

Long-term Safety and Efficacy of Reslizumab in Patients with Eosinophilic Asthma



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What is already known about this topic? Placebo-controlled trials in patients with eosinophilic asthma show that intravenous reslizumab, an anti-IL-5 monoclonal antibody, has a safety profile similar to placebo. Reslizumab reduces asthma exacerbations and improves lung function and asthma control.

What does this study add to our knowledge? This open-label extension study with overall reslizumab exposure up to 3 years, when including exposure during the double-blind treatment periods of the 3 pivotal studies, demonstrates acceptable safety and maintenance of improved lung function and asthma control in patients with moderate-to-severe eosinophilic asthma treated with intravenous reslizumab.

How does this study impact current management guidelines? The safety and efficacy results of this study support reslizumab treatment for long-term control of moderate-to-severe eosinophilic asthma. There is no evidence of an increased incidence of adverse events with long-term reslizumab exposure compared with the reslizumab-naïve group or compared with the placebo-treated patients in the double-blind trials.

BACKGROUND: In placebo-controlled trials, reslizumab, an anti-IL-5 monoclonal antibody, significantly reduced asthma exacerbations and improved lung function and asthma control in patients with eosinophilic asthma.

OBJECTIVE: This open-label extension study evaluated safety and efficacy of reslizumab for up to 24 months.

METHODS: After participation in 1 of 3 placebo-controlled, phase III trials in moderate-to-severe eosinophilic asthma, patients received reslizumab 3.0 mg/kg intravenously every 4 weeks for up to 24 months. Adverse events (AEs), lung function, and patient-reported asthma control were evaluated.

RESULTS: In the open-label extension, 1,051 patients received ≥ 1 reslizumab dose (480 reslizumab-naïve, 571 reslizumab-experienced); median (range) exposure was 319 (36-840) and 343 (36-863) days in reslizumab-naïve and reslizumab-experienced patients, respectively. Continuous exposure, including during the placebo-controlled studies, was ≥ 12 months for 740 patients and ≥ 24 months for 249 patients. The most common AEs were worsening of asthma and nasopharyngitis. Serious AEs affected 78 of 1,051 (7%) patients; 18 of 1,051 (2%) discontinued treatment because of AEs; and there were 3 deaths (all non-treatment-related). Fifteen adult patients (15 of 1,023; 1%) had

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GlaxoSmithKline, Amgen, and AstraZeneca. Y. Shalit and M. Garin are employed by Teva. J. Zangrilli was employed by Teva at the time of this study; has a patent for the use of reslizumab to treat moderate-to-severe eosinophilic asthma. M. Castro has received consultancy fees from Astmatx/Boston Scientific, IPS/Holaira, and Neostem; has received consultancy fees and has participated in advisory boards for Genentech; has received research support from Amgen, Cepion/Cephalon/Teva, Novartis, GlaxoSmithKline, Sanofi-Aventis, Vectura, KaloBios, and Medimmune; has received speaker fees from GlaxoSmithKline, Genentech, Boston Scientific, Boehringer Ingelheim, and Teva; receives royalties from Elsevier; has stock in Sparo Inc.

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* This was the affiliation of J. Zangrilli at the time of the study but he is no longer employed there.
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Abbreviations used

ACQ- Asthma Control Questionnaire
ADA- Antidrug antibody
AE- Adverse event
ASUI- Asthma Symptom Utility Index
AQLQ- Asthma Quality of Life Questionnaire
CI- Confidence interval
FEF₂₅₋₇₅- Forced expiratory flow at 25% to 75% of the FVC
FEV₁- Forced expiratory volume in 1 second
FVC- Forced vital capacity
GI- Gastrointestinal
ICS- Inhaled corticosteroid
IL-5- Interleukin-5
IV- Intravenous
QoL- Quality of life
SABA- Short-acting β -agonist
SD- Standard deviation

malignancies of diverse tissue types. Reslizumab-experienced patients maintained improved lung function and asthma control; reslizumab-naïve patients had improvements in these measures throughout open-label treatment. Blood eosinophil counts appeared to be returning to baseline after reslizumab discontinuation.

CONCLUSIONS: In patients with moderate-to-severe eosinophilic asthma, intravenous reslizumab 3.0 mg/kg displays favorable long-term safety and sustained long-term efficacy. Initial improvements in lung function and asthma control were maintained for up to 2 years. These findings substantially add to our understanding of the long-term safety and efficacy of anti-IL-5 strategies. © 2017 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 2017;5:1572-81)

Key words: Reslizumab; Asthma; Eosinophil; Anti-IL-5; Long-term safety; Open-label extension study

Recent advances in the treatment of patients with inadequately controlled asthma have focused on targeting inflammatory pathways that contribute to the heterogeneity and severity of the disease. Eosinophils play key roles in the promotion and maintenance of airway inflammation and are associated with remodeling.¹⁻³ The presence of elevated eosinophils in the blood and sputum has been associated with asthma severity and increased risk of asthma exacerbations.⁴⁻⁹ Indeed, the blood eosinophil level is a useful biomarker to help identify patients with severe eosinophilic asthma who may be responsive to anti-IL-5 antibody therapy.¹⁰⁻¹² Reslizumab is an IgG4/k humanized monoclonal antibody that targets IL-5 (a key factor in eosinophil viability), thereby disrupting the maturation, activation, and survival of eosinophils.^{13,14} Intravenous (IV) reslizumab was recently approved in the USA, EU, and Canada as an add-on maintenance treatment of patients with severe asthma aged ≥ 18 years and with an eosinophilic phenotype. The phase III BREATHE clinical program in asthma consisted of 4 completed placebo-controlled safety and efficacy studies in patients with asthma uncontrolled on at least a medium-dose inhaled corticosteroid (ICS) with or without another asthma

controller. Three of the studies (1 lung function 16-week study and 2 exacerbation 52-week studies) were in patients aged ≥ 12 years with eosinophilic asthma (screening blood eosinophil count $\geq 400/\mu\text{L}$)^{15,16} and the fourth was a placebo-controlled lung-function study in patients unselected for eosinophilic asthma (adults only).¹¹ The overall results from the placebo-controlled trials showed that reslizumab IV significantly reduced exacerbations, relieved asthma symptoms, and improved asthma-related quality of life (QoL) and lung function in patients with eosinophilic asthma whose symptoms were inadequately controlled on an ICS-based treatment regimen. For example, in the 2 phase III 52-week studies in patients with eosinophilic asthma, the relative risks of asthma exacerbations with reslizumab IV versus placebo were 0.5 (95% confidence interval [CI]: 0.37-0.67) and 0.41 (0.28-0.59), both $P < .0001$.¹⁶

After participation in any of the phase III placebo-controlled trials in eosinophilic asthma, patients treated with either reslizumab IV or placebo were eligible to enter an open-label extension study of reslizumab for up to 2 additional years, the results of which are presented here. The primary objective of this study was to obtain long-term safety data for reslizumab IV 3.0 mg/kg administered once every 4 weeks for up to an additional 2 years in adolescent and adult patients with moderate-to-severe eosinophilic asthma. Efficacy assessments, including lung function and patient-reported measures of asthma control and QoL, were also assessed.

