CHEST

Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels

A Randomized Phase 3 Study

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BACKGROUND: This phase 3 study further characterizes the efficacy and safety of reslizumab (a humanized anti-IL-5 monoclonal antibody) in patients aged 12 to 75 years with asthma inadequately controlled by at least a medium-dose inhaled corticosteroid and with a blood eosinophil count $\geq$ 400 cells/μL.

METHODS: Patients were randomized to receive reslizumab 0.3 or 3.0 mg/kg or placebo administered once every 4 weeks for 16 weeks (total four doses). The primary end point was change from baseline in pre-bronchodilator FEV_1 over 16 weeks. Secondary end points included FVC, forced expiratory flow at 25% to 75% of FVC ($FEF_{25\%-75\%}$), patient-reported control of asthma symptoms, short-acting β-agonist (SABA) use, blood eosinophil levels, and safety.

RESULTS: Reslizumab significantly improved FEV_1 (difference vs placebo [reslizumab 0.3 and 3.0 mg/kg], 115 mL [95% CI, 16-215; $P = .0237$] and 160 mL [95% CI, 60-259; $P = .0018$]). Clinically meaningful increases in FVC (130 mL) and $FEF_{25\%-75\%}$ (233 mL/s) were observed with reslizumab 3.0 mg/kg. Reslizumab improved scores on the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) vs placebo (greater effects seen with 3.0 mg/kg; $P < .05$). The minimally important difference was reached for the AQLQ (reslizumab 3.0 mg/kg) but not on the ACQ. Scores on the Asthma Symptom Utility Index and SABA use were improved with reslizumab. The most common adverse events were worsening of asthma, headache, and nasopharyngitis; most events were mild to moderate in severity.

CONCLUSIONS: Reslizumab improved lung function, asthma control and symptoms, and quality of life. It was well tolerated in patients with inadequately controlled asthma (despite standard therapy) and elevated blood eosinophil levels. Overall, the 3.0-mg/kg dose of reslizumab provided greater improvements in asthma outcomes vs the 0.3-mg/kg dose, with comparable safety.

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ABBREVIATIONS: ACQ = Asthma Control Questionnaire; ADA = antidrug antibody; AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; ASUI = Asthma Symptom Utility Index; $FEF_{25\%-75\%}$ = forced expiratory flow at 25% to 75% of FVC; ICS = inhaled corticosteroids; LABA = long-acting β-agonist; LS = least squares; SABA = short-acting β-agonist

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Asthma is a heterogeneous disease, with many patients experiencing persistent symptoms despite use of recommended asthma therapies. Although numerous factors may account for poor treatment responses, underlying pathobiological differences are increasingly recognized as playing a role.[1] Patients with inflammation-predominant asthma have an increased risk of recurrent exacerbations and hospitalizations.[2] This subgroup is characterized by eosinophilic infiltration of airway mucosa, with an associated increase in eosinophils in the blood, sputum, and BAL fluid.[2,3] Eosinophils have been implicated in epithelial dysfunction, airway remodeling, hyperresponsiveness, and late-phase allergic response.[4-6]

Eosinophil activation and maintenance depend on IL-5, an eosinophil viability-enhancing factor; inhibition of IL-5–mediated signaling disrupts maturation and survival of eosinophils.[7,8] Clinical studies with anti-IL-5 therapies have demonstrated decreases in eosinophil levels, as well as significant improvements in many of the clinically relevant parameters associated with eosinophilic asthma such as reduction in exacerbation frequency and improved symptom control.[9-11] Reslizumab, a humanized anti-IL-5 monoclonal (IgG4/κ) antibody, binds to circulating IL-5 and downregulates the IL-5 signaling pathway.[8,12] In preclinical studies, reslizumab demonstrated high binding affinity for IL-5 and potently inhibited IL-5 activity in a lung eosinophilia model.[12] These studies provided the rationale for targeting IL-5 with reslizumab in patients with asthma and elevated eosinophil levels.

Reslizumab met clinical proof-of-concept for lung function improvement and asthma control in a phase 2 study of asthma patients with sputum eosinophilia (≥ 3%).[13] Assessment of sputum eosinophilia is not practical for large-scale clinical trials and most community health-care providers. Secondary analysis of existing data sets suggested that a blood eosinophil count ≥ 400 cells/μL was highly specific for sputum eosinophils ≥ 3%[14,15]; this level was subsequently used as a surrogate for sputum eosinophilia in the reslizumab phase 3 asthma program (BREATH). Additional analyses also support the relationship between elevated blood eosinophil count and sputum eosinophilia,[16] including a meaningful treatment effect being observed in a subset of patients with a baseline eosinophil count ≥ 400 cells/μL in a phase 3 trial.[17] Overall, these findings support the use of elevated blood eosinophil levels as an appropriate biomarker for identifying a potential responder asthma population for reslizumab.

