

Effects of Reslizumab on Asthma Outcomes in a Subgroup of Eosinophilic Asthma Patients with Self-Reported Chronic Rhinosinusitis with Nasal Polyps



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What is already known about this topic? An estimated 7% of patients with asthma have chronic rhinosinusitis with nasal polyps (CRSwNP) and more than 80% have radiographic evidence of sinonasal inflammation. Aspirin sensitivity is associated with elevated blood eosinophils and increased asthma severity.

What does this article add to our knowledge? In patients with elevated blood eosinophils and self-reported CRSwNP, reslizumab reduced asthma exacerbations and improved patient-reported asthma outcomes, regardless of whether or not the patient had concurrent self-reported aspirin sensitivity.

How does this study impact current management guidelines? Reslizumab may be considered as a treatment option in patients with severe eosinophilic asthma and CRSwNP.

BACKGROUND: An estimated 7% of patients with asthma have chronic rhinosinusitis with nasal polyps (CRSwNP), and more than 80% have at least some radiographic evidence of sinonasal inflammation. Aspirin sensitivity is strongly associated with elevated blood eosinophil levels and increased asthma severity. Intravenous (IV) reslizumab has been shown to improve asthma control in patients with nasal polyps.

OBJECTIVE: These *post hoc* analyses of pooled data from 2 BREATH phase 3 clinical trials, studies 1 and 2 (NCT01287039 and NCT01285323), examined asthma-related outcomes in patients with comorbid, self-reported CRSwNP with and without aspirin sensitivity.

METHODS: Patients aged 12–75 years with elevated blood eosinophils (≥ 400 cells/ μ L) and inadequately controlled asthma were randomized to receive placebo or reslizumab (3 mg/kg IV) every 4 weeks for 52 weeks. Patients continued their background asthma maintenance therapy during the study. Information regarding the presence of CRSwNP was obtained through patient-reported medical history.

RESULTS: Add-on reslizumab treatment reduced the frequency of clinical asthma exacerbations by 83% versus placebo among patients with CRSwNP. Among patients with and without aspirin sensitivity, reductions of 79% and 84%, respectively, were observed. Patients with CRSwNP (with and without aspirin

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Conflicts of interest: S. F. Weinstein has received research grants from GlaxoSmithKline (GSK), Teva Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, and Sanofi-Aventis; and is on the Advisory Board for Teva Pharmaceuticals and Genentech. R. K. Katial has received fees as a consultant from Teva Pharmaceuticals, AstraZeneca, and MEDA; and has received speaker fees from MEDA. P. Bardin has provided educational lectures for GSK, Boehringer Ingelheim, AstraZeneca, and Menarini; has received unrestricted research grants from GSK, Teva Pharmaceuticals, and Novartis; and has participated in Advisory Boards for GSK, AstraZeneca, Boehringer Ingelheim, and

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Abbreviations used

ACQ- Asthma control questionnaire
 AQLQ- Asthma quality of life questionnaire
 CAE- Clinical asthma exacerbations
 CMH- Cochran-Mantel-Haenszel
 CRS- Chronic rhinosinusitis
 CRSwNP- Chronic rhinosinusitis with nasal polyps
 CT- Computed tomography
 FEV₁- Forced expiratory volume in 1 second
 ICS- Inhaled corticosteroids
 IV- Intravenous
 LS- Least-squares
 mAb- Monoclonal antibody
 MCID- Minimum clinically important difference
 NP- Nasal polyps
 OCS- Oral corticosteroids
 RR- Rate ratio

sensitivity) treated with reslizumab add-on therapy also had significant improvements in lung function, as measured by forced expiratory volume in 1 second, compared with placebo. Among patients with CRSwNP, reslizumab was also associated with improvements in patient-reported asthma control and asthma quality of life.

CONCLUSIONS: Patients with eosinophilic asthma and self-reported CRSwNP, with and without aspirin sensitivity, are highly responsive to treatment with reslizumab for asthma-related outcomes. These findings suggest that prospective investigation of reslizumab in this patient population is warranted. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:589-96)

Key words: Eosinophilic asthma; Chronic rhinosinusitis; Nasal polyps; Reslizumab; Aspirin-exacerbated respiratory disease

The association between asthma, chronic rhinosinusitis (CRS), and nasal polyps (NP) is well established. It is estimated that 7% of patients with asthma have CRS with NP (CRSwNP) and more than 80% have radiographic evidence of sinonasal inflammation,¹ whereas asthma is reported in 26% to 48% of patients with CRSwNP.²⁻⁴ There is evidence that NP are more common in patients with asthma,⁵ that patients with CRSwNP are more likely to have asthma than those with CRS without NP,^{6,7} and that increased asthma severity is associated with greater sinonasal inflammation.⁸ Asthma in patients with CRSwNP tends to be severe, with a substantial effect on quality of life.^{9,10}

CRSwNP is associated with elevated eosinophil levels in patients with asthma,^{3,11-15} and the presence of NP may aid the identification of the subgroup of patients with uncontrolled eosinophilic asthma who are likely to benefit from anti-IL5 treatment.¹⁶ Eosinophilic CRSwNP is associated with increased Th2 cytokine levels, such as interleukins IL-4, IL-5, and IL-13, increased expression of the IL-5 receptor, and local production of IgE.¹⁷⁻²¹ IL-5 is a key factor involved in the chemotaxis, differentiation, activation, and survival of eosinophils, and plays a central role in the pathogenesis of eosinophilic NP.^{17-19,22} IL-5 levels have been shown to be increased in NP tissue compared

with nasal tissue from healthy individuals, and IL-5 levels correlate with the observed degree of tissue eosinophilia.^{13,17,23,24} High levels of eosinophils, IL-5, and IgE have been shown to be associated with recurrence of NP and need for sinus surgery.^{25,26} Aspirin sensitivity is also strongly associated with increased asthma severity and in certain cases with elevated eosinophil levels,²⁷⁻³⁰ and along with CRSwNP these are recognized features of aspirin-exacerbated respiratory disease.

