

Effect of intravenously administered reslizumab on spirometric lung age in patients with moderate-to-severe eosinophilic asthma

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ABSTRACT

Background: Spirometric lung age expresses lung function relative to chronological age. It has been effective in encouraging smoking cessation and has been used in the assessment of asthma. Reslizumab, a humanized anti-interleukin-5 monoclonal antibody, is approved as add-on therapy for adults with severe asthma and elevated blood eosinophils.

Objective: To assess the effect of reslizumab versus placebo on the change in lung age over 52 weeks and the correlation between change in lung age and quality of life in moderate-to-severe asthma.

Methods: This was a post hoc analysis of two randomized, double-blind, placebo-controlled trials. Patients ages 12–75 years with moderate-to-severe, inadequately controlled asthma and elevated blood eosinophils received intravenous reslizumab 3.0 mg/kg or placebo every 4 weeks for 1 year. Spirometry was performed every 4 weeks, and the Asthma Quality of Life Questionnaire (AQLQ) score was assessed at baseline and weeks 16, 32, and 52.

Results: Mean improvement in lung-age deficit at week 52 was –8.73 years for reslizumab versus –3.80 years for placebo, a treatment difference of 5 years ($p < 0.0001$). A statistically significant effect was seen as early as 4 weeks. In AQLQ responders (≥ 0.5 increase in AQLQ score), a statistically significant inverse relationship between the change from baseline in lung age and AQLQ score at weeks 16, 32, and 52 was observed among patients treated with reslizumab only. Among lung-age responders (≥ 5 years' reduction), a statistically significantly greater proportion of patients on reslizumab achieved ≥ 0.5 increase in the AQLQ score versus placebo at all time points.

Conclusion: Reslizumab reduced lung-age deficit by 5 years in patients with moderate-to-severe inadequately controlled eosinophilic asthma. Improvement in lung age correlated with improved quality of life. Lung age is a simple indication of pulmonary function and could be a valuable tool in asthma education.

Clinical trials NCT01287039 and NCT01285323, www.clinicaltrials.gov.

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Asthma is a common, chronic, heterogeneous respiratory disease that affects >334 million people worldwide.¹ Asthma is characterized by variable symptoms of wheeze, shortness of breath, chest tightness and/or cough, and expiratory airflow limitation. In particular, expiratory lung function varies over time and magnitude to a greater extent in patients with asthma versus healthy populations.² Asthma manifests as severe disease in ~5–10% of

patients.³ It has been estimated that ~5% of all adult patients with asthma are thought to fulfill the criteria for eosinophilic asthma,⁴ and that ~20–45% of patients with severe or difficult-to-treat asthma have elevated eosinophils.^{5–7} Eosinophilia is generally associated with more severe asthma, which manifests in an increased risk of asthma exacerbations and airflow limitation.^{8–12}

Although appropriate patient education is now recognized as an integral part of effective asthma management,² many patients with asthma do not routinely receive adequate disease education.¹³ Even when education is provided, patients may continue to perceive the disease as an episodic rather than a chronic problem. For example, one study reported that 53% of patients hospitalized due to asthma believed that they only had asthma when they were having symptoms, which led to poor treatment adherence.¹⁴ Indeed, medication adherence varies widely among patients with asthma, from ~20% to 70% for inhaled corticosteroids (ICS),¹⁵ leads to sub-optimal outcomes.¹⁶ Other barriers to effective asthma management include poor physician com-

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munication skills and deficits in patient health literacy.^{13,17}

Spirometric lung age allows lung function to be expressed relative to chronological age and is calculated by comparing spirometric performance with predicted reference values derived from linear regression equations, which reflect average lung function performance of healthy, non-smoking individuals of corresponding age and sex.¹⁸ The concept of lung age was first proposed in 1985 as a way to simplify the communication of spirometry data and as a tool to motivate smoking cessation,¹⁸ and has been effective in randomized clinical trials.^{19,20} Because lung age seems effective in communicating complex spirometry data to smokers, it may offer similar benefits of lung age to patients with asthma as part of an overall educational program. The impact of asthma on lung age has previously been assessed, and lung age has been suggested as a strategy to motivate smoking cessation in patients with asthma; however, the utility of lung age as an asthma management tool has been unexplored.^{21–23}