The aim of the present phase 3 trial (part of the BREATH program) was to further characterize the effect of reslizumab on FEV_1 at two different dose levels (0.3 and 3.0 mg/kg) in patients with persistent asthma and elevated blood eosinophil counts (≥ 400 cells/μL) whose symptoms were inadequately controlled with inhaled corticosteroids (ICS), with or without additional asthma controllers.

Methods

Patients

Eligible patients were aged 12 to 75 years with inadequately controlled asthma (Asthma Control Questionnaire [ACQ]-7 score ≥ 1.5), airway reversibility (≥ 12% to short-acting β-agonist [SABA]), were receiving treatment with at least a medium-dose ICS (fluticasone propionate ≥ 440 μg/d or equivalent), and had at least one blood eosinophil count ≥ 400 cells/μL during the screening period. Other permissible baseline medications included long-acting bronchodilators, leukotriene inhibitors, or cromolyn. The dose of permitted baseline medications had to have been stable for 30 days prior to screening and expected to remain unchanged throughout. Compliance to current therapy was assessed at screening by interview and by asking patients to demonstrate their inhaler technique. Patients who did not use their inhaler correctly were shown the correct method and allowed 2 weeks during the screening period to stabilize. Maintenance oral corticosteroids were not allowed. There were no FEV_1 or asthma exacerbation inclusion requirements.

Key exclusion criteria are provided in e-Appendix 1. The study was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulatory requirements. Relevant health authorities and local ethics committees or institutional review boards approved the study protocols (e-Table 1); all patients provided written informed consent.

Study Design and Treatments

This study was a randomized, double-blind, placebo-controlled, parallel-group, fixed-dosage, phase 3 trial conducted at 68 locations globally.[18] The study consisted of a 2- to 4-week screening period and a 16-week double-blind treatment period, with a final evaluation 4 weeks after the last infusion (end-of-treatment visit); after this visit, patients could enroll in an optional open-label extension study or return for a final end-of-study visit. Eligible patients were

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randomized (1:1:1) to receive infusions of reslizumab 0.3 mg/kg, reslizumab 3.0 mg/kg, or placebo administered once every 4 weeks (total of 4 doses). Patients were stratified according to age group (12-17 years or ≥ 18 years) and history of asthma exacerbations within 12 months prior to screening (yes/no). Exacerbations were defined as one of the following: a reduction in FEV_1 of ≥ 20%, hospitalization due to asthma, emergency treatment of asthma, or use of systemic corticosteroids for ≥ 3 days. Patients were to refrain from using SABAs for 6 h prior to each study visit (including screening). Patients taking long-acting β-agonists (LABAs) were to withhold use for 12 h prior to each study visit.

Efficacy Assessments and End Points

Efficacy assessments included pre-bronchodilator spirometry (FEV_1, FVC, and forced expiratory flow at 25% to 75% of FVC [$FEF_{25\%-75\%}$]), asthma symptoms (ACQ,[19] ACQ-6, ACQ-5) and Asthma Symptom Utility Index [ASUI[20]]), Asthma Quality of Life Questionnaire (AQLQ[21]), rescue inhaler use, and blood eosinophil levels. Rescue inhaler use was assessed via patient recall of the number of inhalations over the preceding 3 days. Given the limited 16-week duration of the study, it was not designed to assess asthma exacerbations as an efficacy end point.

Efficacy end points were assessed at baseline and every 4 weeks thereafter up to week 16 or at early withdrawal, except for AQLQ, which was first assessed at week 16. Safety and tolerability were evaluated according to reported adverse events (AEs) coded by using the Medical Dictionary for Regulatory Activities version 15.0, clinical laboratory test results, vital signs, ECG findings, physical examination, use of concomitant medication, and determination of antidrug antibodies (ADAs).