Inhibition of IL-5 signaling has, therefore, been identified as a promising therapeutic approach for the treatment of eosinophilic CRSwNP.^{31,32} Reslizumab is an IgG4 kappa humanized monoclonal antibody (mAb) targeting the eosinophil viability-enhancing factor IL-5, and disrupts the maturation, activation, and survival of eosinophils.³³ In a pilot study investigating a single dose of reslizumab for treating 24 patients with CRSwNP, 50% achieved a reduction in NP score at 4 weeks.³¹ High IL-5 levels (>40 pg/mL) in nasal secretions at baseline were predictive of response.³¹ In a phase 2 clinical study of patients with inadequately controlled asthma and sputum eosinophilia, in the subgroup of patients with NP, reslizumab 3 mg/kg every 4 weeks significantly improved the patients' mean asthma control questionnaire-7 (ACQ-7) score compared with placebo.³⁴ Most notably, in 3 phase 3 placebo-controlled clinical trials from the BREATH program, including >1200 patients with inadequately controlled asthma and elevated blood eosinophil levels, intravenous (IV) reslizumab administered every 4 weeks was associated with a ≥50% reduction in asthma exacerbations, and significantly improved multiple measures of asthma control including forced expiratory volume in 1 second (FEV₁), asthma symptoms, and asthma-related quality of life.³⁵⁻³⁷

In this *post hoc* analysis of data in the combined patient population from 2 of the phase 3 trials from the BREATH program (referred to henceforth as the combined study population), we hypothesized that asthma-related outcomes with reslizumab versus placebo in the subgroup of patients with comorbid CRSwNP, with or without aspirin sensitivity, would be similar to those in the combined study population without CRSwNP.

METHODS

Study design

Patients with CRSwNP (with and without aspirin sensitivity) were identified, based on their reported medical histories, for inclusion in this *post hoc* analysis of pooled data in the combined study population from 2 duplicate 52-week studies forming part of the BREATH clinical trial program (study 1: NCT01287039 and study 2: NCT01285323). Other studies that investigated the effect of reslizumab and placebo in patients with eosinophilic asthma were excluded from this *post hoc* analysis due to differences in patient population and study duration.^{35,37}

The methodology for the 2 duplicate 52-week trials has been reported in detail elsewhere.³⁵ Briefly, patients aged 12-75 years with elevated blood eosinophils (≥400 cells/μL) and inadequately controlled asthma on at least medium-dose inhaled corticosteroids (ICS) were randomized to placebo or reslizumab (3 mg/kg IV every 4 weeks) for 52 weeks. Patients continued their background asthma maintenance therapy during the study. Ongoing treatment with oral corticosteroids (OCS, up to 10 mg per day of prednisone or equivalent total daily dose) was permitted during the studies. Information regarding the presence of CRS, NP, or aspirin sensitivity

was obtained by the investigative sites through the patient-reported medical history that consisted of yes/no questions regarding the comorbidities of interest. Nasal endoscopy, computed tomography (CT) sinus, and aspirin challenge were not required per protocol to verify the presence of CRSwNP or aspirin sensitivity.

Outcomes

The objective of this *post hoc* analysis was to examine asthma-related outcomes in the subgroup of patients with comorbid CRSwNP, with or without aspirin sensitivity. A clinical asthma exacerbation (CAE) was defined by worsening of asthma symptoms or lung function that required additional medical intervention beyond the usual care involving any of the following: systemic corticosteroid burst for ≥ 3 days; increase in baseline ICS dose (doubling or more); an unscheduled visit to a physician's office for urgent asthma treatment; an emergency department visit or hospitalization for asthma.³⁵ Lung function was measured by FEV₁. Patient-reported asthma control and asthma quality of life were measured using the ACQ-6 and asthma quality of life questionnaire (AQLQ), respectively. The number of upper respiratory tract infections observed during the study period was also assessed as a specific adverse event of interest.

Statistical analyses

The frequency of CAEs over 52 weeks for reslizumab versus placebo was represented by a rate ratio (RR). RRs were estimated using a stratified Cox regression model with baseline use of OCS (yes or no) and geographical region (United States or other) as stratification factors.

The mean change in FEV₁ over 52 weeks was calculated using a mixed-effect model repeated measurements analysis and adjusted for treatment, study visit, treatment by visit interaction, region, OCS used at enrollment, and sex as fixed factors, and height and baseline value, and patient as random effects. Data are presented as least-squares (LS) mean change from baseline.

Changes from baseline in ACQ-6 and AQLQ scores are presented as LS means. A Cochran-Mantel-Haenszel (CMH) test, stratified by study, region, and OCS use at enrollment, was used to analyze the proportion of patients achieving a 0.5-point decrease from baseline in ACQ-6 (the minimum clinically important difference [MCID]).³⁸ To analyze the proportion of patients achieving a 0.5-point increase from baseline in AQLQ (the MCID³⁹), the CMH test was further stratified to include age, group, and asthma exacerbations within 12 months before randomization.