METHODS

Study design

This was an international multicenter, nonrandomized, open-label extension study designed to assess the long-term safety and efficacy of treatment with reslizumab IV (NCT01290887). The study consisted of a baseline visit (end-of-treatment visit for the prior placebo-controlled studies) followed by clinical visits every 4 weeks during the open-label treatment period, an end-of-treatment visit conducted 4 weeks after the last dose of reslizumab, and a final follow-up evaluation conducted 90 days (± 7 days) after the end-of-treatment visit.

Patients

Eligible patients must have completed treatment in a preceding randomized (reslizumab vs placebo), double-blind asthma exacerbation study or received ≥ 2 doses of reslizumab in a pulmonary function study.^{15,16} Patients enrolled in the previous studies were aged 12-77 years with inadequately controlled asthma (Asthma Control Questionnaire [ACQ] score ≥ 1.5) and elevated blood eosinophils (≥ 400 cells/ μL) and were receiving at least a medium dose of ICS (fluticasone propionate ≥ 440 $\mu\text{g/day}$, or equivalent) with or without another controller.^{15,16}

Patients were excluded from the open-label study if they had a clinically meaningful comorbidity that would interfere with the study schedule or procedures, or compromise the patient's safety; had another confounding underlying lung disorder; or had any aggravating factors that were inadequately controlled. Patients were also excluded if they had a current infection or disease that might have precluded assessment of asthma or were a current smoker. Patients were restricted from taking concurrent immunomodulatory or investigational medications. Patients were not excluded if they were receiving systemic corticosteroids (up to 10 mg/day) for asthma.

The study was conducted in accordance with the Declaration of Helsinki, local laws, and the International Conference on

Harmonisation Good Clinical Practice Guideline, and approved by the relevant regulatory authority and independent ethics committee. All patients provided written informed consent for participation in the open-label trial during the end-of-treatment visit in the previous double-blind studies.

Procedures

Patients received reslizumab by IV infusion at a dosage of 3.0 mg/kg after baseline procedures were completed and every 4 weeks for up to 24 months.

Outcomes

The primary objective was to obtain long-term safety data for reslizumab 3.0 mg/kg administered once every 4 weeks in adolescent and adult patients with moderate-to-severe eosinophilic asthma for up to 24 months. Safety assessments included adverse events (AEs) coded using the Medical Dictionary for Regulatory Activities v15.0; clinical laboratory tests (chemistry, hematology, and urinalysis); physical examination; vital signs measurements; and use of concomitant medications.

The secondary objectives of the study were to evaluate the long-term efficacy of reslizumab assessed by pulmonary function tests, including forced expiratory volume in 1 second (FEV₁), percent predicted FEV₁, forced vital capacity (FVC), and forced expiratory flow at 25% to 75% of the FVC (FEF₂₅₋₇₅), patient-reported measures of asthma control (ACQ, Asthma Quality of Life Questionnaire [AQLQ], and Asthma Symptom Utility Index [ASUI]), and short-acting β -agonist (SABA) use. Clinical asthma exacerbations were not defined during the long-term extension study. Efficacy analyses, except for AQLQ, were measured every 4 weeks for the first 16 weeks, at 24 weeks, and every 12 weeks thereafter until the end-of-treatment visit or early termination; AQLQ was measured every 24 weeks until the end-of-treatment visit or early termination. Blood samples for blood eosinophil determination were obtained at weeks 4, 8, and 24, and every 24 weeks thereafter, including the end-of-treatment visit (4 weeks after the last infusion) or early withdrawal, and at the 90-day follow-up evaluation. Immunogenicity was assessed by testing for the presence of anti-reslizumab antibodies every 24 weeks throughout the study and at the end of treatment or early withdrawal. Blood samples for blood eosinophil determination and immunogenicity were also obtained from patients experiencing a serious AE, an AE leading to withdrawal, or an exacerbation of asthma symptoms.

Statistical analyses

The sample size was determined by the number of patients rolled over from the 3 double-blind, placebo-controlled, phase III studies of reslizumab in eosinophilic asthma. Safety and efficacy analyses were conducted on the safety analysis set, consisting of all patients who received ≥ 1 dose of reslizumab in the open-label study. Analyses are descriptive, including summary statistics at baseline and at each assessment time point. CIs around the ratio of AE frequencies between reslizumab-experienced and reslizumab-naïve patients were calculated. The integrated safety results for the placebo arms from the 3 placebo-controlled studies are provided for comparison with the reslizumab-experienced group in the open-label study. For efficacy assessments, results are displayed by treatment at study entry and prespecified time points, as well as the study end (the time point when the last observation was obtained at a post-baseline scheduled visit or at the early termination visit). All data were processed and summarized using SAS v9.3 (SAS Institute Inc, Cary, NC).

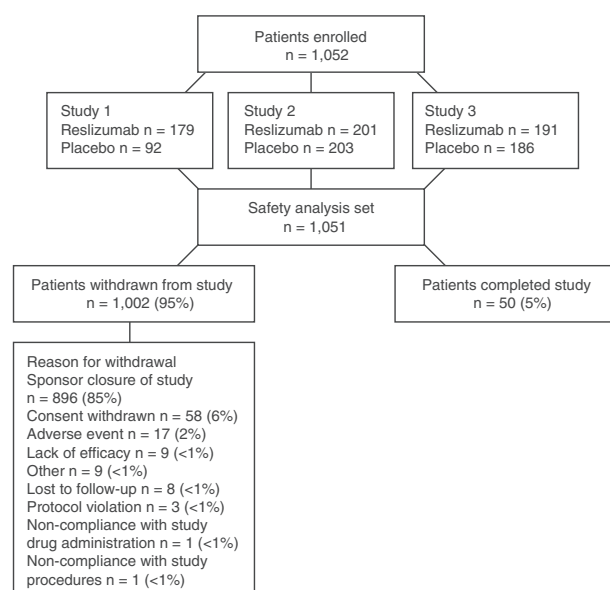


FIGURE 1. Disposition of patients in the open-label study: enrollment, reasons for withdrawal, and patients completing the study. “Placebo” = reslizumab-naïve. “Reslizumab” = reslizumab-experienced. The safety analysis set includes all patients who received ≥ 1 dose of reslizumab; 1 patient withdrew before receiving study treatment.

RESULTS

Patients

Patients were enrolled in this open-label extension study after participation in 3 previous randomized, placebo-controlled, phase III studies of reslizumab (Figure 1). Study recruitment was ended with 1,052 patients enrolled (740 were planned); at that time, 5,506 infusions of reslizumab had been administered in the open-label study and substantial safety and efficacy data had been collected. Patients were permitted to continue reslizumab on a compassionate use basis where local laws allowed. Of the 1,052 patients, 481 (46%) were reslizumab-naïve (received placebo in the prior trial) and 571 (54%) were reslizumab-experienced. One patient withdrew before receiving a single dose of reslizumab. In total, 1,051 (99%) patients received ≥ 1 dose of reslizumab and were included in the safety analysis set. Participation in the study ended for the majority of patients at the time of study termination by the study sponsor (n = 896; 85%). An additional 106 patients withdrew for other reasons, including withdrawn consent (6%), AEs (2%), and lack of efficacy (<1%).