Statistical Analysis

The primary objective was to determine whether reslizumab 0.3 mg/kg or 3.0 mg/kg improved FEV_1 compared with placebo over 16 weeks in patients with persistent asthma and elevated blood eosinophil levels. The primary analysis was conducted in the full analysis set, consisting of all randomized patients who received ≥ 1 dose of study drug. Pulmonary function tests, ACQ, AQLQ, ASUI, and SABA assessments were excluded from the full analysis set if they were obtained at scheduled visits that were preceded by usage (within 7 days) of a limited subset of medications that could significantly confound interpretation (including oral or systemic corticosteroids, or the addition of a LABA or a long-acting muscarinic antagonist if not taken at baseline) and in violation of the protocol. Assessment of ACQ-6 and ACQ-5 was not predefined. The safety analysis set included patients receiving ≥ 1 dose of study drug.

FEV_1 was analyzed by using a mixed effect model for repeated measures, with fixed effects (ie, treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (ie, height, baseline value), and patient as the random effect. More details on the primary end point analysis are provided in e-Appendix 2.

For secondary efficacy end points, a stratified Cochran-Mantel-Haenszel test was used to analyze the proportion of patients achieving a minimally important difference of ≥ 0.5-point reduction in ACQ or ≥ 0.5-point improvement in AQLQ scores. The mixed effect model for repeated measures was used for secondary pulmonary function measures, ASUI scores, SABA therapy, and blood eosinophil levels. No adjustment for multiplicity was applied.

Results

Patients

Of 1,025 screened patients, 315 were randomly assigned to treatment (Fig 1). Of the 710 patients not enrolled, 626 (88%) did not meet inclusion criteria, the most common reason being baseline blood eosinophil levels < 400 cells/μL. Of the enrolled patients, 265 (84%) completed the study. The most common reason for study discontinuation was occurrence of AEs. The efficacy analysis set (full analysis set) and safety analysis set (patients receiving ≥ 1 dose of study drug) included 311 (99%) patients. At the end of treatment, 271 patients (179 reslizumab-treated, 92 receiving placebo) elected to roll over into an open-label extension study of the 3.0-mg/kg dose.[22]

Patient demographic and baseline disease characteristics were similar between groups (Table 1). The majority of patients were taking an ICS plus a LABA; mean ACQ scores were indicative of a population with inadequately controlled asthma.

Efficacy Outcomes

Overall change in FEV_1 over 16 weeks improved significantly with reslizumab 0.3 mg/kg (115 mL; $P = .0237$) and 3.0 mg/kg (160 mL; $P = .0018$) compared with placebo (Fig 2, Table 2). FEV_1 improved as early as 4 weeks with reslizumab 3.0 mg/kg vs placebo (treatment difference, 153 mL); this improvement was maintained for the duration of the study. Baseline eosinophil levels ≥ 400 cells/μL (< 500 [but ≥ 400]; and ≥ 500 cells/μL) did not consistently influence the magnitude of improvements in FEV_1; the exception was a trend toward a larger treatment effect (compared with the overall effect) for the 3.0-mg/kg dose beginning at an eosinophil count ≥ 700 cells/μL (e-Fig 1). In addition, short-term variability in blood eosinophil counts (ie, primary inclusion of ≥ 1 blood eosinophil count ≥ 400 cells/μL during screening vs ≥ 400 cells/μL at all assessments including baseline) had no notable effect on the primary efficacy outcome. However, it is important to note that the number of patients in the sensitivity analyses was low (difference from placebo, 135 mL [≥ 1 screen eosinophil < 400 cells/μL] vs 155 mL [all ≥ 400 cells/μL]; 3.0 mg/kg reslizumab).

Reslizumab 3.0 mg/kg produced substantial improvements in FVC (treatment difference, 130 mL) and $FEF_{25\%-75\%}$ (treatment difference, 233 mL/s) vs placebo over the 16-week treatment period (e-Fig 2, Table 2); negligible or no improvements in FVC and