The incidence of upper respiratory tract infections for reslizumab versus placebo in patients with CRSwNP was represented by an RR. A 2-sided *P* value was calculated using the Wald method.

Statistical analysis was performed using SAS v9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline demographics and disease characteristics

A total of 953 patients were included in studies 1 and 2. Of these, 150 patients (16%) had self-reported CRSwNP; the combined study population without CRSwNP therefore comprised 803 patients. Among the 150 patients with CRSwNP, 56 patients also reported aspirin sensitivity and 93 patients were without aspirin sensitivity; 1 patient from the placebo group was missing aspirin sensitivity status because the data field was not completed for this patient for this specific medical history

question. This patient was included in the overall CRSwNP population, but not included within the "with or without aspirin sensitivity" subgroups. Baseline patient demographics and disease characteristics among patients with CRSwNP, with and without aspirin sensitivity, and in the combined study population of patients without CRSwNP are shown in Table I. Baseline characteristics were similar among patients with CRSwNP with and without aspirin sensitivity (Table I). Compared with the combined study population without CRSwNP, patients with CRSwNP and those without aspirin sensitivity were older, and had lower body mass index and later onset of asthma (Table I). Mean blood eosinophil levels at baseline were high in all patients, with counts being significantly higher in patients with CRSwNP (884 cells/ μ L) and in those with and without aspirin sensitivity (777 and 952 cells/ μ L, respectively) than in the combined study population without CRSwNP (612 cells/ μ L). The number of CAEs in the previous 12 months was significantly lower in the combined study population without CRSwNP (1.83) than in patients with CRSwNP (2.68) and with or without aspirin sensitivity (2.34 and 2.86, respectively). In total, 88% of patients with CRSwNP used a long-acting β -agonist in addition to ICS, and 17% used OCS. Allergic sensitization (presence of at least 1 positive ImmunoCAP test ≥ 0.35) was more common in the overall population without CRSwNP (66%) than in the CRSwNP subgroups (Table I).

Clinical asthma exacerbation frequency

For all CAEs, the adjusted mean rate among all patients with CRSwNP was 0.56 with reslizumab versus 3.22 with placebo ($P < .001$; Figure 1). The adjusted mean CAE rate with reslizumab versus placebo was 0.59 versus 3.87 ($P < .001$) in patients without aspirin sensitivity, and 0.45 versus 2.12 ($P = .002$) in patients with aspirin sensitivity (Figure 1). These findings equate to relative reductions in the rate of CAE with reslizumab versus placebo of 84% (RR 0.15; 95% CI, 0.07, 0.32) in patients with CRSwNP without aspirin sensitivity, and 79% (RR 0.21; 95% CI, 0.08, 0.58) in patients with CRSwNP with aspirin sensitivity (Figure 1). The respective reduction in the rate of CAEs with reslizumab versus placebo in the combined study population without CRSwNP was 44% (Figure 1).

For CAEs requiring systemic corticosteroids for ≥ 3 days, the adjusted mean rate among all patients with CRSwNP was 0.51 with reslizumab versus 3.10 with placebo ($P < .001$; Figure 2). The adjusted mean rate with reslizumab versus placebo was 0.61 versus 3.56 ($P < .001$) in patients without aspirin sensitivity, and 0.29 versus 1.95 ($P = .001$) in patients with aspirin sensitivity (Figure 2). These findings equate to reductions in the CAE rate with reslizumab versus placebo of 83% in patients with CRSwNP without aspirin sensitivity and 85% in patients with CRSwNP with aspirin sensitivity (Figure 2). The respective reduction in the rate of CAEs with reslizumab versus placebo in the combined study population without CRSwNP was 47% (Figure 2).

Lung function

Patients with CRSwNP treated with reslizumab showed greater improvements in FEV₁ versus placebo, with improvements evident at 4 weeks and sustained for the duration of the study (Figure E1, available in this article's Online Repository at

TABLE 1. Baseline demographics and disease characteristics of patients with CRSwNP (with and without aspirin sensitivity), irrespective of treatment with reslizumab or placebo

	Combined study population without CRSwNP (N = 803)	Patients with CRSwNP* (N = 150) [†]	Patients with CRSwNP without aspirin sensitivity (N = 93)	Patients with CRSwNP with aspirin sensitivity (N = 56)
Age, mean (SD), y	46.0 (14.4)	51.1 (11.2) [‡]	51.5 (11.7) [‡]	50.4 (10.6) [‡]
Male, %	37	38	44	29
BMI, mean (SD), kg/m ²	27.6 (5.9)	26.4 (4.8) [‡]	26.1 (5.0) [‡]	26.9 (4.6)
Age of asthma onset, mean (SD), y	26.4 (18.4)	33.5 (15.4) [‡]	34.9 (15.1) [‡]	31.6 (15.7) [‡]
No. of CAEs within last 12 mo, mean (SD)	1.83 (1.61)	2.68 (2.69) [‡]	2.86 (2.57) [‡]	2.34 (2.89) [‡]
FEV ₁ , mean (SD), L	1.99 (0.76)	1.97 (0.66)	1.97 (0.72)	1.98 (0.55)
% predicted FEV ₁ , mean (SD)	66.78 (20.08)	66.2 (17.8)	65.35 (19.76)	68.00 (13.82)
FVC, mean (SD), L	3.03 (1.04)	3.08 (0.88)	3.09 (0.88)	3.09 (0.87)
FEV ₁ /FVC, mean (SD), L	0.66 (0.12)	0.64 (0.11)	0.64 (0.12)	0.65 (0.10)
FEV ₁ % reversibility, mean (SD)	27.7 (18.9)	25.1 (16.5)	26.4 (17.2)	22.8 (15.2)
LABA use, n (%)	648 (81)	132 (88) [‡]	84 (90) [‡]	47 (84)
OCS use, n (%)	120 (15)	26 (17)	19 (20)	7 (13)
ACQ-6, mean (SD) score	2.45 (0.90)	2.63 (0.96) [‡]	2.61 (0.98)	2.65 (0.96)
AQLQ, mean (SD) score	4.28 (1.08)	4.13 (1.09)	4.30 (1.08)	4.10 (1.11)
Blood eosinophils, mean (SD), cells/μL	612 (503)	884 (1050.5) [‡]	952 (1260.0) [‡]	777 (557.6) [‡]
Allergic sensitization (specific IgE), [§] n (%)	272 (66)	31 (41) [‡]	22 (43) [‡]	9 (36) [‡]

