

Original Article

Efficacy of Intravenous Reslizumab in Oral Corticosteroid–Dependent Asthma

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What is already known about this topic? Reslizumab efficacy has been demonstrated in phase 3 asthma clinical trials, but only limited data have been published for oral corticosteroid–dependent patients.

What does this article add to our knowledge? Reslizumab is efficacious in the oral corticosteroid–dependent population, and was associated with reductions in systemic corticosteroid burden in the overall population.

How does this study impact current management guidelines? These data support the benefit of biologic add-on therapy to improve asthma outcomes in patients with severe oral corticosteroid–dependent asthma.

BACKGROUND: Reslizumab displays efficacy in patients with inadequately controlled eosinophilic asthma; previous reports in oral corticosteroid–dependent asthma are limited.

OBJECTIVE: To assess efficacy of reslizumab in oral corticosteroid–dependent patients and benefits on oral corticosteroid burden.

METHODS: We report *post hoc* analyses of pooled data from duplicate, placebo-controlled phase 3 trials. Patients aged 12 to 75 years with inadequately controlled, moderate-to-severe asthma were randomized 1:1 to receive intravenous reslizumab 3.0 mg/kg or placebo every 4 weeks for 52 weeks, stratified by oral corticosteroid use at enrollment and by region. Assessments included efficacy and predictors of clinical asthma exacerbation response in oral corticosteroid–dependent patients, and systemic corticosteroids burden in the overall population.

RESULTS: Patients were randomized to reslizumab ($n = 477$) or placebo ($n = 476$); 73 (15%) patients in each group were taking oral corticosteroids at baseline. Reslizumab was favored over placebo for all efficacy end points in oral corticosteroid–dependent patients, with numerically greater improvements in oral corticosteroid–dependent patients than the overall population. Having 2 or more versus 1 clinical asthma exacerbation in the previous 12 months was the strongest positive predictor of reduced exacerbation risk with reslizumab (risk reduction, 77.5% vs 15.2%; $P \leq .02$). Significantly fewer new systemic corticosteroid prescriptions were issued per patient receiving reslizumab versus placebo (mean $\pm$ SD, 0.5 ± 1.07 vs 1.0 ± 1.52 ; $P < .0001$). Total and per-patient systemic corticosteroid burdens were lower: 121,135 versus 290,977 mg and 254 versus 611 mg/patient, respectively (both $P < .0001$).

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The studies (NCT01287039 and NCT01285323) described in this article were funded by Teva Pharmaceuticals, Inc. The primary outcomes of these studies have been published previously. The sponsor had a role in the design and conduct of the studies, and in the collection, analysis, and interpretation of the data presented in this article. The authors of this report include employees of the sponsor. All authors participated in the development of the report and approved it for submission for publication.

Conflicts of interest: P. Nair has received grant support from AstraZeneca (AZ), Novartis, Teva, GlaxoSmithKline (GSK), and Sanofi in relation to clinical trials; has received consultancy fees from Roche, Teva, GSK, and Knopp; and has received honoraria for lectures from Novartis. P. Bardin has provided educational lectures for GSK, Boehringer Ingelheim (BI), AZ, Novartis, and Menarini; has received unrestricted research grants from GSK, Teva, and Novartis; and has participated in advisory boards for GSK, AZ, BI, and Novartis. M. Humbert

has received personal fees from AZ, GSK, Novartis, Roche, and Teva. K. R. Murphy has received consultancy and speaker fees and has participated in advisory boards for AZ, BI, Genentech, Greer, Meda, Merck, Mylan, Novartis, and Teva. M. Garin and R. Vanlandingham are employees of Teva Pharmaceuticals. L. Hickey is a former employee of Teva Pharmaceuticals. P. Chanez has provided consultancy services for BI, Centocor, GSK, Merck Sharp & Dohme (MSD), AZ, Novartis, Teva, Chiesi, SNCF, and ALK; has served on advisory boards for BI, Centocor, GSK, AZ, Novartis, Teva, Chiesi, Boston Scientific, ALK, and MSD; has received lecture fees from Boston Scientific, BI, Centocor, GSK, AZ, Novartis, Teva, and Chiesi; and has received industry-sponsored grants from ALK, BI, Centocor, GSK, AZ, Novartis, Teva, Chiesi, and Roche.

Received for publication April 8, 2019; revised August 14, 2019; accepted for publication September 30, 2019.

Available online ■ ■ ■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.09.036>

*Abbreviations used**AE- Adverse event**IV- Intravenous**OCS- Oral corticosteroid**SAE- Serious adverse event**SCS- Systemic corticosteroid*

CONCLUSIONS: Oral corticosteroid–dependent patients benefited from reslizumab across asthma efficacy outcome measures. Reslizumab-treated patients required fewer new systemic corticosteroid prescriptions and had a lower systemic corticosteroid burden compared with placebo. © 2019 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Severe asthma; Eosinophil; IL-5; Oral corticosteroid; Prednisone; Reslizumab

INTRODUCTION

Elevated blood eosinophil levels are associated with severe asthma and symptoms, reduced lung function, and increased risk of asthma exacerbations,¹⁻⁴ often requiring emergency department visits or hospitalization. Despite new therapies for severe asthma, a significant number of patients have frequent need for burst oral corticosteroids (OCSs) or are on daily maintenance OCS, contributing to significant side-effect–related morbidity.⁵

In patients with eosinophilic asthma, the cytokine IL-5 plays an important role in driving eosinophilia and has been identified as a key therapeutic target with the potential to control eosinophilic asthma symptoms.⁶ The OCS-sparing efficacy of the IL-5 inhibitor mepolizumab and the IL-5 receptor inhibitor benralizumab are well established.^{7,8}

Reslizumab is an IgG₄ kappa humanized mAb that also targets IL-5, disrupting the maturation, activation, and survival of eosinophils,⁹ thereby reducing airway eosinophil levels.^{10,11} Reslizumab is indicated as an add-on maintenance treatment for adult patients with severe eosinophilic asthma¹² and administered intravenously and dosing according to a patient's body weight.