Intravenous (IV) reslizumab is a humanized anti-interleukin-5 (IL-5) monoclonal antibody approved in the United States and Europe as add-on therapy for adult patients (≥ 18 years of age) with severe asthma and elevated blood eosinophils. In two 52-week, randomized, double-blind, placebo-controlled trials, IV reslizumab demonstrated significant improvements in clinical asthma exacerbations, forced expiratory volume in 1 second (FEV₁), and the Asthma Quality of Life Questionnaire (AQLQ) score at 52 weeks in patients ages 12–75 years with inadequately controlled moderate-to-severe asthma and blood eosinophils of ≥ 400 cells/ μ L.²⁴ The objective of this *post hoc* analysis was to assess the effect of IV reslizumab compared with placebo on the change in spirometric lung age over 52 weeks of treatment and to investigate the correlation between the change in lung age and the AQLQ score.

METHODS

Data were obtained from two 52-week, randomized, double-blind, placebo-controlled trials (NCT01287039 and NCT01285323) performed at 232 centers in Asia, Australia, North America, South America, South Africa, and Europe.¹⁵ The studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice guidelines, and the ethics committee at each participating site.

Patients

Participants were enrolled if they met the following criteria: ages 12–75 years; moderate-to-severe asthma,

inadequately controlled (Asthma Control Questionnaire-7 score ≥ 1.5) when using medium-to-high doses of ICS-based therapy; blood eosinophils ≥ 400 cells/ μ L; one or more exacerbations in the previous year; and FEV₁ reversibility of $\geq 12\%$ with a short-acting β -agonist. All the patients were receiving at least a medium dose of ICS (fluticasone propionate, ≥ 440 μ g per day or equivalent), with or without another controller drug (including oral corticosteroids [OCS], ≤ 10 mg/day of prednisone or equivalent).

Study Design

Eligible patients were randomized (1:1) to an IV infusion of reslizumab 3.0 mg/kg or placebo every 4 weeks for 1 year. Patients continued their usual asthma treatment at constant doses throughout the treatment period. Prebronchodilator spirometry was performed during clinic visits every 4 weeks after randomization to the end of treatment. The AQLQ score was assessed at baseline and at weeks 16, 32, and 52 (or early withdrawal).

Outcomes

Lung-age deficit was calculated as lung age minus chronological age. A correlation between the change from baseline in lung age and the change from baseline in the AQLQ score was assessed for reslizumab and placebo treatment groups at weeks 16, 32, and 52, stratified by the AQLQ response. AQLQ responders were defined as those with an increase of ≥ 0.5 from baseline over 52 weeks, which represented a minimal important difference.²⁵ In addition, among lung-age responders (defined as showing a clinically relevant reduction of ≥ 5 years over 52 weeks of treatment), the proportion of patients who were also AQLQ responders and the mean change from baseline in the AQLQ score was assessed for reslizumab and placebo treatment groups at weeks 16, 32, and 52.

Statistical Analysis

In this *post hoc* analysis, spirometric lung age was calculated by using the Morris and Temple equations¹⁸ for reslizumab and placebo over 52 weeks, as follows:

- Males: lung age (years) = $2.870 \times \text{height (inches)} - (31.250 \times \text{observed FEV}_1) - 39.375$
- Females: lung age (years) = $3.560 \times \text{height} - (40.000 \times \text{observed FEV}_1) - 77.280$

For the statistical model to analyze lung-age deficit, a mixed model with repeated measures was used with fixed factors when adjusting for study, sex, region, OCS use at enrollment, treatment, visit, treatment-by-visit interaction, covariates for height and baseline lung age, and the patient as a random effect. The correlation between the change from baseline in lung