Baseline demographics and disease characteristics were similar between the reslizumab-naïve and reslizumab-experienced groups (Table I). The study population was 61% female and 77% white, with a mean age of 47 years (range, 12–77) and a mean body mass index of 27.7 kg/m² (standard deviation [SD], 5.77). As expected (based on the published results of the placebo-controlled treatment periods^{14,15}), lung function, patient-reported measures of asthma control (ACQ, AQLQ, and ASUI), and SABA use at baseline were better on average in reslizumab-experienced patients compared with reslizumab-naïve patients (Table I). Mean baseline blood eosinophil counts were

TABLE I. Summary of baseline demographic and disease characteristics

	Reslizumab-naïve (n = 481)	Reslizumab-experienced (n = 571)	Total (N = 1052)
Mean age, y (range)	47 (12-75)	47 (13-77)	47 (12-77)
Adolescent, n (%) [*]	15 (3)	13 (2)	28 (3)
Sex, n (%)			
Female	314 (65)	332 (58)	646 (61)
Male	167 (35)	239 (42)	406 (39)
Race, n (%)			
White	371 (77)	437 (77)	808 (77)
Black	22 (5)	22 (4)	44 (4)
Asian	39 (8)	48 (8)	87 (8)
Other [†]	49 (10)	64 (11)	113 (11)
Mean (SD) BMI (kg/m ²)	27.6 (5.42)	27.7 (6.04)	27.7 (5.77)
Mean (SD) FEV ₁ (L)	2.096 (0.7856)	2.285 (0.8222)	2.199 (0.8108)
Mean (SD) % predicted FEV ₁	70.739 (19.7560)	75.116 (19.9404)	73.115 (19.9664)
Mean (SD) FVC (L)	3.163 (1.0357)	3.366 (1.0779)	3.273 (1.0632)
Mean (SD) ACQ score	1.832 (1.0912)	1.450 (0.9870)	1.624 (1.0527)
Mean (SD) AQLQ score	5.170 (1.2160)	5.496 (1.1431)	5.347 (1.1875)
Mean (SD) ASUI score	0.803 (0.1910)	0.861 (0.1479)	0.832 (0.1728)
Mean (SD) blood eosinophil count (cells/μL)	528 (379.2)	78 (148.0)	284 (357.7)
SABA use in past 3 d, n (%)	300 (62)	297 (52)	597 (57)
Mean (SD) puffs/d	2.130 (2.4996)	1.568 (2.3982)	1.827 (2.4604)
Taking LABA, n (%)	86 (18)	101 (18)	187 (18)
Taking ICS, n (%)	152 (32)	193 (34)	345 (33)
Taking OCS, n (%)	54 (11)	41 (7)	95 (9)

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ASUI, Asthma Symptom Utility Index; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; OCS, oral corticosteroid; SABA, short-acting β-agonist; SD, standard deviation.

^{*}Individuals aged 12-17 y.

[†]Includes American Indian or Alaskan Native, and Pacific Islander.

higher in the reslizumab-naïve group (528 cells/μL) compared with the reslizumab-experienced group (78 cells/μL).

Treatment exposure

Considering only the open-label extension study, excluding prior placebo-controlled studies, median (range) treatment

TABLE II. Treatment exposure (months) combining the double-blind studies and open-label study

	Reslizumab-naïve (n = 481)	Reslizumab-experienced (n = 571)	Total (N = 1052)
Treated patients, n (%)	480 (>99) [*]	571 (100)	1051 (>99) [*]
Exposure to reslizumab, n (%)			
≥1 mo	480 (100)	571 (100)	1051 (100)
≥3 mo	440 (92)	571 (100)	1011 (96)
≥6 mo	394 (82)	566 (>99)	960 (91)
≥9 mo	297 (62)	554 (97)	851 (81)
≥12 mo	198 (41)	542 (95)	740 (70)
≥15 mo	105 (22)	474 (83)	579 (55)
≥18 mo	60 (13)	426 (75)	486 (46)
≥21 mo	42 (9)	331 (58)	373 (35)
≥24 mo	17 (4)	232 (41)	249 (24)

^{*}One patient withdrew before receiving study treatment.

exposure was 319 (36-840) days in the reslizumab-naïve group and 343 (36-863) days in the reslizumab-experienced group. Approximately half of the patients in each group received more than 12 months of reslizumab treatment and 17% were treated for more than 18 months (Tables E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org). The upper limits of the treatment exposure ranges cited above result from a subset of patients receiving >24 infusions as a bridge to various types of expanded-access programs (Tables E1 and E2). All study visits before switching to these programs were included in the analyses.

Considering continuous exposure, including the placebo-controlled studies, of the 571 reslizumab-experienced patients in the open-label study, 483 had previous exposure to 3.0 mg/kg reslizumab and 88 had previous exposure to 0.3 mg/kg. The mean (SD) duration of overall exposure to 3.0 mg/kg reslizumab in the 483 patients with previous experience at this reslizumab dose (combining the double-blind and open-label studies; Table II) was 656 (154) days (approximately 22 months; range, 177-1,080 days [6-36 months]). There were 740 patients with ≥12 months' exposure and 249 patients with ≥24 months' continuous exposure.

Safety

Treatment with reslizumab was well tolerated, with ≥1 AE occurring in 66% of patients; similar incidences of AEs were observed in the reslizumab-naïve (75%) and reslizumab-experienced (67%) groups (Table III). Treatment-related AEs were reported in 10% and 7% of reslizumab-naïve and reslizumab-experienced patients, respectively. Most individual treatment-related AEs occurred in <1% of patients, except for headache (2%). Serious AEs were reported in 7% of patients (7% and 8% of reslizumab-naïve and reslizumab-experienced patients, respectively); 2% of patients discontinued treatment because of AEs (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). There were 3 deaths (Table III); none were assessed as related to treatment.