ACQ, Asthma control questionnaire; AQLQ, asthma quality of life questionnaire; BMI, body mass index; CAE, clinical asthma exacerbation; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LABA, long-acting beta-agonist; OCS, oral corticosteroid; SD, standard deviation.

*Patient reported (nasal endoscopy and/or CT sinus were not completed as part of this study).

[†]One patient from the placebo group missing aspirin sensitivity status (the data field was not completed for this patient for this specific medical history question).

[‡] $P < .05$ vs the combined study population without CRSwNP.

[§]Presence of at least one ImmunoCAP test positive (≥ 0.35), measured in only 1 of the 2 studies. Percentages relate to the study population of the study in which ImmunoCAP measurements were recorded.

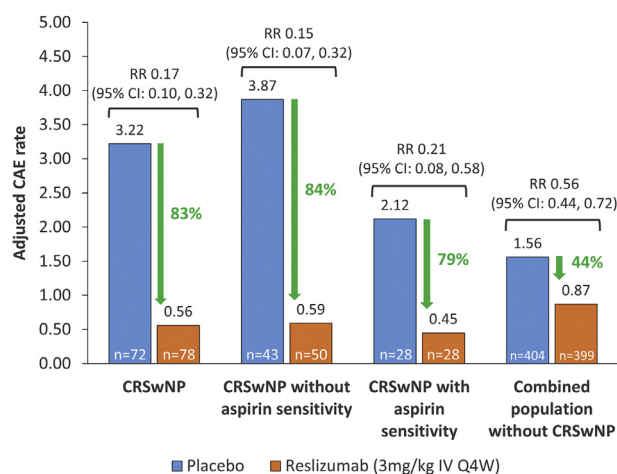


FIGURE 1. Frequency of all clinical asthma exacerbations (CAE) over 52 weeks with reslizumab IV or placebo in patients with eosinophilic asthma with CRSwNP (with or without aspirin sensitivity) and in the combined population of patients without CRSwNP. CI, Confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; IV, intravenous; Q4W, every 4 weeks; RR, rate ratio.

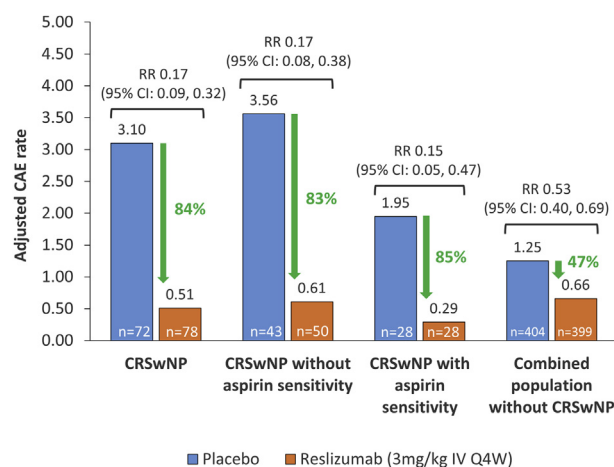


FIGURE 2. Frequency of clinical asthma exacerbations (CAE) requiring a course of systemic corticosteroids prescribed for ≥ 3 days over 52 weeks with reslizumab IV or placebo in patients with eosinophilic asthma with CRSwNP (with or without aspirin sensitivity) and in the combined population of patients without CRSwNP. CI, Confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; IV, intravenous; Q4W, every 4 weeks; RR, rate ratio.

www.jaci-inpractice.org). Among all patients with CRSwNP, the LS mean change from baseline in FEV₁ over 52 weeks was 0.327 L with reslizumab versus 0.002 L with placebo ($P < .001$; Figure E1). The LS mean change from baseline in FEV₁ over

52 weeks with reslizumab versus placebo was 0.315 L versus -0.036 L ($P < .001$) in patients without aspirin sensitivity, and 0.451 L versus 0.124 L ($P = .004$) in aspirin-sensitive patients (Figure E1).