The results from 2 pivotal, 52-week, phase 3 trials (part of the BREATHE program) in patients with inadequately controlled moderate-to-severe eosinophilic asthma and a history of asthma exacerbations demonstrated that IV reslizumab, dosed at 3.0 mg/kg IV every 4 weeks, significantly reduced the risk of clinical asthma exacerbations, and improved asthma control, lung function, and quality of life.¹³ However, beyond these reports, there are only limited data demonstrating the effectiveness of IV reslizumab in patients with severe OCS-dependent eosinophilic asthma.¹⁴ To date, there are no published OCS-sparing data pertaining to IV reslizumab 3.0 mg/kg, which is the recommended dose. There is evidence to suggest that, specifically in patients with prednisone-dependent eosinophilic asthma, underdosing with an anti-IL-5 neutralizing antibody may not be effective or may worsen asthma.¹⁵ This is particularly relevant in patients on moderate to high doses of prednisone. The mechanism is proposed to be related to the development of

immune complexes between IL-5, anti-IL-5 mAbs, and the endogenous IgG autoantibodies, and subsequent complement activation.¹⁶ Immune complex formation with complement activation was not demonstrated in patients treated with reslizumab. Given these results, it is hypothesized that the weight-based dosing regimen of IV reslizumab results in sufficient systemic reslizumab exposures and airway reslizumab concentrations to prevent autoimmune-associated asthma worsening in OCS-dependent patients.

The main objective of this current analysis of phase 3 data was to assess the ability of weight-based IV reslizumab to improve asthma outcomes in patients dependent on maintenance OCSs. Baseline predictors of reduction in asthma exacerbation risk and incidence of adverse events (AEs) were also examined in patients who were taking OCS at baseline. We hypothesized that the beneficial effects of reslizumab in those patients who required daily OCS for their asthma control would be at least as great as in those who did not require daily OCS in addition to inhaled corticosteroids. A secondary objective was to assess the effect of reslizumab on cumulative systemic corticosteroid (SCS) burden during a 52-week treatment period compared with placebo in the overall study population.

METHODS

Study design and patients

Patients with inadequately controlled, moderate-to-severe asthma participated in duplicate, multicenter, double-blind, parallel-group, placebo-controlled phase 3 trials (part of the reslizumab BREATHE program). In both studies (NCT01287039 and NCT01285323), patients were randomized 1:1 to receive IV reslizumab 3.0 mg/kg once every 4 weeks or matching placebo for 52 weeks and were stratified by regular maintenance OCS use at enrollment (OCS vs non-OCS as determined by site) and by region (the United States or other). Detailed methods have been described previously.¹³ The primary outcome of the trials was the annual frequency of clinical asthma exacerbations in the intent-to-treat population. Clinical asthma exacerbations were defined as worsening asthma that resulted in use of SCS, including OCS and injectable corticosteroids, in patients not already receiving them, or a doubling of SCS dose for 3 or more days, or the need for emergency intervention including emergency department visit, hospitalization, or unscheduled physician visit.¹³ Such interventions were required to be associated with a greater than or equal to 20% decrease in FEV₁ from baseline, a greater than or equal to 30% decrease in reduction in peak expiratory flow rate from baseline on 2 consecutive days, or a physician-identified worsening of asthma signs and symptoms. All clinical asthma exacerbation events were adjudicated by an independent review committee.

Patients were aged 12 to 75 years and had inadequately controlled eosinophilic asthma on medium-to-high doses of inhaled corticosteroid (ICS)-based therapy as described previously.¹³ Eligible patients had experienced at least 1 asthma exacerbation in the year before study entry. Allowed baseline OCS use was limited to less than or equal to 10 mg prednisone or equivalent daily, and maintenance OCS use during the study was permitted with the same dose limitation.

Per protocol, baseline asthma controller medications, including maintenance daily OCS, could not be changed during the study.

Full details of the inclusion and exclusion criteria have also been reported previously.¹³

Written informed consent was obtained from all study participants. The study protocols were reviewed and approved by the appropriate review boards or institutional ethics committees and health authorities. The studies were conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines, and applicable regulatory requirements.

Current analyses

Post hoc analyses of pooled data from the 2 studies were performed to determine the efficacy of reslizumab in the subpopulation of patients taking OCS at baseline versus those who were not. The following efficacy outcomes were assessed: all clinical asthma exacerbations, clinical asthma exacerbations requiring SCS, clinical asthma exacerbations requiring emergency department visit or hospitalization, FEV₁, percent predicted FEV₁, and forced vital capacity.

A further objective was to determine predictors of clinical asthma exacerbation response in OCS-dependent patients including the effect of age, sex, race, body mass index, weight, number of exacerbations in the previous year, late-onset asthma, atopic status, chronic rhinosinusitis with nasal polyps, and blood eosinophil count. Exacerbation risk was stratified by each of these baseline characteristics.

Post hoc analyses were also performed to determine the effect of reslizumab compared with placebo on cumulative SCS requirement during the 52-week study period. The number of new SCS prescriptions and cumulative SCS dose (prednisone-equivalent) in each study treatment group were examined. SCS use in several at-risk patient categories was also examined, including the following: Global Initiative for Asthma step 4/5 patients (taking medium- to high-dose inhaled corticosteroids plus long-acting β -agonists and who would otherwise be regarded as severe), patients with high body weight (≥ 81 kg), and patients who had chronic rhinosinusitis with nasal polyps.

New prescriptions for SCS (IV, intramuscular, or oral) indicated for cases of clinical asthma exacerbations and/or for asthma with a start date after the first dose of study drug were counted. All new discrete SCS prescriptions, except those with start date of less than 7 days after the end date of the previous prescription, which were counted as part of the previous prescription, were included in the analysis. The total cumulative dose of SCS use was calculated as the sum of prescriptions multiplied by duration and expressed as prednisone-equivalent doses.

Statistical analyses

Statistical analyses for the individual studies have been reported in detail previously.¹³

For the current analysis of reslizumab efficacy in patients receiving baseline OCS, adjusted clinical asthma exacerbation rates and rate ratios, corresponding 95% CIs, and *P* values were based on a negative binomial model adjusted for geographical region (the United States or other), treatment arm, baseline OCS use, and interaction between baseline OCS use and treatment arm. This model was run including each of the selected baseline demographic and asthma characteristic subgroups to explore predictors of clinical asthma exacerbation response in OCS-dependent patients.