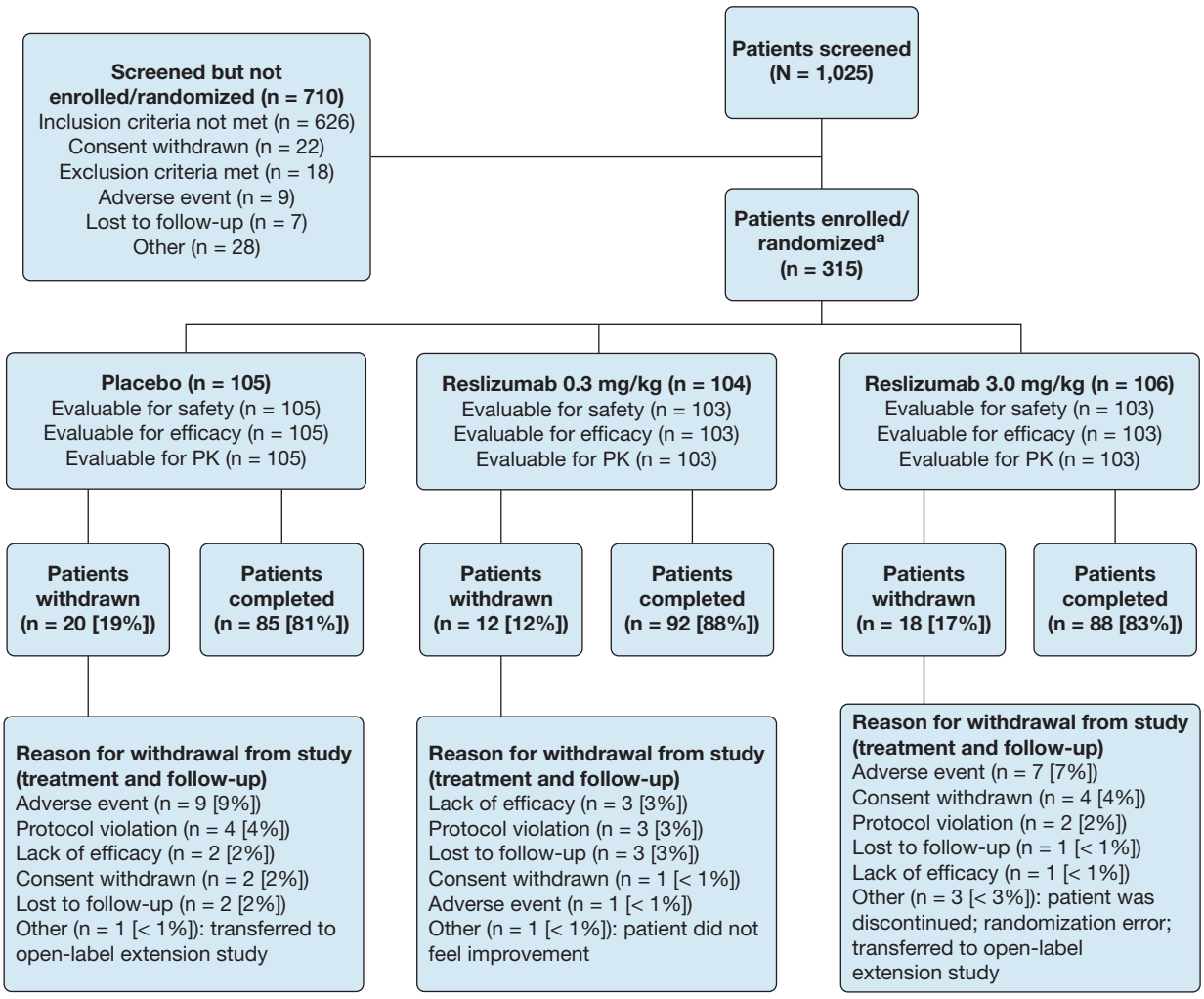

Figure 1 – *Patient disposition.* [a]*Following participation in this study, 271 patients (92 receiving placebo, 179 receiving reslizumab) were enrolled in an open-label extension study to obtain long-term safety and efficacy data for reslizumab. PK = pharmacokinetics.*

$FEF_{25\%-75\%}$ were observed for reslizumab 0.3 mg/kg. Reslizumab 0.3 mg/kg and 3.0 mg/kg improved rescue inhaler use (e-Fig 3, Table 2), ACQ, and asthma symptoms (e-Fig 4, Table 2); overall improvements in ACQ were numerically greater for the 3.0-mg/kg dose. Similar results as those observed for ACQ were seen for ACQ-5 and ACQ-6 (reslizumab 3.0 mg/kg). Improvements in AQLQ scores were observed for reslizumab 3.0 mg/kg. Decreases in blood eosinophil levels were observed for both reslizumab doses and were greatest for reslizumab 3.0 mg/kg (Fig 3, Table 2). Sensitivity analyses without data exclusion for concomitant medication violations were consistent with results of the primary analysis (e-Table 2). The proportion of patients with an minimally important difference of ≥ 0.5 improvement from baseline to end point in AQLQ total score was higher with reslizumab 3.0 mg/kg vs placebo (64% vs 48%, respectively; $P = .0189$) and higher with reslizumab 0.3 mg/kg (59%; P = not significant). For ACQ, a similar proportion of patients in the reslizumab groups and placebo group achieved a 0.5-point reduction from their baseline score to end point (P = not significant).