The most commonly reported AEs in both reslizumab-experienced and reslizumab-naïve patients were worsening of asthma, nasopharyngitis, upper respiratory tract infection,

TABLE III. Summary of AEs (safety analysis set)

AE, n (%)	Reslizumab-naïve (n = 480)	Reslizumab-experienced (n = 571)	Total (N = 1,051)
Any AEs*	359 (75)	385 (67)	744 (71)
Severe AEs	31 (6)	47 (8)	78 (7)
Treatment-related AEs	49 (10)	41 (7)	90 (9)
Discontinuations due to AEs	6 (1)	12 (2)	18 (2)
Serious AEs	33 (7)	45 (8)	78 (7)
Deaths†	1 (<1)	2 (<1)	3 (<1)
AEs occurring in >2% of patients‡			
Asthma	145 (30)	159 (28)	304 (29)
Nasopharyngitis	69 (14)	81 (14)	150 (14)
Upper respiratory tract infection	51 (11)	57 (10)	108 (10)
Sinusitis	35 (7)	43 (8)	78 (7)
Headache	34 (7)	39 (7)	73 (7)
Bronchitis	33 (7)	29 (5)	62 (6)
Allergic rhinitis	19 (4)	31 (5)	50 (5)
Influenza	21 (4)	24 (4)	45 (4)
Urinary tract infection	16 (3)	28 (5)	44 (4)
Pharyngitis	19 (4)	21 (4)	40 (4)
Acute sinusitis	13 (3)	25 (4)	38 (4)
Back pain	16 (3)	21 (4)	37 (4)
Rhinitis	15 (3)	17 (3)	32 (3)
Cough	12 (3)	18 (3)	30 (3)
Arthralgia	14 (3)	15 (3)	29 (3)
Hypertension	10 (2)	19 (3)	29 (3)
Oropharyngeal pain	16 (3)	12 (2)	28 (3)
Gastroenteritis	12 (3)	16 (3)	28 (3)
Lower respiratory tract infection	12 (3)	12 (2)	24 (2)

AE, Adverse event.

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

†One patient with anal cancer in the reslizumab-naïve group. There were 2 deaths during the open-label study in the reslizumab-experienced group: 1 patient with a history of bronchiectasis had hemoptysis, aspiration pneumonia, and cardiorespiratory arrest, and 1 patient had a cardiac arrest.

‡Medical Dictionary for Regulatory Activities preferred terms.

sinusitis, and headache (Table III). The overall incidence of worsening of asthma among patients receiving reslizumab (safety analysis population) was 28% versus 46% in the pooled placebo population in the preceding studies. The incidence of other AEs was generally comparable: nasopharyngitis 14% versus 14%, urinary respiratory tract infections 10% versus 9%; sinusitis 8% versus 6%; headache 7% versus 11% reported for the reslizumab safety analysis population versus the pooled historical placebo group, respectively. Local infusion-related AEs (eg, pain at site of administration) were rare (<1%); mild-to-moderate chills related to reslizumab infusion, which did not lead to treatment discontinuation, occurred in 2 patients (<1%). No anaphylaxis

cases were reported. There were 2 drug hypersensitivity reactions reported and 2 events of drug eruption reported; all were related to other allergen exposure and did not result in discontinuation of reslizumab. The frequency of serious infections was low overall (1%) and presented across a variety of infectious agents and organ systems; there was no specific pattern of infections that would suggest a specific risk due to reslizumab treatment. There were no reports of helminthic parasitic or suspected opportunistic infections reported. Three patients were diagnosed with skin basal-cell carcinomas. Twelve other malignancies were diagnosed in adult patients (aged 43-70 years; 3 with breast cancer, 2 malignant melanoma, and 1 each of malignant melanoma *in situ*, lymphoma, prostate cancer, anal cancer, gastrointestinal [GI] metastases to lung [due to prior GI malignancy], borderline ovarian tumor, and ovarian epithelial cancer). As a prior history of malignancy was not exclusionary, 5 of the 15 patients had a history of malignancy and 2 of the reported malignancies were the same as those diagnosed before reslizumab exposure (1 melanoma and 1 lung metastasis due to prior GI malignancy). The pattern of AEs by system organ class was as expected for predominantly adult patients with moderate-to-severe asthma (Table E4, available in this article's Online Repository at www.jaci-inpractice.org). There was no clinically meaningful difference in the classes of events between reslizumab-experienced and reslizumab-naïve patients. The overall pattern and frequency of AEs during the open-label period was similar to that observed for placebo-treated patients during the double-blind treatment periods of the 3 feeder studies (Table E5, available in this article's Online Repository at www.jaci-inpractice.org).

There were no clinically relevant changes in laboratory test results or vital signs. Anti-reslizumab antibody findings were similar between patients in the reslizumab-naïve and reslizumab-experienced groups at baseline (4% positive for each group). During the study, 5% of patients in both groups showed treatment-emergent antidrug antibody (ADA) response. ADA was frequently observed at 1 time point only, and in general the titer was low. Based on visual inspection, ADA positivity was not associated with diminished ability of reslizumab to suppress blood eosinophils quickly and in a sustained manner (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org), and no specific AEs were associated with ADA positivity.

Efficacy

As expected, FEV₁ was better at baseline in the reslizumab-experienced versus reslizumab-naïve group (Figure 2, A). An improvement in FEV₁ was noted in the reslizumab-naïve group by the first on-treatment assessment at week 4 (0.082 L, $P < .0001$) and sustained over 96 weeks. The improvement in FEV₁ observed in the reslizumab-experienced patients during previous double-blind treatment was maintained throughout the open-label period (Table IV, Figure 2, A). Similar trends were observed in FVC and FEF₂₅₋₇₅ over 96 weeks (Figure 2, B and C). Mean daily SABA use at baseline was slightly higher in the reslizumab-naïve versus reslizumab-experienced group (2.1 vs 1.6 puffs, respectively). No notable differences in mean daily SABA use were observed in either treatment group over time (data not shown).

An improvement in ACQ score was also observed in the reslizumab-naïve group at the week 4 assessment (−0.278, $P < .0001$) (Figure 3, A; Table IV). Reslizumab-experienced