FEV₁, FEV₁ percent predicted, and forced vital capacity mean changes from baseline were analyzed using a mixed-effect repeated-measurement model with treatment, study visit, treatment by visit interaction, region, OCS use, and OCS use by treatment as fixed factors and baseline value as a covariate. Unstructured covariance was assumed.

Descriptive statistics were reported for AEs that occurred during the study treatment period in the OCS-dependent population.

For the overall population and at-risk subgroups, the number of SCS prescriptions for patients receiving reslizumab versus placebo was compared using a negative binomial regression model adjusted for stratification factors (baseline OCS use [yes or no] and geographical region [the United States or other]). The percentage of patients prescribed SCS during the treatment period was summarized. ANOVA with fixed effects for treatment, baseline OCS use, and geographical region was used to analyze cumulative SCS use (burden, reported in milligram [prednisone-equivalent]) over 52 weeks with respect to total cumulative dose for treatment group and mean cumulative dose per patient. Before analysis, all SCS preparations were converted to prednisone-equivalent doses.

RESULTS

Patients

In total, across both studies, 953 patients were randomized to either reslizumab (*n* = 477 [245 in study 1 and 232 in study 2]) or placebo (*n* = 476 [244 and 232, respectively]). Of these, 73 (15%) patients in each group were taking maintenance OCS at baseline, with a median dose of 7 mg (Q1, 5 mg; Q3, 10 mg; interquartile range, 5 mg). The baseline demographic and clinical characteristics for patients who were receiving OCS are detailed in Table I. As shown, the baseline characteristics of these patients were well matched between the 2 treatment groups and were consistent with a population of patients with severe, symptomatic, inadequately controlled asthma.

Approximately 56% (82 of 146) of patients in the OCS-dependent subpopulation were on high-dose inhaled corticosteroids at enrollment. Data are not available to show whether the remainder had a trial of high-dose inhaled corticosteroid treatment before initiating OCS.

Clinical efficacy analyses in patients receiving maintenance OCS at baseline

The number and frequency of all clinical asthma exacerbations, clinical asthma exacerbations requiring SCS, and clinical asthma exacerbations requiring emergency department hospitalization for patients who received OCS at baseline and for those who did not are shown in Figure 1, A to C. In terms of exacerbation rate ratio, reslizumab was statistically significantly favored over placebo for all clinical asthma exacerbations (OCS at baseline: 0.32; 95% CI, 0.18-0.55; no OCS: 0.50; 95% CI, 0.39-0.64) and clinical asthma exacerbations requiring SCS (OCS at baseline: 0.28; 95% CI, 0.15-0.51; no OCS: 0.46; 95% CI, 0.35-0.61). For clinical asthma exacerbations resulting in a hospitalization, or a visit to the emergency department, there was a significant difference in favor of reslizumab for patients with OCS at baseline (0.22; 95% CI, 0.06-0.89), but no significant difference for patients without OCS at baseline (0.84; 95% CI, 0.46-1.55). However, differences in treatment effect between subgroups were not statistically significant (all interaction *P* values $>.05$) (Figure 1, A-C).

In patients receiving OCS at baseline, the percentage probability of not experiencing a clinical asthma exacerbation by week 52 was 63.8% (95% CI, 51.2%-73.9%) for reslizumab versus 35.7% (95% CI, 24.3%-47.2%) for placebo: hazard ratio 0.407 (95% CI, 0.248-0.666), *P* = .0004. In patients not receiving OCS at baseline, the percentage probability of not experiencing a clinical asthma exacerbations by week 52 was 67.6% (95% CI,

TABLE I. Baseline characteristics of patients who were receiving OCSs (≤ 10 mg/d) at baseline (pooled data from 2 phase 3 studies)

Characteristic	OCS at baseline (n = 146)		No OCS at baseline (n = 807)		Overall population (N = 953)	
	Placebo (n = 73)	Reslizumab (n = 73)	Placebo (n = 403)	Reslizumab (n = 404)	Placebo (n = 476)	Reslizumab (n = 477)
Age (y), mean $\pm$ SD	49.6 $\pm$ 14.6	50.1 $\pm$ 11.7	46.7 $\pm$ 14.2	45.9 $\pm$ 14.1	47.1 $\pm$ 14.3	46.5 $\pm$ 13.8
Male sex, n (%)	30 (41)	34 (47)	135 (33)	157 (39)	165 (35)	191 (40)
Weight (kg), mean $\pm$ SD	74.6 $\pm$ 15.9	75.1 $\pm$ 17.7	75.3 $\pm$ 17.7	75.2 $\pm$ 17.5	75.2 $\pm$ 17.4	75.2 $\pm$ 17.5
Weight ≥ 81 kg, n (%)	19 (26)	25 (34)	143 (35)	133 (33)	162 (34)	158 (33)
BMI (kg/m ²), mean $\pm$ SD	26.9 $\pm$ 5.1	27.0 $\pm$ 6.0	27.6 $\pm$ 5.8	27.4 $\pm$ 5.8	27.5 $\pm$ 5.7	27.4 $\pm$ 5.8
Underweight*, n (%)	1 (1.4)	2 (2.7)	10 (2.5)	10 (2.5)	11 (2.3)	12 (2.5)
Normal*, n (%)	33 (45.2)	26 (35.6)	127 (31.5)	132 (32.7)	160 (33.6)	158 (33.1)
Overweight*, n (%)	22 (30.1)	28 (38.4)	152 (37.7)	159 (39.4)	174 (36.6)	187 (39.2)
Obese*, n (%)	16 (21.9)	17 (23.3)	113 (28.0)	103 (25.5)	129 (27.1)	120 (25.2)
White race, n (%)	62 (85)	57 (78)	289 (72)	284 (70)	351 (74)	341 (71)
Late-onset asthma (≥ 40 y), n (%)	20 (27)	24 (33)	110 (27)	119 (29)	130 (27)	143 (30)
Atopy (historical)†, n (%)	42 (58)	38 (52)	256 (64)	247 (61)	298 (63)	285 (60)
Atopy (ImmunoCAP)‡, n (%)	20 (43)	24 (52)	142 (72)	117 (59)	162 (66)	141 (58)
Presence of CRSwNP, n (%)	13 (18)	13 (18)	59 (15)	65 (16)	72 (15)	78 (16)
High-dose ICS use at enrollment§, n (%)	45 (62)	37 (51)	163 (40)	166 (41)	208 (44)	203 (43)
LABA use at enrollment, n (%)	62 (85)	61 (84)	321 (80)	336 (83)	383 (80)	397 (83)
FEV ₁ (L), mean $\pm$ SD						
Prebronchodilator	1.78 $\pm$ 0.74	1.78 $\pm$ 0.74	2.00 $\pm$ 0.73	2.05 $\pm$ 0.76	1.97 $\pm$ 0.73	2.01 $\pm$ 0.76
% predicted	60.3 $\pm$ 20.1	60.6 $\pm$ 19.8	67.6 $\pm$ 19.1	68.0 $\pm$ 19.9	66.5 $\pm$ 19.4	66.9 $\pm$ 20.0
% reversibility	24.9 $\pm$ 15.9	28.1 $\pm$ 15.9	27.9 $\pm$ 21.8	26.9 $\pm$ 15.8	27.5 $\pm$ 21.1	27.0 $\pm$ 15.8
FVC (L), mean $\pm$ SD	2.915 $\pm$ 0.973	2.881 $\pm$ 0.990	3.024 $\pm$ 1.040	3.104 $\pm$ 1.011	3.008 $\pm$ 1.030	3.070 $\pm$ 1.010
Blood eosinophils (cells/ μ L), mean $\pm$ SD	717 $\pm$ 980	607 $\pm$ 428	644 $\pm$ 554	662 $\pm$ 650	655 $\pm$ 637	654 $\pm$ 621
No. of clinical asthma exacerbations in previous year, mean $\pm$ SD	3.3 $\pm$ 3.4	2.6 $\pm$ 2.2	1.8 $\pm$ 1.6	1.7 $\pm$ 1.4	2.1 $\pm$ 2.1	1.9 $\pm$ 1.6