Safety and Tolerability

Treatment with reslizumab at both study doses was generally well tolerated. A lower proportion of patients receiving reslizumab 0.3 mg/kg (n = 59 [57%]) and 3.0 mg/kg (n = 61 [59%]) experienced ≥ 1 AE compared with placebo (n = 66 [63%]) (Table 3). Treatment-related AEs were reported in eight (8%) patients in the placebo group, 12 (12%) in the 3.0-mg/kg reslizumab group, and six (6%) in the 0.3-mg/kg reslizumab group; the majority of AEs were mild to moderate in severity and were self-limiting. The most common AEs were worsening of

TABLE 1] Patient Demographic and Baseline Disease Characteristics (Randomized Patients)

Characteristic	Placebo (n = 105)	Reslizumab 0.3 mg/kg (n = 104)	Reslizumab 3.0 mg/kg (n = 106)
Demographics			
Mean age, y	44.2	44.5	43.0
Adolescents (aged 12-17 y), No. (%)	5 (5)	5 (5)	5 (5)
Adults (aged ≥ 18 y), No. (%)	100 (95)	99 (95)	101 (95)
Sex, %			
Female	59	57	58
Male	41	43	42
Race, %			
White	81	77	85
Black	7	6	5
Asian	0	2	2
Other[a]	12	15	8
Ethnicity, %			
Non-Hispanic, non-Latino	70	70	71
Hispanic or Latino	28	28	29
BMI, mean, kg/m^2	27.7	27.6	27.4
Disease characteristics			
Mean time since diagnosis, y	20.7	20.0	20.4
Exacerbation within 12 mo, %	54	56	57
ACQ score, mean	2.471	2.481	2.590
AQLQ score, mean	4.374	4.501	4.175
ASUI score, mean	0.674	0.675	0.655
Airway reversibility, mean, %	25.4	24.2	26.2
FEV_1, mean, L	2.222	2.157	2.192
FEV_1, mean, % predicted	71.1	68.8	70.4
Rescue use: mean No. of inhalations/d	2.3	1.9	2.2
Blood eosinophils, mean (range), cells/mL[b]	601 (100-3,700)	648 (100-3,700)	592 (100-2,300)
Treated with LABA, %	80	78	75
Total daily dose of ICS, mean, μg[c]	756.7	756.3	813.5

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ASUI = Asthma Symptom Utility Index; ICS = inhaled corticosteroids; LABA = long-acting β-agonist.
[a]Includes American Indian, Alaska Native, Pacific Islander, and other.
[b]Patients had at least one blood eosinophil level ≥ 400 cells/μL during the 2- to 4-wk screening period.
[c]Fluticasone propionate equivalent.

asthma, headache, nasopharyngitis, upper respiratory tract infection, and sinusitis.

Five patients experienced serious AEs, including acute myocardial infarction in the placebo group (n = 1), and asthma exacerbation (n = 2), sinusitis (n = 1), and pneumonia, road traffic accident, rib fracture, and asthma exacerbation (n = 1) in the reslizumab 3.0-mg/kg group. No serious AEs were considered related to the study drug. Ten (10%) patients in the placebo group, one (< 1%) in the 0.3-mg/kg reslizumab group, and six (6%) in the 3.0-mg/kg reslizumab group withdrew from the study due to AEs (Table 3), most commonly because of an asthma exacerbation. Of note, a requirement for systemic corticosteroid therapy for asthma worsening required withdrawal according to the study protocol. One patient was withdrawn from the reslizumab 3.0-mg/kg group for mild myalgia that was assessed as treatment-related by the investigator. No deaths occurred during the study.

ADA responses were detected in 12% and 11% of patients in the reslizumab 0.3-mg/kg and 3.0-mg/kg groups, respectively. Eight percent of patients who were

