigue                                                        | 4 (7.5)                           | 2 (3.8)             |
| Pharyngolaryngeal pain                                         | 3 (5.7)                           | 0                   |
| Back pain                                                      | 2 (3.8)                           | 0                   |
| Bronchitis                                                     | 2 (3.8)                           | 3 (5.7)             |
| Erythema                                                       | 2 (3.8)                           | 1 (1.9)             |
| Headache                                                       | 2 (3.8)                           | 5 (9.4)             |
| Hypersensitivity                                               | 2 (3.8)                           | 1 (1.9)             |

Values represent number (%).

that treatment with anti-IL-5 reduced asthma exacerbations and the need for prednisone while improving asthma control and FEV<sub>1</sub>. In our 15-week study, few patients in either treatment group experienced exacerbations even though their baseline asthma control was worse than that observed in the study by Haldar and colleagues (19). Although the percentage of exacerbations in the reslizumab group was lower than that in the placebo group, the difference between the treatment groups did not reach statistical significance, probably because of the short duration of the study.

A novel aspect of the current study was the effect of reslizumab in those patients with uncontrolled asthma and nasal polyposis (Table 3). Nasal polyposis with or without chronic rhinosinusitis is due to chronic airway inflammation with abundant eosinophils and IFN- $\gamma$ , IL-4, IL-5, and IL-13 production (21–23). Furthermore, the mechanism of tissue eosinophilia in nasal polyposis is due to the delay of eosinophil apoptosis induced by IL-5 (24). A previous study of reslizumab in patients with chronic rhinosinusitis and nasal polyposis demonstrated that the best predictor of nasal symptom response to this therapy was nasal IL-5 levels (25). Therefore, it is likely that in this subset, patients with nasal polyposis have a disease process that is driven in part by eosinophils, as demonstrated by their higher baseline blood and sputum eosinophil levels, and response to inhibition of IL-5.

Reslizumab was generally well tolerated. The overall incidence of adverse events in the reslizumab group was similar to that of the placebo group, and most adverse events were mild or moderate in severity. Only nasopharyngitis occurred more frequently in the reslizumab group than in the placebo group, and this may have been the result of the disparity in nasal polyps between the treatment groups, because most of the patients with nasopharyngitis adverse events had nasal polyps at baseline. When upper respiratory adverse events were combined, the incidence in the reslizumab group was similar to that in the placebo group.

Previous studies have demonstrated a link between persistent airway eosinophilia and subsequent exacerbations of asthma (26). Furthermore, management strategies aimed at reducing sputum eosinophilia have demonstrated a reduction in exacerbations without an increase in need for corticosteroid use (5, 6). Together with the studies of mepolizumab (11, 19), these results suggest that reducing airway eosinophilia by anti-IL-5 therapy should reduce exacerbations of asthma. In our study, we observed a trend in this direction; however, the 15-week duration of this study limits the interpretive value of the results. The study may not have been long enough to evaluate the effect of reslizumab on clinical asthma exacerbations because few exacerbations were

observed even in the placebo group. In addition, our study did not enroll subjects who were taking oral corticosteroids or who had previous exacerbations requiring systemic corticosteroids. Therefore, the low frequency of exacerbations observed in our study may have been determined by the lack of a prior history of exacerbations. Although patients had poorly controlled asthma at baseline according to their ACQ score (mean, 2.8), this measure of asthma control probably reflects short-term events and not the long-term risk of exacerbations.

In conclusion, we have identified a phenotype of patients with uncontrolled, eosinophilic asthma who benefited from anti-IL-5 therapy with reslizumab. The reduction in eosinophils after inhibition of IL-5 improved asthma control (as measured by the ACQ) and airway function, particularly in patients with higher ACQ scores and nasal polyposis.

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