BMI, Body mass index; CRSwNP, chronic rhinosinusitis with nasal polyps; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β -agonist.

*BMI missing for 1 patient who received placebo in the OCS and no OCS at baseline groups; Underweight, <18.5 kg/m²; Normal, 18.5 – <25 kg/m²; Overweight, 25 – <30 kg/m²; Obese, ≥ 30 kg/m².

†Defined as history of atopic dermatitis, or allergic rhinitis, or allergy shots.

‡Defined as having ≥ 1 positive immunoCAP test result (≥ 0.35), only assessed in study 1 (OCS: Placebo N = 46, Reslizumab N = 46; Non-OCS: Placebo N = 198, Reslizumab N = 199; Overall: Placebo N = 244, Placebo N = 245).

§High-dose ICS defined as >500 μ g/d fluticasone, >440 μ g/d mometasone, >800 μ g/d budesonide, >320 μ g/d ciclesonide, >400 μ g/d beclomethasone, or >2000 μ g/d triamcinolone.

||Excluding 1 patient who had 0 clinical asthma exacerbations in the previous 12 mo.

62.7%–72.1%) for reslizumab versus 50.1% (95% CI, 44.9%–55.0%) for placebo; hazard ratio 0.569 (95% CI, 0.454–0.713), $P < .0001$.

Significant improvements were observed with reslizumab compared with placebo in FEV₁ (Figure 2), percent predicted FEV₁, and forced vital capacity, regardless of baseline OCS status (FEV₁: OCS at baseline: 0.2 L; 95% CI, 0.03–0.37; no OCS: 0.12 L; 95% CI, 0.07–0.18; percent predicted FEV₁: OCS at baseline: 7.8%; 95% CI, 2.2%–13.5%; no OCS: 3.8%; 95% CI, 1.9%–5.6%; forced vital capacity: OCS at baseline: 0.22 L/s; 95% CI, 0.03–0.42; no OCS: 0.11 L/s; 95% CI, 0.04–0.18). Numerically greater improvements in lung function with reslizumab versus placebo were seen in patients who were taking OCS at baseline versus those who were not; however, these treatment effect differences were not statistically significant (all interaction P values $> .05$).

Predictors of response in OCS-dependent patients

Analysis of the effect of demographic and baseline clinical asthma characteristics on clinical asthma exacerbation response within OCS-dependent patients showed a numerically lower

frequency of exacerbations observed with reslizumab compared with placebo in all subgroups examined (Figure 3). A significantly larger reduction in clinical asthma exacerbation risk with reslizumab was associated with a history of 2 or more exacerbations versus 1 exacerbation in the year before the studies: a reduction of 77.5% (95% CI, 58.0%–88.0%) versus a reduction of 15.2% (95% CI, –150.2% to 71.2%) ($P = .028$ for interaction test). All other baseline characteristics analyzed were not associated with a statistically significant difference in treatment effects (Figure 3).

Adverse events

Table II summarizes AEs by treatment group in patients taking OCS at baseline. Of the 73 patients in each group who were taking OCS at baseline, 61 patients (83.6%) receiving reslizumab and 65 (89%) receiving placebo experienced at least 1 on-treatment AE.