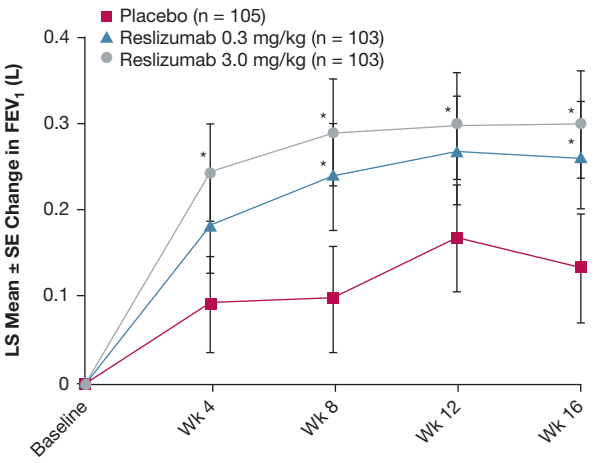

Figure 2 – *Change in FEV_1 over 16 wks. *P ≤ .05 vs placebo. Only wk 16 was controlled for type I error; all other P values were not adjusted to control for multiplicity. LS = least squares.*

subsequently randomized to receive reslizumab had a positive ADA response at baseline (ie, before exposure to the drug). This finding is not unexpected in an assay that is designed to be highly sensitive. Positive ADA responses were of low titer, and the majority of patients were positive at only one time point over the 16-week treatment period. The AE profile of ADA-positive patients was similar to that observed in the overall population. The overall pattern of blood eosinophil suppression by reslizumab in treatment-emergent ADA-positive patients, as a group, was similar to that in ADA-negative patients, indicating that any ADAs, if present, were not neutralizing.

Discussion

In the present study, the choice of a blood eosinophil threshold of ≥ 400 cells/μL was used to select patients with a high likelihood of having active eosinophilic airway inflammation and therefore most likely to benefit from reslizumab. The randomized patient population was consistent with the intended inadequately controlled asthma population based on average ACQ score, AQLQ score, and baseline symptoms; 78% of patients were using a LABA in addition to ICS. Treatment with reslizumab 0.3 mg/kg and 3.0 mg/kg significantly improved pre-bronchodilator FEV_1 over 16 weeks vs placebo. Improvements in FEV_1 were larger for reslizumab 3.0 mg/kg compared with reslizumab 0.3 mg/kg and were observed after the first dose of

TABLE 2] Efficacy End Points Over 16 Weeks (Full Analysis Set)

Variable	Placebo (n = 105)	Reslizumab 0.3 mg/kg (n = 104)	Reslizumab 3.0 mg/kg (n = 106)
FEV_1, L (primary end point)			
No.	103	101	102
LS mean ± SE	0.126 ± 0.0549	0.242 ± 0.0556	0.286 ± 0.0548
Δ (95% CI)[a]		0.115 (0.016 to 0.215)	0.160 (0.060 to 0.259)
P value		.0237	.0018
FVC, L			
No.	103	101	102
LS mean ± SE	0.172 ± 0.0614	0.220 ± 0.0623	0.301 ± 0.0613
Δ (95% CI)[a]		0.048 (−0.058 to 0.155)	0.130 (0.023 to 0.237)
P value		.3731[b]	.0174[b]
$FEF_{25\%-75\%}$, L/s			
No.	103	101	102
LS mean ± SE	−0.145 ± 0.1342	−0.114 ± 0.1361	0.089 ± 0.1342
Δ (95% CI)[a]		0.030 (−0.209 to 0.270)	0.233 (−0.005 to 0.472)
P value		.8020[b]	.0552[b]
SABA use, puffs/d			
No.	102	101	102
LS mean ± SE	−0.3 ± 0.28	−1.0 ± 0.28	−0.9 ± 0.27
Δ (95% CI)[a]		−0.648 (−1.152 to −0.144)	−0.624 (−1.126 to −0.121)
P value		.0119[b]	.0151[b]

(Continued)

TABLE 2] *(Continued)*

Variable	Placebo (n = 105)	Reslizumab 0.3 mg/kg (n = 104)	Reslizumab 3.0 mg/kg (n = 106)
ACQ			
No.	103	101	101
LS mean ± SE	−0.494 ± 0.1231	−0.732 ± 0.1250	−0.853 ± 0.1233
Δ (95% CI)[a]		−0.238 (−0.456 to −0.019)	−0.359 (−0.577 to −0.140)
P value		.0329[b]	.0014[b]
ACQ-5			
No.	103	101	101
LS mean	−0.568	−0.788	−0.917
Δ (95% CI)[a]		−0.220 (−4.60 to 0.020)	−0.349 (−0.590 to −0.109)
P value		.0726	.0045
ACQ-6			
No.	103	101	101
LS mean	−0.514	−0.751	−0.838
Δ (95% CI)[a]		−0.236 (−0.465 to −0.007)	−0.323 (−0.553 to −0.094)
P value		.043	.0058
AQLQ[c]			
No.	101	96	99
LS mean ± SE	0.779 ± 0.1817	1.057 ± 0.1881	1.138 ± 0.1829
Δ (95% CI)[a]		0.278 (−0.036 to 0.591)	0.359 (0.047 to 0.670)
P value		.0822[b]	.0241[b]
ASUI			
No.	103	101	101
LS mean ± SE	0.082 ± 0.0218	0.132 ± 0.0221	0.129 ± 0.0218
Δ (95% CI)[a]		0.051 (0.012 to 0.089)	0.047 (0.009 to 0.085)
P value		.0094[b]	.0160[b]
Blood eosinophil level, cells/μL			
No.	103	101	102
LS mean ± SE	−35 ± 27.1	−358 ± 27.7	−529 ± 27.0
Δ (95% CI)[a]		−323 (−370 to −275)	−494 (−542 to −447)
P value		.0000[b]	.0000[b]