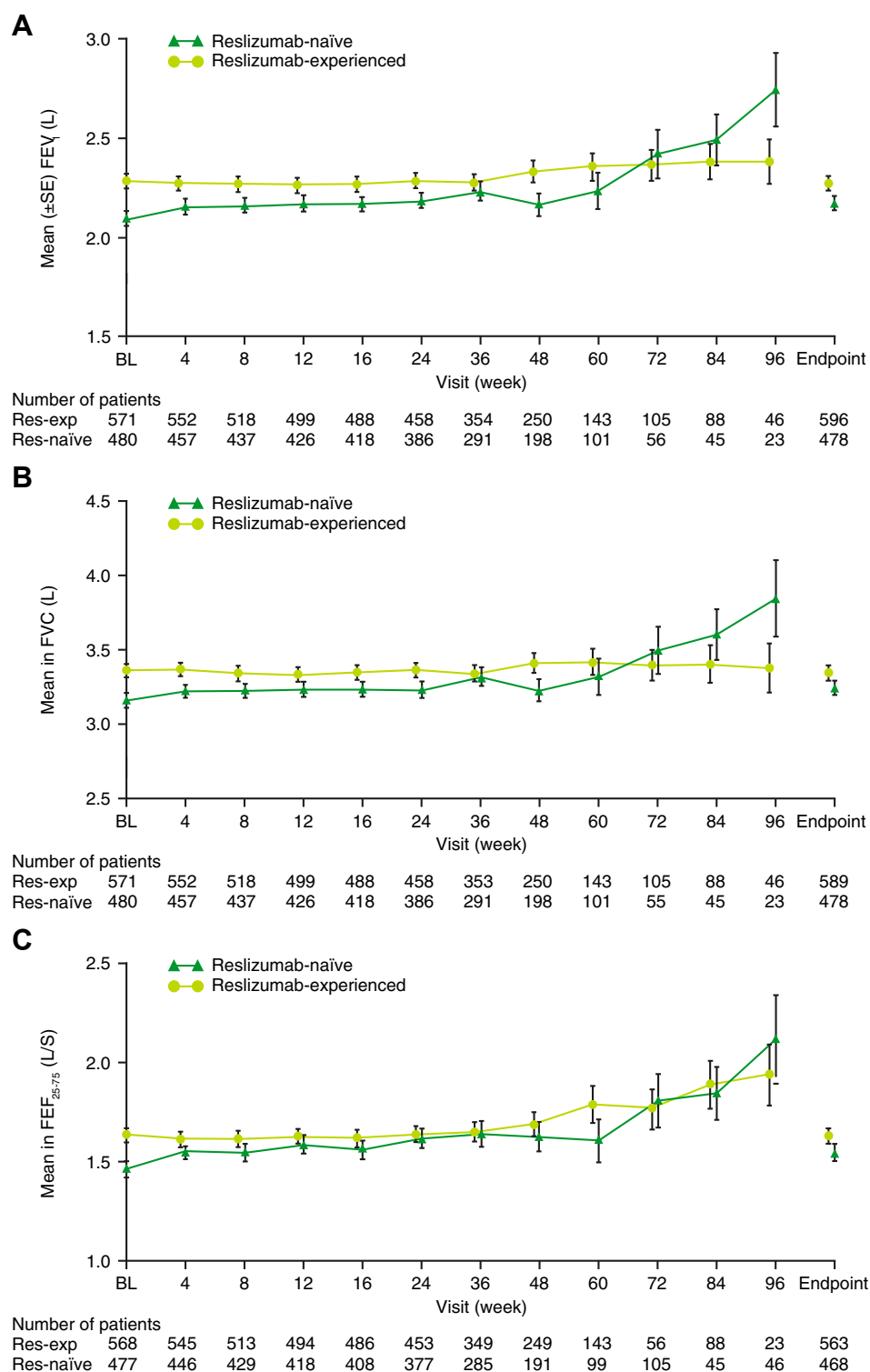


FIGURE 2. Changes in pulmonary function tests (A) FEV₁, (B) FVC, and (C) FEF₂₅₋₇₅ over 96 weeks. Spirometry was obtained throughout the treatment period at the time points shown. BL, Baseline; exp, experienced; FEF₂₅₋₇₅, forced expiratory flow at 25% to 75% of the FVC; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; Res, reslizumab; SE, standard error.

patients appeared to maintain the improvement in asthma control gained during the prior double-blind treatment period, as assessed by ACQ score, throughout the duration of the open-label study (Figure 3, A). Similar treatment effects (ie, early

improvement at first on-treatment assessment and sustained effects in patients previously treated with reslizumab) were observed for QoL and symptoms (AQLQ and ASUI scores; Figure 3, B and C).

TABLE IV. Changes in FEV₁ and ACQ from baseline during the open-label study

	Reslizumab-naïve group				Reslizumab-experienced group			
	N	Mean	SD	P value*	n	Mean	SD	P value*
FEV ₁ (L)								
Change to week 4	457	0.082	0.3181	<.0001	552	0.001	0.2982	.9625
Change to week 16	418	0.090	0.3489	<.0001	488	−0.007	0.3138	.6094
ACQ score								
Change to week 4	456	−0.278	0.8099	<.0001	552	−0.032	0.7012	.2789
Change to week 16	416	−0.360	0.7855	<.0001	487	−0.153	0.7459	<.0001

ACQ, Asthma Control Questionnaire; FEV₁, forced expiratory volume in 1 s; SD, standard deviation.*P value is based on the *t*-test to examine the hypothesis that change = 0.

A decrease from baseline in blood eosinophil count was noted in the reslizumab-naïve group at the first assessment (week 4), while remaining suppressed throughout treatment in reslizumab-experienced patients (Figure 4). Eosinophil counts began to rise in both the reslizumab-naïve and reslizumab-experienced groups by the follow-up visit (3 months after the end-of-treatment visit or approximately 4 months after the last dose of reslizumab), but still remained below the baseline levels observed in the reslizumab-naïve group.

DISCUSSION

In this open-label extension study, the safety and efficacy of reslizumab 3.0 mg/kg administered once every 4 weeks was evaluated in adolescent and adult patients with moderate-to-severe eosinophilic asthma for up to 2 years, with an overall exposure (including the prior placebo-controlled studies) of up to 3 years. This study is the first to report on the long-term safety profile of reslizumab in patients with eosinophilic asthma, and it represents the greatest exposure of any study so far performed with an anti-IL-5 antibody in asthma. The findings substantially add to our understanding of the safety profile of sustained eosinophil lowering in patients with uncontrolled asthma with an eosinophilic phenotype. Reslizumab was well tolerated in these patients, irrespective of previous reslizumab exposure at the start of the open-label study (ie, reslizumab-naïve or reslizumab-experienced). There was no evidence of increased incidence of AEs that might be related to long-term exposure in patients treated for up to 36 months (ie, the reslizumab-experienced group) compared with the reslizumab-naïve group or compared with the placebo-treated patients in the double-blind trials. Our data, along with experience with mepolizumab (eg, 6-year observational study in patients with hyper-eosinophilic syndrome¹⁷; open-label study of up to 22 months of treatment in patients with severe eosinophilic asthma¹⁸), indicate that patients treated with anti-IL-5 antibodies do not develop a “characteristic” set of AEs due to the associated reduction in eosinophil levels.⁸

Overall, the safety and immunogenicity profile of reslizumab in this open-label extension study was similar to previous reports of shorter-term reslizumab treatment,^{11,15,16} and no particular AE or laboratory assessment emerged as a concern with longer duration of reslizumab exposure. Fifteen adult patients had malignancies of diverse and common tissue types reflective of expectations for a primarily adult study population, without evidence of clustering. This distribution of cancer types was consistent with global incidence data listing breast,

colorectal, prostate, and non-Hodgkin lymphoma among the 10 most common cancers worldwide, with incidence rates over 7 per 100,000 in 2013.¹⁹ The preponderance of female patients in this study (61%) may account for the higher frequencies of female reproductive neoplasm versus other reported tumors. Three systemic reactions clinically consistent with anaphylaxis were previously reported during or shortly after reslizumab infusion (within 20 minutes) in placebo-controlled reslizumab trials.^{11,16} These reactions were characterized by various combinations of skin or mucosal involvement, dyspnea, wheezing, GI symptoms, and chills; these reactions were treated at the study site, and the patients discontinued further treatment. However, no such events were reported during this open-label extension phase, including among patients previously treated with placebo and therefore newly exposed to reslizumab in the open-label study.