Among patients receiving OCS at baseline, 12 (16.4%) of those in the reslizumab group and 13 (17.8%) of those in the placebo group had at least 1 serious adverse event (SAE). Two SAEs, considered to be treatment related, occurred in the

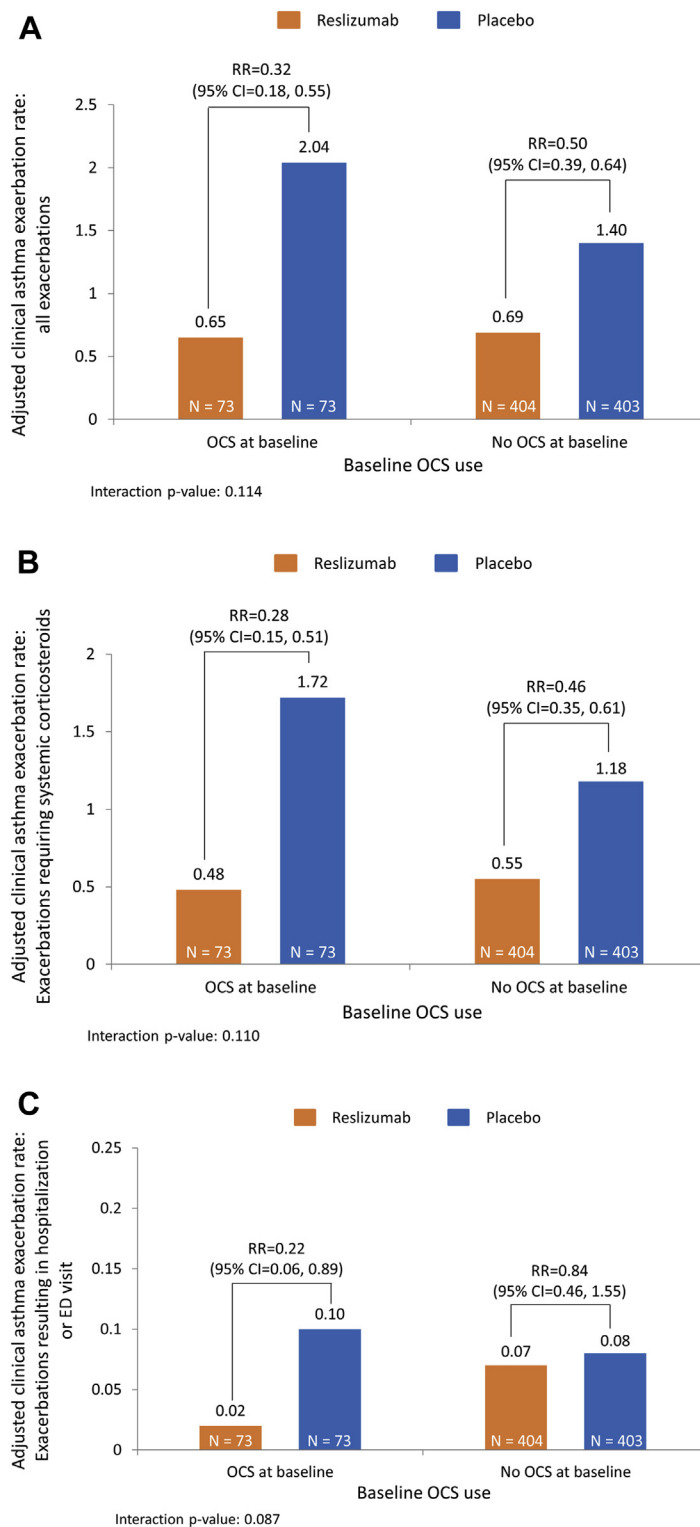


FIGURE 1. (A) Number and frequency of all clinical asthma exacerbations. (B) Clinical asthma exacerbations requiring systemic corticosteroids. (C) Clinical asthma exacerbations resulting in a hospitalization or a visit to the ED, during the 52-week period in patients receiving OCS at baseline versus those not receiving OCS at baseline. ED, Emergency department; RR, rate ratio. *Note:* Interaction *P* value tests for a difference in rate ratio between baseline OCS groups.

reslizumab group, 1 SAE reported as anaphylactic reaction, characterized by pruritus, skin reaction, and lower abdominal pressure that responded to standard treatment at the site, and 1

adenocarcinoma of the lung; no SAEs were related to study drug in the placebo group. Two additional malignancies were reported: treatment-emergent malignancy of colon carcinoma with

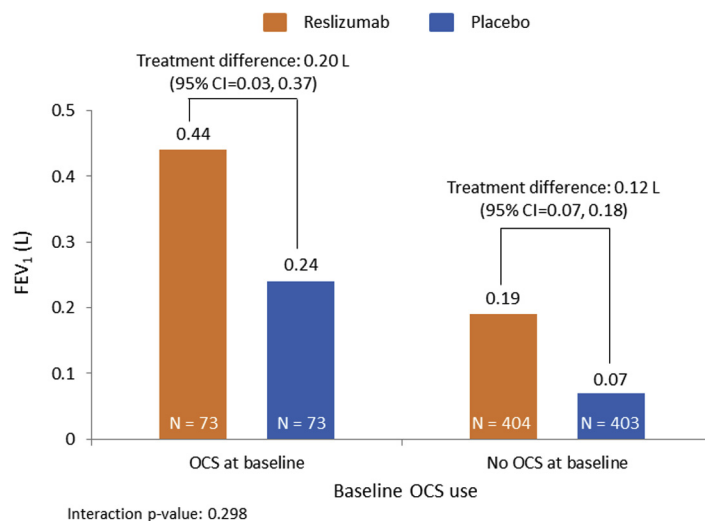


FIGURE 2. Least square mean change from baseline FEV₁ at week 52 in patients receiving OCS at baseline versus those not receiving OCS at baseline. *Note:* Interaction *P* value tests for a difference in rate ratio between baseline OCS groups.