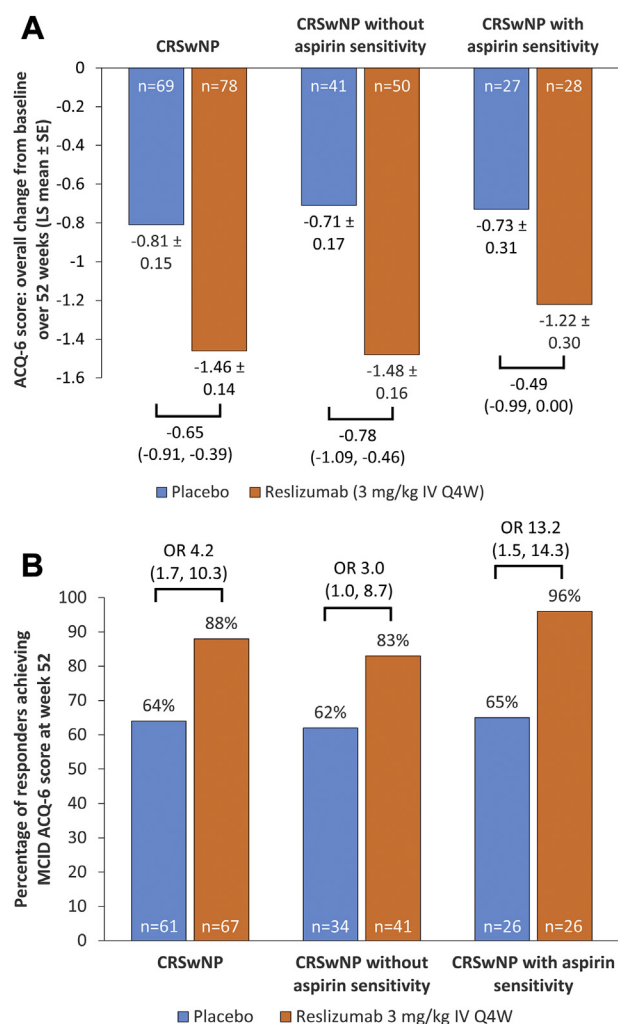


FIGURE 3. Change from baseline at week 52 in ACQ-6 score (A) and proportion of patients with improvements exceeding the minimal clinically important difference (MCID) (B) with reslizumab IV or placebo in patients with eosinophilic asthma with CRSwNP (with or without aspirin sensitivity). A, ACQ-6 score change from baseline; B, ACQ-6 responders. Values in parentheses represent 95% confidence intervals. MCID defined as a 0.5-point decrease from baseline in ACQ-6 score. ACQ, Asthma control questionnaire; CRSwNP, chronic rhinosinusitis with nasal polyps; IV, intravenous; LS, least squares; OR, odds ratio; Q4W, every 4 weeks; SE, standard error.

Patient-reported outcomes

Among all patients with CRSwNP, the LS mean ACQ-6 score at 52 weeks was reduced from baseline by 1.46 points with reslizumab versus 0.81 points with placebo (treatment difference -0.65 ; $P < .001$; Figure 3, A). For patients without aspirin sensitivity, the LS mean ACQ-6 score fell by -1.48 points with reslizumab versus -0.71 points with placebo (treatment difference -0.78 ; $P < .001$; Figure 3, A). In those with aspirin sensitivity, there was a greater reduction from baseline in the LS mean ACQ-6 score with reslizumab versus placebo (-1.22 vs -0.73 points); however, this difference did not reach statistical significance (-0.49 ; $P = .0501$; Figure 3, A).

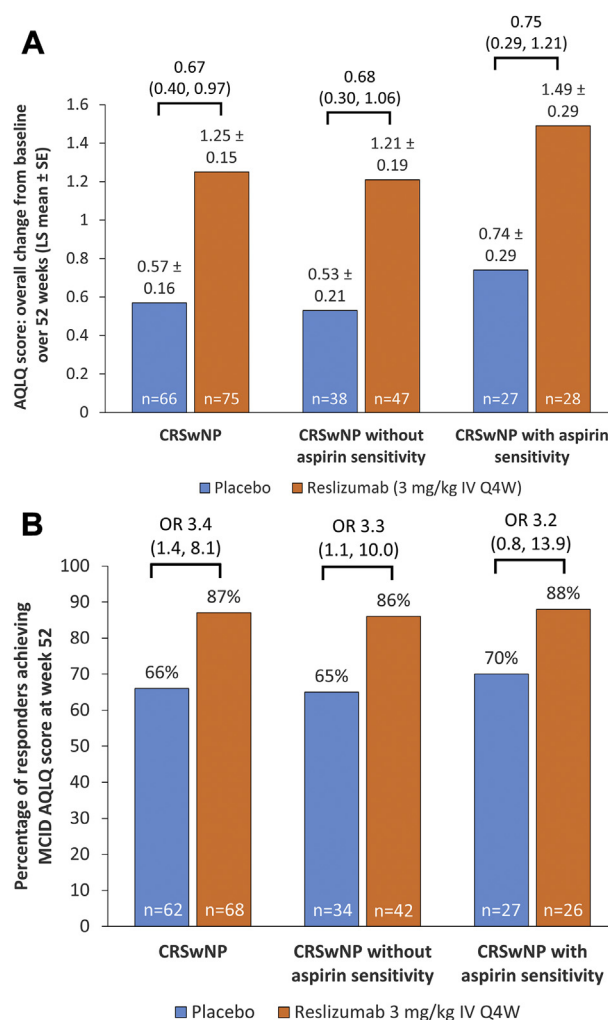


FIGURE 4. Change from baseline at week 52 in AQLQ score (A) and proportion of patients with improvements exceeding the minimal clinically important difference (MCID) (B) with reslizumab IV or placebo in patients with eosinophilic asthma with CRSwNP (with or without aspirin sensitivity). A, AQLQ score change from baseline; B, AQLQ responders. Values in parentheses represent 95% confidence intervals. MCID defined as a 0.5 increase from baseline in AQLQ score. AQLQ, Asthma quality of life questionnaire; CRSwNP, chronic rhinosinusitis with nasal polyps; IV, intravenous; LS, least squares; OR, odds ratio; Q4W, every 4 weeks; SE, standard error.