Improvements in lung function, including FEV₁ and asthma control based on ACQ scores, were observed in reslizumab-naïve patients as early as 4 weeks after the first reslizumab dose, consistent with the early improvement in lung function and asthma control observed in the double-blind trials. These measures appeared to be maintained, without diminution, during continuous reslizumab exposure in reslizumab-experienced patients; similar observations in other lung function (FVC and FEF₂₅₋₇₅), QoL, and symptom scores (AQLQ and ASUI) were supportive of these patterns. The strength of this observation diminishes beyond 48 weeks of open-label exposure, when the sample size begins to drop, with corresponding substantial increases in variability around the measure. The present results are consistent with data from previous reslizumab studies.^{11,15,16,20} Although the frequency of clinical asthma exacerbations was not directly collected in this study, this measure is indirectly captured by overall maintenance of asthma control as indicated by sustained ACQ score improvements.

As most patients in the prior placebo-controlled studies were enrolled directly into the current open-label extension, and therefore had no previous post-treatment follow-up visit, this trial represents the most robust data on eosinophil recovery at follow-up. At the beginning of the open-label extension study, baseline blood eosinophil counts were higher in the reslizumab-naïve group compared with the reslizumab-experienced group. In the reslizumab-naïve group, by the week 4 assessment, eosinophil reductions were similar to those observed in patients receiving continuous reslizumab exposure. At the follow-up visit (within 120 days of the last reslizumab dose), eosinophil levels appeared to have begun to return to baseline. Given that eosinophil levels rise after treatment discontinuation, the immunomodulatory

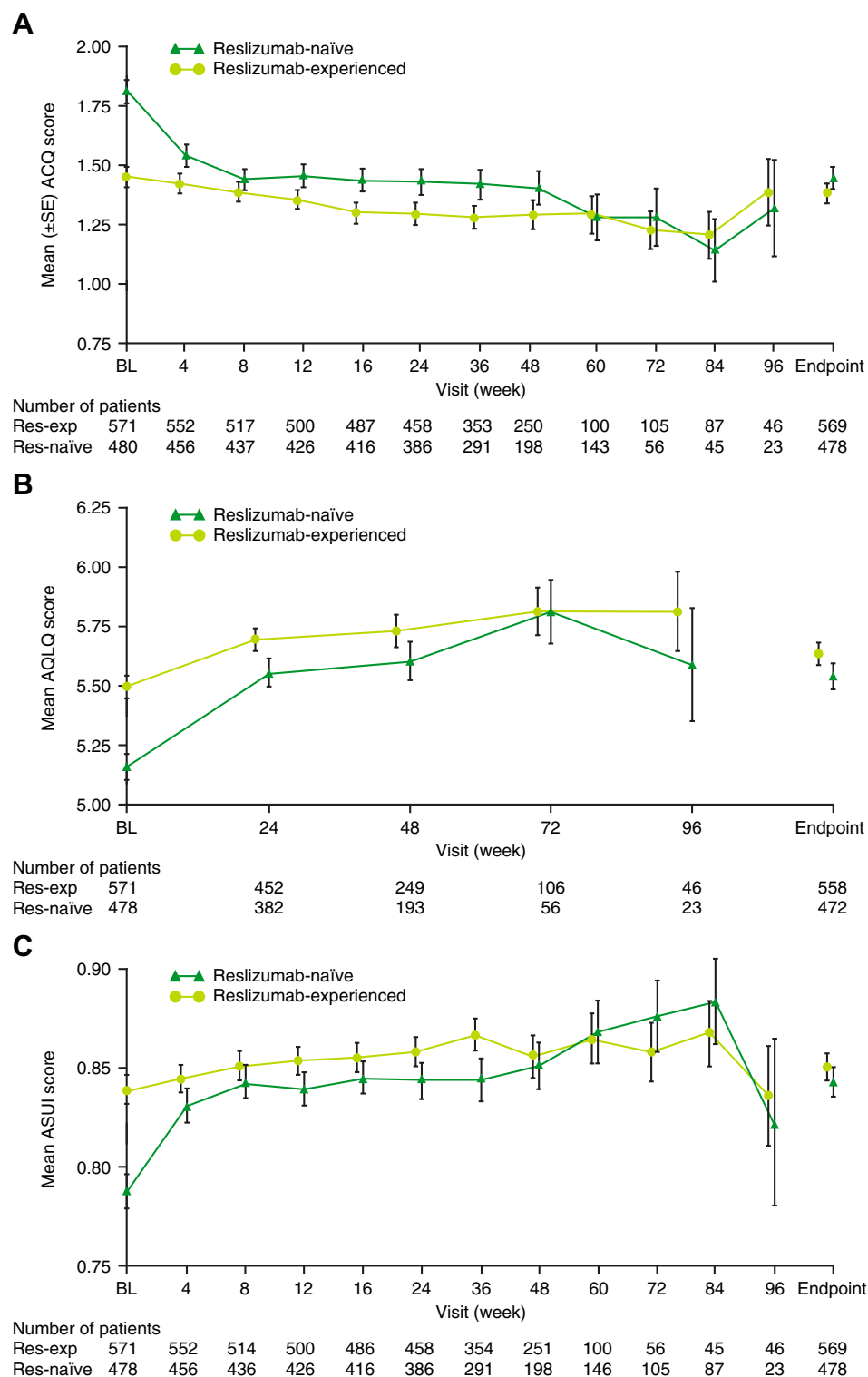


FIGURE 3. Changes in (A) ACQ, (B) AQLQ, and (C) ASUI scores over 96 weeks. Standard patient-reported asthma outcomes were obtained throughout the treatment period at the time points shown. *ACQ*, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *ASUI*, Asthma Symptom Utility Index; *BL*, baseline; *exp*, experienced; *Res*, reslizumab; *SE*, standard error.

effect of reslizumab does not appear to be sustained in the absence of exposure. Results from studies of other IL-5 inhibitors suggest that after cessation of treatment, blood eosinophils return toward baseline (without apparent rebound) with an associated

increase in asthma symptomatology and exacerbation risk.²¹ Clinicians should consider the potential return to baseline eosinophil levels, lung function, and asthma control if reslizumab therapy is discontinued.