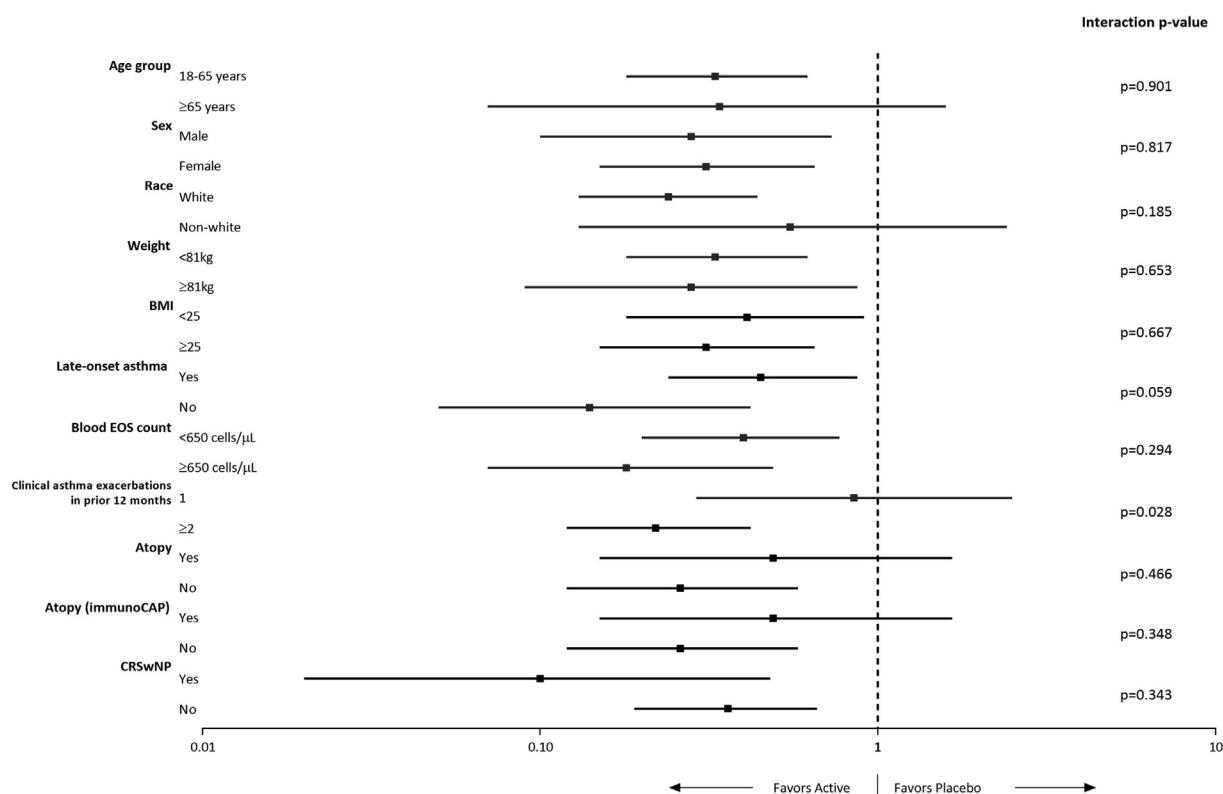


FIGURE 3. Subgroup analysis of the effects of reslizumab treatment on clinical asthma exacerbation response (rate ratio treatment/placebo; 95% CI) in patients receiving OCS at baseline. *Note:* Interaction *P* value tests for a difference in rate ratio between groups defined by specified baseline characteristics. *BMI*, Body mass index; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *EOS*, eosinophil.

liver metastasis and lung metastasis was reported in 1 patient in the placebo group; lung microcellular carcinoma was reported in 1 patient in the reslizumab group. There was 1 additional case of anaphylactic reaction in the reslizumab group, which was a nonserious reaction to walnuts. Three patients in the placebo

group and 4 patients in the reslizumab group had serious infections of various etiologies (gastroenteritis, pneumonia, urinary tract infection, cellulitis, and tracheobronchitis). Three patients and 2 patients, respectively, discontinued treatment because of AEs, consisting of the 3 patients with malignancies, the patient

TABLE II. Summary of AEs in the OCS-dependent population

AE, n (%)	OCS at baseline (n = 146)		Overall population (N = 953)	
	Reslizumab (n = 73)	Placebo (n = 73)	Reslizumab (n = 477)	Placebo (n = 476)
Patients with ≥ 1 AE*	61 (83.6)	65 (89.0)	374 (78)	407 (86)
Patients with ≥ 1 treatment-related AE	15 (20.5)	15 (20.5)	70 (15)	63 (13)
Patients with ≥ 1 SAE	12 (16.4)	13 (17.8)	42 (9)	57 (12)
Patients with ≥ 1 treatment-related SAE†	2 (2.7)	0	4 (< 1)	0
Patients with ≥ 1 SAE resulting in death	0	0	0	0
Patients with ≥ 1 AE leading to discontinuation	3 (4.1)	2 (2.7)	12 (3)	17 (4)
AEs occurring in $\geq 5\%$ of patients in either treatment arm of the OCS-dependent population‡				
Asthma	25 (34.2)	44 (60.3)	164 (34)	246 (52)
Nasopharyngitis	14 (19.2)	12 (16.4)	73 (15)	89 (19)
Back pain	8 (11.0)	2 (2.7)	25 (5)	21 (4)
Headache	6 (8.2)	10 (13.7)	52 (11)	47 (10)
Oropharyngeal pain	6 (8.2)	0	19 (4)	11 (2)
Sinusitis	6 (8.2)	5 (6.8)	30 (6)	39 (8)
Upper respiratory tract infection	6 (8.2)	5 (6.8)	47 (10)	48 (10)
Pneumonia	5 (6.8)	1 (1.4)	9 (2)	8 (2)
Dyspnea	4 (5.5)	2 (2.7)	12 (3)	17 (4)
Hypercholesterolemia	4 (5.5)	2 (2.7)	10 (2)	8 (2)
Palpitations	4 (5.5)	1 (1.4)	9 (2)	10 (2)
Urinary tract infection	4 (5.5)	4 (5.5)	20 (4)	21 (4)
Bronchitis	3 (4.1)	7 (9.6)	15 (3)	38 (8)
Arthralgia	2 (2.7)	4 (5.5)	10 (2)	15 (3)
Fatigue	2 (2.7)	7 (9.6)	7 (1)	14 (3)
Influenza	2 (2.7)	5 (6.8)	24 (5)	30 (6)
Gastroenteritis	0	4 (5.5)	6 (1)	12 (3)
Pharyngitis	0	8 (11.0)	17 (4)	21 (4)

*AEs that began or worsened after treatment with reslizumab, includes follow-up period.

†Two SAEs occurring in patients in the reslizumab group were considered to be treatment-related: 1 SAE reported as an anaphylactic reaction that was characterized by pruritus, skin reaction, and lower abdominal pressure and that responded to standard treatment at the site, and 1 adenocarcinoma of the lung.