The responder rate, in terms of change in ACQ-6 score at week 52 (ie, proportion of patients with ≥ 0.5 -point reduction in score), was significantly higher among patients with CRSwNP treated with reslizumab versus placebo (88% vs 64%; $P = .002$; Figure 3, B). The responder rate was also significantly higher with reslizumab versus placebo among patients without (83% vs 62%; $P = .04$) and with (96% vs 65%; $P = .009$) aspirin sensitivity (Figure 3, B).

Among all patients with CRSwNP, the LS mean AQLQ score at week 52 increased from baseline by 1.25 points with reslizumab versus 0.57 points with placebo (treatment difference 0.69; $P < .001$; Figure 4, A). For patients without aspirin sensitivity,

the LS mean AQLQ score increased by 1.21 points with reslizumab versus 0.53 points with placebo (treatment difference 0.68; $P < .001$), and in those with aspirin sensitivity it increased by 1.49 points versus 0.74 (treatment difference 0.75; $P = .002$; Figure 4, A). There was also a significantly higher responder rate with reslizumab versus placebo in patients with CRSwNP overall (87% vs 66%; $P = .005$) and in those without aspirin sensitivity (86% vs 65%; $P = .03$; Figure 4, B). However, among patients with aspirin sensitivity, the difference between groups did not reach statistical significance (88% vs 70%; $P = .13$; Figure 4, B).

Differences in the mean change between reslizumab and placebo exceeded the MCID for both ACQ-6 and AQLQ scores, except for ACQ-6 scores in patients with CRSwNP with aspirin sensitivity (Figures 3 and 4).

Data on respiratory tract infections are provided in this article's [Online Repository](http://www.jaci-inpractice.org) at www.jaci-inpractice.org.

DISCUSSION

In the pivotal BREATH clinical trials, reslizumab demonstrated efficacy in reducing the frequency of CAEs, and improving lung function, asthma control, and quality of life in patients with inadequately controlled asthma and elevated blood eosinophil levels (≥ 400 cells/ μ L).³⁵ In the current *post hoc* analyses of a subgroup of patients from these trials, patients with a self-reported medical history of CRSwNP were highly responsive to treatment with reslizumab 3 mg/kg every 4 weeks for asthma-related outcomes.

It is noteworthy that the overall effects on CAE rate were not inferior in the patient subgroup with comorbid CRSwNP than in the combined study population without CRSwNP. Baseline eosinophil levels were high in both the CRSwNP subgroup and combined study population without CRSwNP. Although baseline eosinophils levels were significantly higher in the CRSwNP population, it is not expected that higher baseline levels are the main predictor of efficacy in this population. For other efficacy endpoints, it has previously been shown that a positive relationship was observed between baseline blood eosinophils and change from baseline in FEV₁ for reslizumab.⁴⁰ However, the interaction between treatment and the relationship between baseline eosinophils and FEV₁ did not achieve statistical significance, suggesting that the cutoff for efficacy is approximately >400 cells/ μ L.⁴⁰

Previous findings from subgroup analyses of a phase 2 clinical study of patients with inadequately controlled asthma and sputum eosinophilia also suggested that reslizumab was effective in improving asthma control in patients with NP.³⁴ The phase 2 study, however, did not require patients to have exacerbation history, was not primarily designed to assess CAE frequency, and the study duration was limited to 15 weeks. Thus, our *post hoc* analysis of two 52-week phase 3 clinical trials provides a strong dataset to further investigate the impact of reslizumab on asthma exacerbations and other measures of asthma control in patients with CRSwNP, and overall the findings suggest that the additional comorbidities of CRSwNP do not diminish treatment response to reslizumab.

These analyses demonstrated similar efficacy of reslizumab treatment in eosinophilic patients with CRSwNP and aspirin sensitivity and patients with CRSwNP but without aspirin sensitivity, indicating that anti-IL5 therapy is effective in both patient populations, as might be expected. To date, the literature

regarding the role of eosinophils in aspirin sensitivity is unclear. Some previous studies have shown an increase in levels of eosinophilic cationic protein and eosinophils in aspirin-sensitive patients.^{41,42} In contrast, a retrospective study by Fountain et al²⁸ that examined patients with CRSwNP failed to show a statistically significant difference in serum eosinophil levels between aspirin-sensitive and aspirin-tolerant populations. Given that the inclusion criteria for these studies selected for patients who were eosinophilic at baseline, additional studies may be required to further elucidate the relationship between IL-5, eosinophils, and aspirin sensitivity.

Reslizumab treatment was associated with fewer reported upper respiratory tract infections compared with placebo. The reason for this observation is unclear but might relate to a reduction in the size of NP (reslizumab would be expected to reduce eosinophilic inflammation in the upper airway) allowing better drainage, thereby ameliorating upper respiratory symptoms. It is also possible that some cases of upper respiratory tract inflammation were misclassified as infection. Nasal endoscopic evaluation at the time of reported infection would provide further insight.