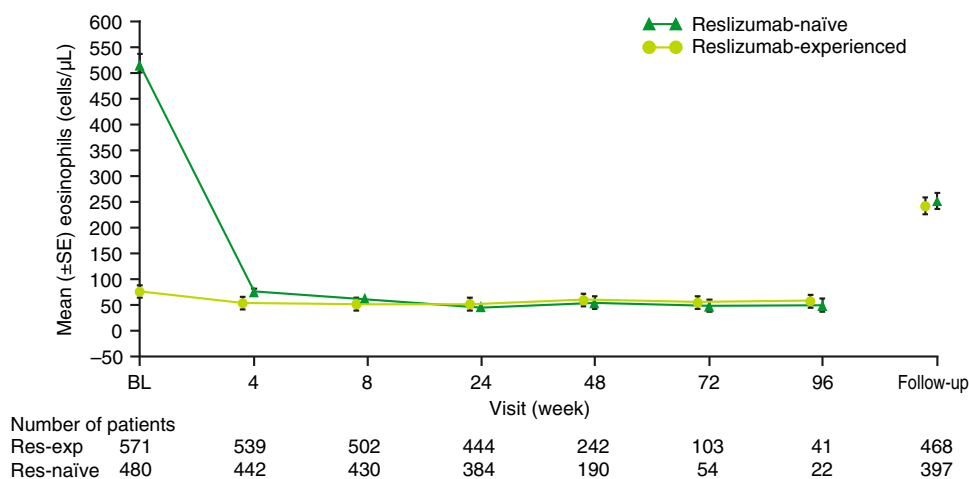


FIGURE 4. Changes in blood eosinophil counts over 96 weeks. Blood eosinophil levels were assessed monthly throughout the treatment period and at follow-up. Note: Eosinophil counts were measured at the follow-up visit, which took place 90 days after the end of treatment (approximately 4 months after the last dose of reslizumab) for all patients including those who discontinued participation early. BL, Baseline; exp, experienced; Res, reslizumab; SE, standard error.

One strength of this study is that more than 1000 patients were evaluated, with over 5500 infusions of reslizumab. In addition, although this was not an efficacy study *per se*, lung function and patient-reported outcome measures were measured over up to 96 weeks of treatment, enabling durability of effect to be assessed. When considering the previous double-blind exposures, 740 patients were exposed to reslizumab for ≥ 1 year and 249 patients for ≥ 2 years. The attrition rate seen here is a consequence of the closure of study sites by the sponsor once sufficient safety data had been generated. It is therefore not possible to draw conclusions regarding expected attrition rates in the clinic from these findings, which could be considered to represent a limitation of this study.

In summary, the results of this open-label extension study demonstrated that continuous treatment with reslizumab 3.0 mg/kg every 4 weeks for up to 2 additional years (after completing the placebo-controlled studies) was well tolerated in patients with moderate-to-severe eosinophilic asthma. No new or unexpected safety concerns were associated with prolonged exposure. The positive treatment effects of reslizumab on lung function and asthma control that occurred during previous clinical studies were sustained for up to an additional 2 years in reslizumab-experienced patients. Consistent with previously reported reslizumab safety and efficacy studies,^{14,15,20} improvements in lung function and patient-reported measures of asthma control and QoL were evident after the first treatment in reslizumab-naïve patients. These safety and efficacy results support the use of reslizumab for long-term control of moderate-to-severe asthma in patients with an eosinophilic phenotype.

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All authors of this manuscript were involved in the acquisition, analysis, or interpretation of the data, and in the preparation or critical revision of the manuscript. All authors had full access to all of the data in the study. All authors agreed with decision to submit for publication, approved the final version of the manuscript, and agreed to be accountable to all aspects of the work (KM, JJ, LB, JMF, YS, MG, JZ, and MC).

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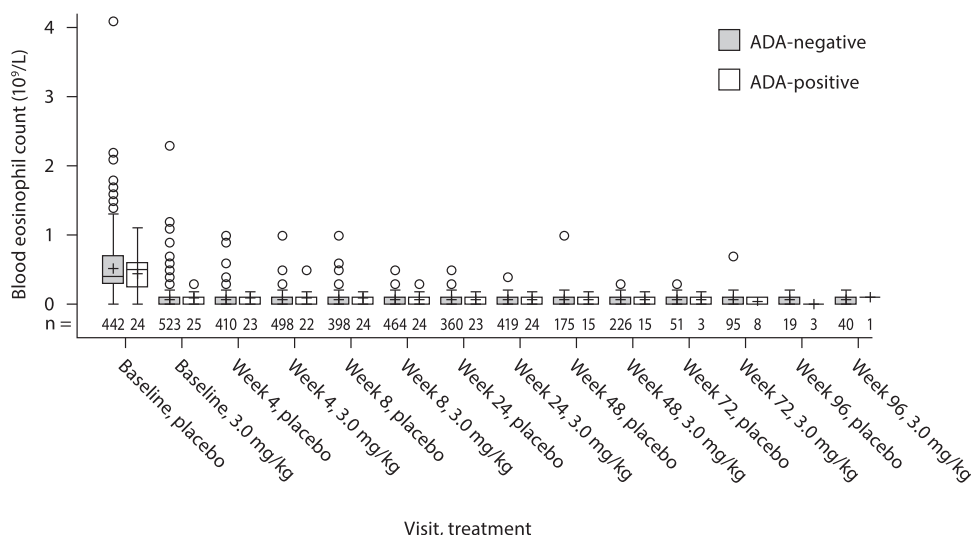


FIGURE E1. Box plots of blood eosinophil count ($10^9/L$) by visit during the open-label study, by double-blind treatment group, and overall ADA status. ADA positivity was not associated with diminished ability of reslizumab to suppress blood eosinophils. ADA, antidrug antibody.

TABLE E1. Treatment exposure (infusions)*

	Reslizumab-naïve (n = 481)	Reslizumab-experienced (n = 571)	Total (N = 1,052)
Treated patients, n (%)	480 (>99)†	571 (100)	1,051 (>99)†
Exposure to reslizumab, n (%)			
≥1 infusion	480 (100)	571 (100)	1,051 (100)
≥3 infusions	440 (92)	523 (92)	963 (92)
≥6 infusions	408 (85)	483 (85)	891 (85)
≥9 infusions	323 (67)	401 (70)	724 (69)
≥12 infusions	227 (47)	290 (51)	517 (49)
≥15 infusions	129 (27)	179 (31)	308 (29)
≥18 infusions	63 (13)	117 (20)	180 (17)
≥21 infusions	46 (10)	90 (16)	136 (13)
≥24 infusions	27 (6)	54 (9)	81 (8)

*Based on treatment in the open-label study only.

†One patient withdrew before receiving study treatment.

TABLE E2. Treatment exposure (months)*

	Reslizumab-naïve (n = 481)	Reslizumab-experienced (n = 571)	Total (N = 1,052)
Treated patients, n (%)	480 (>99)†	571 (100)	1,051 (>99)†
Exposure to reslizumab, n (%)			
≥1 mo	480 (100)	571 (100)	1,051 (100)
≥3 mo	440 (92)	518 (91)	958 (91)
≥6 mo	394 (82)	469 (82)	863 (82)
≥9 mo	297 (62)	364 (64)	661 (63)
≥12 mo	198 (41)	253 (44)	451 (43)
≥15 mo	105 (22)	146 (26)	251 (24)
≥18 mo	60 (13)	102 (18)	162 (15)
≥21 mo	42 (9)	77 (13)	119 (11)
≥24 mo	17 (4)	36 (6)	53 (5)

*Based on treatment in the open-label study only.

†One patient withdrew before receiving study treatment.