‡Medical Dictionary for Regulatory Activities preferred terms.

with reslizumab-associated anaphylactic reaction, and an additional patient in the placebo treatment group with a serious and severe urinary tract infection. No deaths occurred in either group. The rate of infusion-site reactions was low, with 4 patients in the placebo group and 2 patients in the reslizumab group reporting infusion-site reactions; all were mild to moderate in severity and none were serious.

SCS prescriptions and burden in overall pooled population

In the overall population (N = 953), 228 (48%) patients in the placebo group and 140 (29%) patients in the reslizumab group were prescribed SCS for asthma and/or clinical asthma exacerbation after the first dose of study drug through to the end of the study. The total number of new SCS prescriptions issued was markedly lower among patients receiving reslizumab versus placebo (248 vs 480, respectively).

Fewer new SCS prescriptions were issued per patient with reslizumab versus placebo (mean $\pm$ SD, 0.5 ± 1.07 vs 1.0 ± 1.52 , respectively; $P < .0001$). Total SCS burden (total cumulative dose) and per-patient SCS burden (cumulative dose per patient) in prednisone-equivalent milligram were markedly lower with reslizumab versus placebo: 121,135 versus 290,977 mg and 254 versus 611 mg/patient, respectively (both $P < .0001$ for reslizumab vs placebo [analysis of covariance]; Table III).

Total exposure to study medication in the overall population in the pooled 52-week trials (ie, treatment period) was well matched between treatment groups: 442 patient-years for the reslizumab group versus 447.1 patient-years for the placebo group.

In patients who were receiving OCS at baseline (reslizumab n = 73, placebo n = 73), fewer new prescriptions above the baseline OCS dose were issued per patient among those receiving reslizumab versus placebo (mean $\pm$ SD, 0.5 ± 0.75 vs 1.0 ± 1.24 , respectively; $P < .0004$). The per-patient burden of new prescriptions above baseline OCS was also lower among reslizumab recipients who were on OCS at baseline (431 vs 1994 mg/patient [$P < .0001$]).

Patients receiving maintenance OCS at baseline had 66.0 patient-years exposure to reslizumab, and 67.6 patient-years exposure to placebo, again well matched between treatment arms.

With respect to SCS use in the several at-risk patient categories examined from the overall population, including Global Initiative for Asthma step 4/5 patients, patients with high body weight (≥ 81 kg), and patients who had chronic rhinosinusitis with nasal polyps, in each subgroup a higher percentage of patients in the reslizumab group compared with the placebo group were without a new SCS prescription for asthma and/or clinical asthma exacerbation ($P \leq .0005$). Fewer SCS prescriptions were issued overall and per patient among reslizumab recipients versus

TABLE III. No. of new SCS prescriptions (total and per patient), by treatment group

SCS prescriptions (total)	Reslizumab (n = 477)	Placebo (n = 476)	P value
No. of prescriptions per patient, mean $\pm$ SD (range)	0.5 $\pm$ 1.07 (0.0-10.0)	1.0 $\pm$ 1.52 (0.0-12.0)	<.0001*
Patients without any prescriptions, %	70.6	52.1	
Total no. of prescriptions	248	480	
Mean (SE) cumulative dose (mg)† per patient	254	611	<.0001‡
Total cumulative dose (mg)	121,135	290,977	
GINA 4/5	n = 383	n = 380	
No. of prescriptions per patient, mean $\pm$ SD (range)	0.5 $\pm$ 1.09 (0.0-10.0)	1.1 $\pm$ 1.54 (0.0-12.0)	<.0001*
Patients without any prescriptions, %	71.0	48.4	
Total no. of prescriptions	198	404	
Mean $\pm$ SD cumulative dose (mg)† per patient	235 $\pm$ 763	643 $\pm$ 1370	<.0001‡
Total cumulative dose (mg)	90,167	244,463	
Weight $\geq$ 81 kg	n = 158	n = 162	
No. of prescriptions per patient, mean $\pm$ SD (range)	0.5 $\pm$ 0.94 (0.0-6.0)	1.0 $\pm$ 1.59 (0.0-6.0)	.0005*
Patients without any prescriptions, %	68.4	58.6	
Total no. of prescriptions	80	158	
Mean $\pm$ SD cumulative dose (mg)† per patient	284 $\pm$ 943	528 $\pm$ 1274	.0289‡
Total cumulative dose (mg)	44,834	85,499	
CRSwNP	n = 121	n = 124	
No. of prescriptions per patient, mean $\pm$ SD (range)	0.4 $\pm$ 0.68 (0.0-3.0)	1.2 $\pm$ 1.64 (0.0-8.0)	<.0001*
Patients without any prescriptions, %	74.4	44.4	
Total no. of prescriptions	43	149	
Mean $\pm$ SD cumulative dose (mg)† per patient	161	1006	<.0001‡
Total cumulative dose (mg)	12,552	72,400	

CRSwNP, Chronic rhinosinusitis with nasal polyps; GINA 4/5, Global Initiative for Asthma step 4 and step 5.

*Negative binominal comparing reslizumab to placebo.

†In milligram of prednisone equivalents; does not include baseline corticosteroids.

‡ANCOVA comparing reslizumab with placebo.

placebo (both $P \leq .0005$; Table III). Similarly, in each of these subgroups of interest, the total and per-patient SCS burden was lower among patients receiving reslizumab versus placebo (prednisone-equivalent mg; Table III).

DISCUSSION

Our *post hoc* analyses explored pooled data from 2 randomized, placebo-controlled, 52-week phase 3 trials in patients with inadequately controlled asthma and elevated blood eosinophil levels who were treated with IV reslizumab.

In patients who were OCS-dependent at baseline compared with those who were not, reslizumab was favored over placebo for all efficacy end points in both subgroups, including reduction in clinical asthma exacerbation risk and improvement in lung function, with improvements numerically greater for efficacy end points in the OCS-dependent subgroup compared with patients not on OCS at baseline. The differences in treatment effects between these 2 subgroups did not reach statistical significance at the .05 level; however, the power of this analysis was limited by the small size of the OCS-dependent subgroup.