The findings of our analyses suggest that reslizumab, along with other biologics whose actions involve the inhibition of Th2 inflammatory cytokines, may warrant further investigation with respect to clinical outcomes in patients with asthma and comorbid CRSwNP. Mepolizumab, another humanized anti-IL-5 mAb, and dupilumab, a fully human IL-4 receptor α subunit mAb that inhibits IL-4 and IL-13 signaling, have also been investigated in patients with CRSwNP.^{32,43} In a phase 2 study of patients with severe nasal polyposis that was refractory to corticosteroids, significantly improved NP scores and CT scan scores were reported at week 8 versus baseline in 12 of 20 (60%) patients who received mepolizumab, compared with 1 of 10 (10%) patients who received placebo.³² Mepolizumab treatment compared with placebo reduced the need for surgery and improved symptoms in patients with recurrent nasal polyposis.⁴⁴ In a phase 2 study of patients with CRSwNP refractory to intranasal corticosteroids, greater LS mean changes in NP score and Lund-Mackay total score were reported with dupilumab ($N = 30$) compared with placebo plus mometasone furoate nasal spray ($N = 30$) over 16 weeks.⁴³ FEV₁ and ACQ-5 scores improved with dupilumab compared with placebo in patients with comorbid asthma.

The analyses we present here have limitations. First, these were *post hoc* analyses of 2 clinical trials of patients with inadequately controlled eosinophilic asthma. Owing to the small sample size, the number and types of statistical analyses that could be carried out were limited. The 2 clinical trials included in the analysis were designed to assess asthma-related outcomes and not NP-related outcomes, which precludes assessment of outcomes typically used in CRSwNP, such as NP score, and possibly limits the generalizability of our findings in this population. Furthermore, patients were categorized as having CRSwNP and aspirin sensitivity based solely on their self-reported medical history. According to the European Position Paper on Rhinosinusitis and Nasal Polyps, the diagnosis of CRS, with or without NP, requires subjective assessment of symptoms that are supported by demonstrable disease using endoscopy and/or CT changes and mucosal changes within the ostiomeatal complex and/or sinuses.⁴⁵ Although it is appropriate that the definition of CRS is symptom based, as symptoms stimulate patients to

consult a health care professional, the use of endoscopy or CT improves diagnostic accuracy of CRS.⁴⁶ In a study by Bhattacharyya and Lee,⁴⁶ 31% of patients failing to meet symptom or endoscopic criteria had positive CT scans, indicating that patients who are not symptomatic may still have demonstrable disease based on imaging criteria. Therefore, the incidence of CRSwNP in the combined population of our study may have been higher. Indeed, nasal endoscopy, CT sinus, and aspirin challenge would have provided greater diagnostic accuracy in this analysis; however, these studies were originally designed to assess the overall asthma patient population and, therefore, did not include these assessments. Owing to the *post hoc* nature of these analyses, the lack of data on NP-related outcomes, and the limitations to verification of CRSwNP diagnosis, subsequent studies should consider examining outcomes typically used in CRSwNP and utilizing endoscopic and/or imaging measures to demonstrate the presence of CRSwNP.

Overall, our findings suggest that reslizumab is highly effective for asthma-related outcomes in patients with inadequately controlled eosinophilic asthma and self-reported CRSwNP, with similar results in patients who have self-reported aspirin sensitivity. Given these encouraging data, and our current understanding of the role of IL-5 in the pathophysiology of NP, a prospective study of reslizumab treatment in patients with CRSwNP is warranted.

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ONLINE REPOSITORY

RESPIRATORY TRACT INFECTIONS

The overall incidence of upper respiratory tract infections for all patients with chronic rhinosinusitis with nasal polyps was 36% with reslizumab versus 57% with placebo (rate ratio: 0.63; $P = .01$; [Table E1](#)). For those without and with aspirin sensitivity, the corresponding incidences were 36% versus 56% and

36% versus 61%, respectively. Most of the upper respiratory tract infections in the reslizumab group were mild, with 15 (54%) patients experiencing an event that was moderate in severity, and no patients experiencing severe events. In this group, no upper respiratory tract infections were serious adverse events or led to discontinuation. In the placebo group, most of the events were moderate, with 32 (78%) patients experiencing a moderate event, and one patient experiencing a severe event.