TABLE E3. AEs (all causality) leading to withdrawal from the open-label study by SOC and preferred term* (safety analysis set)

AE, n (%)	Reslizumab-naïve (n = 480)	Reslizumab-experienced (n = 571)	Total (N = 1,051)
Patients with ≥1 AE‡ leading to withdrawal	6 (1)	12 (2)	18 (2)
Cardiac disorders	1 (<1)	2 (<1)	3 (<1)
Cardiac arrest	0	1 (<1)	1 (<1)
Cardiorespiratory arrest	0	1 (<1)	1 (<1)
Palpitations	1 (<1)	0	0
General disorders and administration site conditions	1 (<1)	0	1 (<1)
Asthenia	1 (<1)	0	1 (<1)
Fatigue	1 (<1)	0	1 (<1)
Infections and infestations	0	3 (<1)	3 (<1)
Infectious pleural effusion	0	1 (<1)	1 (<1)
Mastoiditis	0	1 (<1)	1 (<1)
Sinusitis	0	1 (<1)	1 (<1)
Injury, poisoning, and procedural complications	1 (<1)	0	1 (<1)
Hand fracture	1 (<1)	0	1 (<1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (<1)	5 (<1)	7 (<1)
Breast cancer	1 (<1)	2 (<1)	3 (<1)
Lymphoma	0	1 (<1)	1 (<1)
Ovarian epithelial cancer	0	1 (<1)	1 (<1)
Prostate cancer	0	1 (<1)	1 (<1)
Colorectal cancer‡	1 (<1)	0	1 (<1)
Nervous system disorders	2 (<1)	1 (<1)	3 (<1)
Nervous system disorder	0	1 (<1)	1 (<1)
Amnesia	1 (<1)	0	1 (<1)
Hypoesthesia	1 (<1)	0	1 (<1)
Pregnancy, puerperium, and perinatal conditions	0	1 (<1)	1 (<1)
Unintended pregnancy	0	1 (<1)	1 (<1)
Psychiatric disorders	1 (<1)	0	1 (<1)
Alcoholism	1 (<1)	0	1 (<1)
Renal urinary disorders	0	1 (<1)	1 (<1)
Proteinuria	0	1 (<1)	1 (<1)
Respiratory, thoracic, and mediastinal disorders	0	1 (<1)	1 (<1)
Hemoptysis	0	1 (<1)	1 (<1)
Pneumonia aspiration	0	1 (<1)	1 (<1)

AE, Adverse event; SOC, system organ class.

*Medical Dictionary for Regulatory Activities preferred terms.

‡AEs that began or worsened after treatment with reslizumab; includes follow-up period.

‡Colorectal lung metastasis.

TABLE E4. Treatment-emergent AEs by SOC during the open-label study ($\geq 5\%$ of patients, any group; safety analysis set)

AE, n (%)	Reslizumab-naïve (n = 480)	Reslizumab-experienced (n = 571)	Total (N = 1,051)	Reslizumab experienced/naïve RR* (95% CI)
Number of patients with ≥ 1 AE	359 (75)	385 (67)	744 (71)	0.9015 (0.8346-0.9738)
Infections and infestations	245 (51)	267 (47)	512 (49)	0.9161 (0.8094-1.0369)
Respiratory, thoracic, and mediastinal disorders	185 (39)	213 (37)	398 (38)	0.9679 (0.8288-1.1303)
Nervous system disorders	75 (16)	66 (12)	141 (13)	0.7398 (0.5438-1.0063)
GI disorders	69 (14)	68 (12)	137 (13)	0.8284 (0.6063-1.1320)
Musculoskeletal and connective tissue disorders	70 (15)	69 (12)	139 (13)	0.8284 (0.6080-1.1293)
Skin and subcutaneous tissue disorders	51 (11)	44 (8)	95 (9)	0.7252 (0.4937-1.0654)
Injury, poisoning, and procedural complications	47 (10)	44 (8)	91 (9)	0.7870 (0.5313-1.1656)
General disorders and administration site conditions	39 (8)	39 (7)	78 (7)	0.8406 (0.5485-1.2883)
Metabolism and nutrition disorders	27 (6)	28 (5)	55 (5)	0.8718 (0.5211-1.4583)
Vascular disorders	15 (3)	27 (5)	42 (4)	1.5131 (0.8145-2.811)

Patients are only counted once in each SOC category. Patients may have reported >1 AE.

AE, Adverse event; CI, confidence interval; GI, gastrointestinal; RR, relative rate; SOC, system organ class.

*The ratio of events for reslizumab-experienced to reslizumab-naïve patients.

TABLE E5. AEs and event rate per 100 patient-years during the open-label study in reslizumab-experienced patients (safety analysis set) and pooled placebo groups of the feeder studies

	Reslizumab-experienced (open-label extension) (n = 571, patient-years = 557.17)		Placebo* (n = 580, patient-years = 472.71)	
	AE, n (%)	Event rate per 100 patient-years	AE, n (%)	Event rate per 100 patient-years
Any AEs†	385 (67)	340.7	473 (82)	549.0
Severe AEs	47 (8)	17.2	61 (11)	18.4
Treatment-related AEs	41 (7)	13.8	63 (11)	34.1
Discontinuations due to AEs	12 (2)	2.7	27 (5)	8.0
Serious AEs	45 (8)	12.9	58 (10)	21.4
Deaths‡	2 (<1)	0.9	1 (<1)	0.2
AEs occurring in $>2\%$ of patients in the current study				
Asthma	159 (28)	54.0	266 (46)	151.5
Nasopharyngitis	81 (14)	23.0	79 (14)	25.5
Upper respiratory tract infection	57 (10)	13.6	52 (9)	15.3
Sinusitis	43 (8)	11.0	34 (6)	10.2
Headache	39 (7)	9.5	63 (11)	20.3
Bronchitis	29 (5)	5.7	43 (7)	11.6
Allergic rhinitis	31 (5)	7.2	19 (3)	4.9
Influenza	24 (4)	6.1	32 (6)	9.1
Urinary tract infection	28 (5)	6.3	24 (4)	6.1
Pharyngitis	21 (4)	4.1	18 (3)	4.2
Acute sinusitis	25 (4)	7.7	11 (2)	2.9
Back pain	21 (4)	4.5	22 (4)	4.6
Rhinitis	17 (3)	3.1	15 (3)	3.8
Cough	18 (3)	3.2	22 (4)	5.5
Arthralgia	15 (3)	2.7	12 (2)	2.7
Hypertension	19 (3)	3.4	7 (1)	1.7
Oropharyngeal pain	12 (2)	2.3	19 (3)	5.0
Gastroenteritis	16 (3)	3.8	12 (2)	3.2
Lower respiratory tract infection	12 (2)	2.5	8 (1)	2.7

AE, Adverse event.

*Integrated results for the placebo arms of the 3 feeder studies during the double-blind treatment period are provided for contrast.

†AEs that began or worsened after treatment with reslizumab; includes follow-up period.

‡There were 2 deaths during the open-label study in the reslizumab-experienced group: 1 patient with a history of bronchiectasis had hemoptysis, complicating bronchiectasis, aspiration pneumonia, and cardiorespiratory arrest, and 1 patient had a cardiac arrest. There was 1 death in a placebo patient due to probable accidental combined drug intoxication with fentanyl.