$FEF_{25\%-75\%}$ = forced expiratory flow at 25% to 75% of FVC; LS = least squares; SABA = short-acting β-agonist. See Table 1 legend for expansion of other abbreviations.
[a]Treatment difference (reslizumab − placebo).
[b]*P* values are not adjusted to control for multiplicity.
[c]AQLQ was only assessed once during the study (at wk 16 or early withdrawal).

treatment. Furthermore, variations in baseline eosinophil levels of > 500 and ≥ 800 cells/μL did not meaningfully influence FEV_1 outputs with the 3.0-mg/kg dose of reslizumab. Overall improvements in FVC and $FEF_{25\%-75\%}$ were observed only for reslizumab 3.0 mg/kg, suggesting that patients may require this higher exposure to the drug to derive meaningful improvements in these lung function parameters. The increase in FVC observed with reslizumab 3.0 mg/kg, indicative of a reduction in air trapping and recruitment of peripheral airways, is particularly interesting because it suggests that a higher dose of reslizumab may be needed to treat active eosinophilic inflammation in the peripheral airways.

Both reslizumab doses improved patient-reported asthma control vs placebo as assessed by using ACQ and ASUI scores. The magnitude of improvement in ACQ-7 and AQLQ was larger for reslizumab 3.0 mg/kg than for reslizumab 0.3 mg/kg. Improvements in ACQ-6 (no lung function domain) were comparable with ACQ-7 results, suggesting that the observed improvements

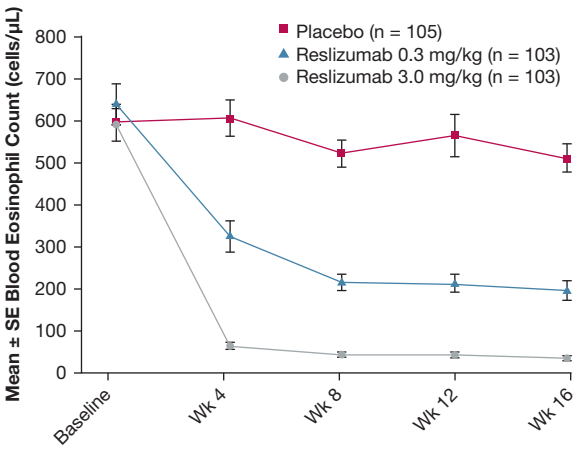

Figure 3 – *Change in blood eosinophil levels over 16 wks.*

in asthma control were not driven by improvement in FEV_1 alone. Decreases in rescue inhaler use were also observed for both reslizumab doses vs placebo. Overall reductions in blood eosinophil levels were greater with reslizumab vs placebo, with the greatest decreases observed with the 3.0-mg/kg dose. At least one-half of patients achieved a ≥ 0.5-point improvement in AQLQ and ACQ score with both doses of reslizumab; the differences for ACQ were not statistically different. However, a recent systematic review and meta-analysis reported by Bateman et al[23] suggests that the established within-patient minimally important difference for the ACQ and AQLQ is not achievable as a group-wise efficacy threshold between treatment arms in clinical studies in which controllers are added to ICS treatment.