In the analysis of baseline predictors of clinical asthma exacerbation response in OCS-dependent patients, a lower frequency of exacerbations was seen with reslizumab compared with placebo, across all subgroups, and a significant difference in reduction in clinical asthma exacerbation risk was associated with a history of at least 2 exacerbations (vs 1 exacerbation) in the year before the studies without statistically significant differences for other baseline demographic or asthma characteristics.

In the overall pooled population and in the OCS-dependent patient subpopulation, patients treated with reslizumab required fewer new SCS prescriptions compared with those receiving placebo and had a lower SCS burden (prednisone-equivalent milligram). Such reductions were also seen in other at-risk patient subgroups including Global Initiative for Asthma step 4/5 patients, patients with high body weight (≥ 81 kg), and patients with chronic rhinosinusitis with nasal polyps. Mean SCS prescriptions, total SCS prescriptions, cumulative SCS dose per patient, and cumulative SCS dose per group were lower for the reslizumab-treated group compared with placebo for the overall population and all analyzed subgroups.

To date, studies investigating the effect of IL-5 inhibitors and IL-5 receptor inhibitors in patients with severe OCS-dependent asthma have been conducted with mepolizumab and benralizumab. Both treatments resulted in a reduction in OCS dose of 50 percentage points greater than that seen with placebo in patients with severe asthma.^{7,8} Patients with oral glucocorticoid-treated asthma who received the anti-IL-4/IL-13 mAb dupilumab achieved a 70% reduction in glucocorticoid dose, compared with a 42% reduction with placebo, with 80% and 50% of patients, respectively, achieving a dose reduction of at least 59%.¹⁷ The results of the current reslizumab analysis are not directly comparable given the differing nature of the study designs; per protocol, patients in the BREATH program trials were not able to change background medications, including OCS, during the treatment period, so we could not directly measure OCS-sparing effect. However, we assessed asthma outcome measures and showed that reslizumab is efficacious in patients who are

OCS-dependent at baseline. Moreover, we showed an overall reduction in new SCS prescriptions and total SCS burden while on treatment with reslizumab, suggesting that reslizumab may be effective in reducing the overall need for SCS in patients with moderate-to-severe asthma and the associated risk of side effects from corticosteroids. The finding that a history of at least 2 clinical asthma exacerbations in the previous year was a baseline predictor of greater reduction in exacerbations in OCS-dependent patients, is consistent with the findings of a previous pooled analysis of benralizumab data, in which history of exacerbations was associated with a greater benralizumab-associated reduction in annual exacerbation risk.¹⁸ The numerical difference in reslizumab-associated response with respect to exacerbation frequency that was seen in patients with chronic rhinosinusitis with nasal polyps compared with those without, although not statistically significant, suggests that patients with a more eosinophilic phenotype may be particularly responsive to anti-IL-5 therapy. Indeed, the level of locally derived IL-5 is an important predictor of anti-IL-5 treatment response.¹⁴

A similar number of OCS-dependent patients in the reslizumab group and placebo group had at least 1 SAE, with 2 patients in the reslizumab group experiencing an SAE considered to be treatment related. Anaphylaxis was reported in 2 patients in the reslizumab group, one related to walnuts and the other related to reslizumab, which was successfully treated at the study site with standard therapy. Discontinuations due to AEs were similar between groups.

Although the primary studies were prospective, our analyses were *post hoc* and not prespecified. The range of OCS doses in OCS-dependent patients was limited because of the protocol restriction of less than or equal to 10 mg of prednisone or equivalent at baseline. Furthermore, the clinical necessity of prescribed baseline OCS doses was not confirmed by the site investigators, because OCS dosing was not systematically optimized before initiation of study treatment. Sixty-two percent of placebo-treated and 51% of reslizumab-treated OCS-dependent patients were receiving high-dose ICS at baseline; therefore, the subgroup assessed in this study likely represent a less-severe OCS-dependent population compared with OCS-sparing studies with other biologics in which high-dose ICS at baseline was required per protocol.^{7,8} In addition, our analyses did not assess any decrease in dose of maintenance OCS during the treatment period in those patients who were OCS-dependent because, per protocol, it was not permitted to change the OCS dose during the treatment periods. Regardless, our results demonstrated an improvement in asthma-related outcome measures as add-on therapy to maintained doses of OCS. Finally, although our objectives included an assessment of AEs in patients taking OCS at baseline, the primary studies were not designed to collect data to assess adverse effects of SCS use such as hyperglycemia or hypertension, improvements in which may result from a reduction in OCS burden.

It is of considerable interest that we found, among the overall patient population, a statistically significant and clinically relevant lower burden of SCS during the 52-week treatment period for patients receiving reslizumab compared with those receiving placebo, including traditionally difficult-to-treat patients with asthma such as those with high baseline body weight (≥ 81 kg). The weight-based dosing of IV reslizumab may be particularly beneficial in OCS-dependent asthma and in patients who may have gained weight as a result of OCS use, because the

pharmacokinetics of mAbs is impacted by weight, resulting in lower systemic concentrations in heavier patients.¹⁹ These results may give some confidence to prescribing clinicians that there may be a reduction in SCS doses and SCS-related side effects in moderate-to-severe, inadequately controlled, exacerbation-prone patients after initiating IV reslizumab treatment. It is important to note that our analyses did not assess differences in maintenance OCS during the treatment period because, per protocol, it was not permitted to change the OCS dose during the treatment periods; therefore, the analysis differs from the analysis in OCS-sparing studies of other biologics.^{7,8}

In summary, the results of this *post hoc* analysis, in addition to the work by Mukherjee et al, suggest a benefit of reslizumab in OCS-dependent severe asthma. However, these findings are yet to be confirmed in clinical trials of IV reslizumab, and this will require further prospectively designed studies. Importantly, a statistically significant and clinically relevant lower burden of SCS use was seen in patients receiving reslizumab compared with those receiving placebo. This finding was noted in the overall population as well as in patients in at-risk subgroups, including individuals with high body weight.

Acknowledgments

Medical writing support was provided by Ian C. Grieve, PhD, of Zoetic Science, an Ashfield company, part of UDG Healthcare plc, and was funded by Teva Pharmaceuticals, Inc. We thank members of the Teva team for providing a full review of the article.

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