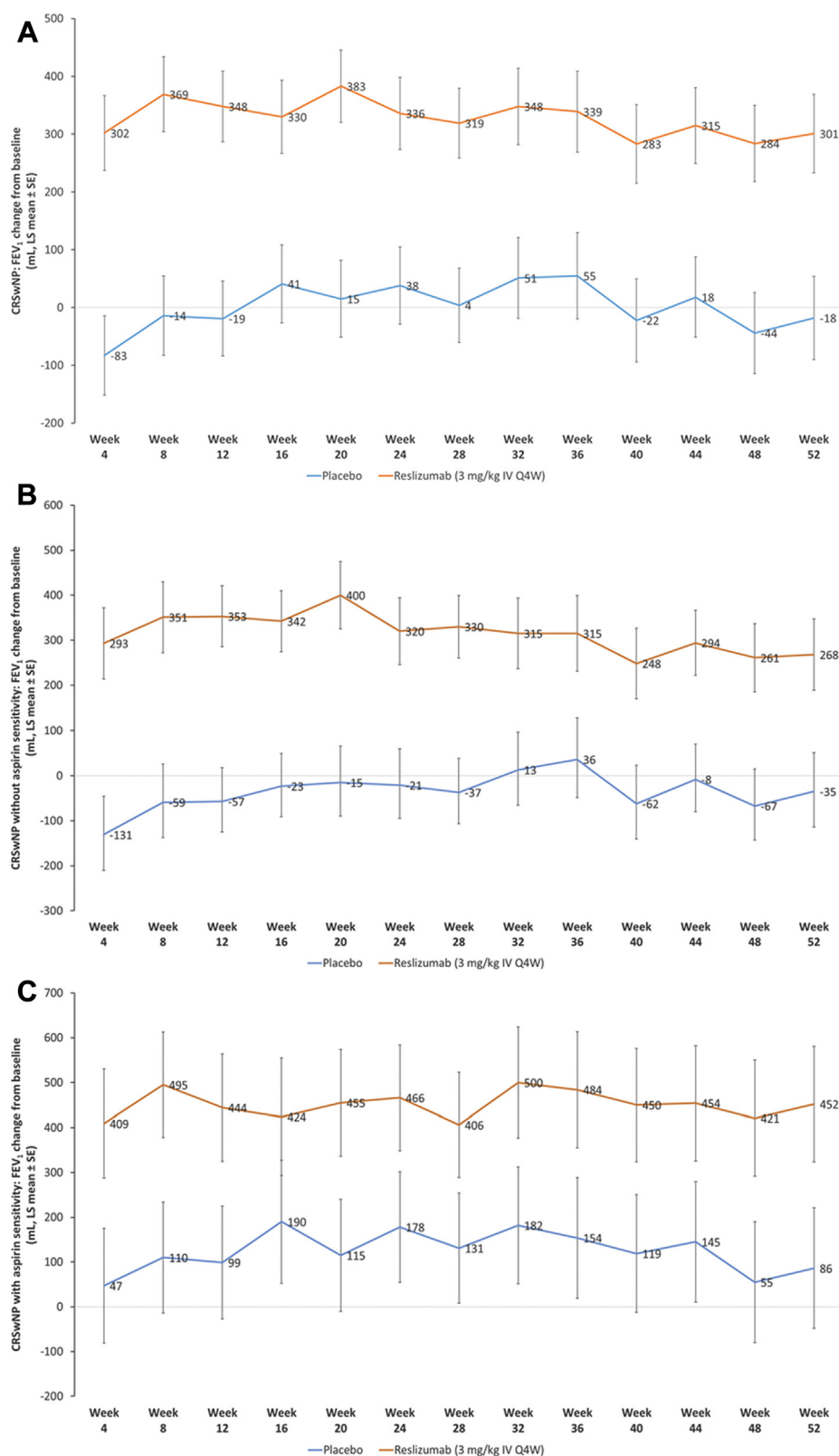


FIGURE E1. Change from baseline in FEV₁ over 52 weeks with reslizumab or placebo in patients with (A) CRSwNP; (B) CRSwNP without aspirin sensitivity; and (C) CRSwNP with aspirin sensitivity. Results were analyzed using mixed-effect model repeat measurements, adjusted for treatment, study visit, treatment by visit interaction, region, OCS used at enrollment, and sex as fixed factors, and height and baseline value, and patient as random effects. For reslizumab versus placebo: $P < .001$ for all timepoints for CRSwNP, and for all timepoints for CRSwNP without aspirin sensitivity; $P < .05$ for all timepoints for CRSwNP with aspirin sensitivity, except for week 16. CRSwNP, Chronic rhinosinusitis with nasal polyps; FEV₁, forced expiratory volume in 1 second; OCS, oral corticosteroid.

TABLE E1. Respiratory tract infections observed during treatment

High-level term Preferred term	Patients with CRSwNP (N = 150)*		Patients with CRSwNP without aspirin sensitivity (N = 93)		Patients with CRSwNP with aspirin sensitivity (N = 56)	
	Placebo (n = 72)	Reslizumab (n = 78)	Placebo (n = 43)	Reslizumab (n = 50)	Placebo (n = 28)	Reslizumab (n = 28)
Upper respiratory tract infections	41 (57)	28 (36)	24 (56)	18 (36)	17 (61)	10 (36)
Sinusitis	11 (15)	9 (12)	5 (12)	3 (6)	6 (21)	6 (21)
Upper respiratory tract infection	10 (14)	5 (6)	8 (19)	1 (2)	2 (7)	4 (14)
Nasopharyngitis	14 (19)	12 (15)	8 (19)	9 (18)	6 (21)	3 (11)
Chronic sinusitis	6 (8)	4 (5)	4 (9)	2 (4)	2 (7)	2 (7)
Acute sinusitis	5 (7)	3 (4)	5 (12)	2 (4)	0	1 (4)
Acute tonsillitis	2 (3)	0	1 (2)	0	1 (4)	0
Pharyngitis	1 (1)	1 (1)	0	1 (2)	1 (4)	0
Rhinitis	4 (6)	3 (4)	3 (7)	3 (6)	1 (4)	0
Tracheitis	1 (1)	0	0	0	1 (4)	0

Reported AEs of respiratory tract infections in patients with CRSwNP reflect clinically relevant worsening of symptoms from baseline.

AE, Adverse event; CRSwNP, chronic rhinosinusitis with nasal polyps.

*One patient from the placebo group is missing aspirin sensitivity status (data field was not completed for this patient for this specific medical history question).