Early clinical studies investigating anti-IL-5 antibodies as therapy in unselected patients with asthma (ie, irrespective of eosinophil levels) have shown limited clinical efficacy.[24-26] In a subsequent randomized study in patients with inadequately controlled asthma and sputum eosinophilia (≥ 3%), treatment with reslizumab 3.0 mg/kg improved FEV_1, asthma control, and the number of exacerbations compared with placebo.[13] The clinical outcomes observed with reslizumab 3.0 mg/kg in the present trial support the efficacy of this dose in asthma patients with elevated blood eosinophil levels, particularly in terms of early improvement in airway function (including indices of air trapping and small airway function) vs the 0.3-mg/kg dose. A companion phase 3 study further confirmed the utility of a blood eosinophil level ≥ 400 cells/μL for selecting reslizumab-responsive patients.[17]

As part of the BREATH program, Castro et al[27] recently demonstrated a significant reduction in asthma exacerbations and improvements in lung function, symptoms, and disease-specific quality of life with reslizumab 3.0 mg/kg vs placebo; the investigators used duplicate randomized, placebo-controlled phase 3 trials

TABLE 3] Summary of AEs (Safety Population)

AE	Placebo (n = 105)	Reslizumab 0.3 mg/kg (n = 103)	Reslizumab 3.0 mg/kg (n = 103)
Any AEs	66 (63)	59 (57)	61 (59)
Treatment-related AEs	8 (8)	6 (6)	12 (12)
Serious AEs	1 (< 1)	0	4 (4)
Discontinuations due to AEs	10 (10)	1 (< 1)	6 (6)
AEs in > 2% of patients in any reslizumab group (preferred term)			
Asthma worsening	20 (19)	6 (6)	16 (16)
Headache	6 (6)	8 (8)	11 (11)
Nasopharyngitis	4 (4)	6 (6)	6 (6)
Upper respiratory tract infection	3 (3)	3 (3)	5 (5)
Sinusitis	3 (3)	3 (3)	4 (4)
Urinary tract infection	3 (3)	1 (< 1)	4 (4)
Dyspnea	1 (< 1)	1 (< 1)	4 (4)
Bronchitis	5 (5)	5 (5)	2 (2)
Nausea and vomiting[a]	0	4 (4)	2 (2)
Allergic rhinitis	4 (4)	4 (4)	1 (< 1)
Pharyngitis	3 (3)	3 (3)	1 (< 1)
Acute sinusitis	2 (2)	3 (3)	1 (< 1)

Data are presented as No. (%). AE = adverse event.
[a]High-level term used to reflect concurrence of these related events in the same patient.

of patients with inadequately controlled asthma, elevated blood eosinophil levels (≥ 400 cells/μL), and history of asthma exacerbation.

Another IL-5 inhibitor, mepolizumab, was studied in patients with asthma inadequately controlled with high-dose ICS plus an additional controller and who had experienced ≥ 2 asthma exacerbation during the past year. "Probable" eosinophilic asthma included patients with blood eosinophil counts ≥ 150 cells/μL or with a history of eosinophil counts ≥ 300 cells/μL[10] or with other surrogate markers of airway eosinophilia.[11] The Dose Ranging Efficacy and Safety with Mepolizumab (DREAM) study found no significant differences compared with placebo in any of the secondary end points tested, including FEV_1 and ACQ. The subsequent Mepolizumab as Adjunctive Therapy in. Patients with Severe Asthma (MENSA) study, however, did find impacts on these end points, with larger improvements observed in patients with higher baseline eosinophil counts.[10] Thus, the consistent clinical improvements observed with reslizumab across multiple measures of asthma control and lung function are probably due to inclusion of patients who are more likely to have active eosinophilic airway inflammation (based on higher screening blood eosinophil count), consistent therapeutic exposures afforded by the weight-based dosing regimen, and to the high affinity of reslizumab for IL-5.[8]

Reslizumab was generally well tolerated in the present study, with a safety profile commensurate with previously reported trials of reslizumab.[13,26,27] Most AEs were mild or moderate in severity and not considered treatment related, and AEs and withdrawals due to AEs were infrequent, the nature and pattern of which raise no specific concerns. Importantly, safety and tolerability were similar between the 0.3-mg/kg and 3.0-mg/kg doses, indicating that the more pronounced clinical benefit achieved with reslizumab 3.0 mg/kg was not associated with decreased safety or tolerability.

Conclusions

IV reslizumab 3.0 mg/kg provided improvements in lung function, asthma symptoms, and quality of life for patients with inadequately controlled asthma and elevated blood eosinophil levels (≥ 400 cells/μL) that were generally greater than those provided with the 0.3-mg/kg dose. These efficacy findings are consistent with results from other reslizumab trials and, combined with the favorable safety profile observed, support the use of reslizumab 3.0 mg/kg in patients with asthma and elevated blood eosinophil counts uncontrolled with an ICS-based regimen.

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Additional information: The e-Appendixes, e-Tables, and e-Figures can be found in the Supplemental Materials section of the online article.

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