Table 1 Baseline characteristics and clinical characteristics

	Placebo (n = 476)*	Reslizumab 3.0 mg/kg (n = 477)	Total (n = 953)
Age, mean $\pm$ SD, y	47.1 $\pm$ 14.3	46.5 $\pm$ 13.8	46.8 $\pm$ 14.0
Sex, male, n (%)	165 (35)	191 (40)	356 (37)
BMI, mean $\pm$ SD, kg/m ²	27.51 $\pm$ 5.66	27.35 $\pm$ 5.80	27.43 $\pm$ 5.73
Age of asthma onset, mean $\pm$ SD, y	27.8 $\pm$ 17.9	27.3 $\pm$ 18.4	27.5 $\pm$ 18.1
High-dose ICS use, n (%)#	208 (44)	203 (43)	411 (43)
OCS use, n (%)	73 (15)	73 (15)	146 (15)
LABA use, n (%)	383 (80)	397 (83)	780 (82)
Lung age, mean $\pm$ SD, y	79.4 $\pm$ 23.5	79.0 $\pm$ 24.4	79.2 $\pm$ 23.9
Lung-age deficit, mean $\pm$ SD, y	32.2 $\pm$ 21.4	32.5 $\pm$ 22.2	32.4 $\pm$ 21.8
FEV ₁ , mean $\pm$ SD			
Prebronchodilation, L	1.97 $\pm$ 0.73	2.01 $\pm$ 0.76	1.99 $\pm$ 0.75
% Predicted	66.50 $\pm$ 19.42	66.89 $\pm$ 20.04	66.70 $\pm$ 19.72
% Reversibility	27.47 $\pm$ 21.05	27.04 $\pm$ 15.77	27.26 $\pm$ 18.59
FVC, mean $\pm$ SD, L	3.01 $\pm$ 1.03	3.07 $\pm$ 1.01	3.04 $\pm$ 1.02
ACQ-6 score, mean $\pm$ SD	2.52 $\pm$ 0.90	2.44 $\pm$ 0.93	2.48 $\pm$ 0.91
AQLQ score, mean $\pm$ SD	4.19 $\pm$ 1.08	4.33 $\pm$ 1.07	4.26 $\pm$ 1.08
Blood eosinophil count, mean $\pm$ SD, cells/Liter	0.66 $\pm$ 0.64	0.65 $\pm$ 0.62	0.66 $\pm$ 0.63
CAEs within the past 12 months, mean $\pm$ SD	2.06 $\pm$ 2.07§	1.87 $\pm$ 1.60§	1.96 $\pm$ 1.85

SD = Standard deviation; BMI = body mass index; ICS = inhaled corticosteroid; OCS = oral corticosteroid; LABA = long-acting β -agonist; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; ACQ-6 = Asthma Control Questionnaire-6; AQLQ = Asthma Quality of Life Questionnaire; CAE = clinical asthma exacerbation.

* Two patients in the placebo group were excluded from the analysis due to unavailability of height data, which meant that lung age could not be calculated for these patients.

High-dose ICS use was defined as the patient receiving any one of the following daily doses: fluticasone >500 μ g, mometasone >440 μ g, budesonide >800 μ g, ciclesonide >320 μ g, beclomethasone >400 μ g, or triamcinolone >2000 μ g.

§ Two patients in the placebo group and four patients in the reslizumab group did not experience a CAE in the year before the study start and were excluded from the mean calculation.

age and AQLQ was assessed by using the Pearson correlation coefficient when calculating confidence intervals (CI), and *p* values were assessed by using the Fischer z transformation. Between-group comparisons for the proportion of patients who were AQLQ responders were obtained by using the Cochran-Mantel-Haenszel test, stratified by study, region, and OCS use at enrollment. Mean changes in the AQLQ score were determined overall and at each week by using inferential statistics from a mixed effect model repeated measurement, with treatment, study, visit, treatment-by-visit interaction, region, and OCS use at enrollment as fixed factors, and covariates for height and baseline value, and the patient as a random effect. An unstructured covariance structure was assumed for the repeated measures. Statistical significance was determined at the two-sided 0.05 level (no adjustments were made for multiplicity). SAS v9.4 software (SAS Institute Inc., Cary, NC) was used for all statistical analyses.

RESULTS

A total of 953 patients were randomized to placebo (*n* = 476) or reslizumab (*n* = 477) in the two randomized, placebo-controlled trials. Two patients on placebo were excluded from the analysis because unavailability of height data meant that lung age could not be calculated. Therefore, 474 and 477 patients who were receiving placebo and reslizumab, respectively, were included in this analysis. Baseline demographics and clinical characteristics are summarized in Table 1.

Effect of Reslizumab on Patients' Lung Age

Mean $\pm$ standard deviation (SD) lung age at baseline was 79.4 $\pm$ 23.5 years in the placebo group and 79.0 $\pm$ 24.4 years in the reslizumab group (Table 1). Corresponding mean $\pm$ SD lung-age deficits at baseline were 32.2 $\pm$ 21.4 years and 32.5 $\pm$ 22.2 years, respectively. Overall, the mean lung-age deficit decreased over the 52-week treatment period in both groups (Fig. 1). How-

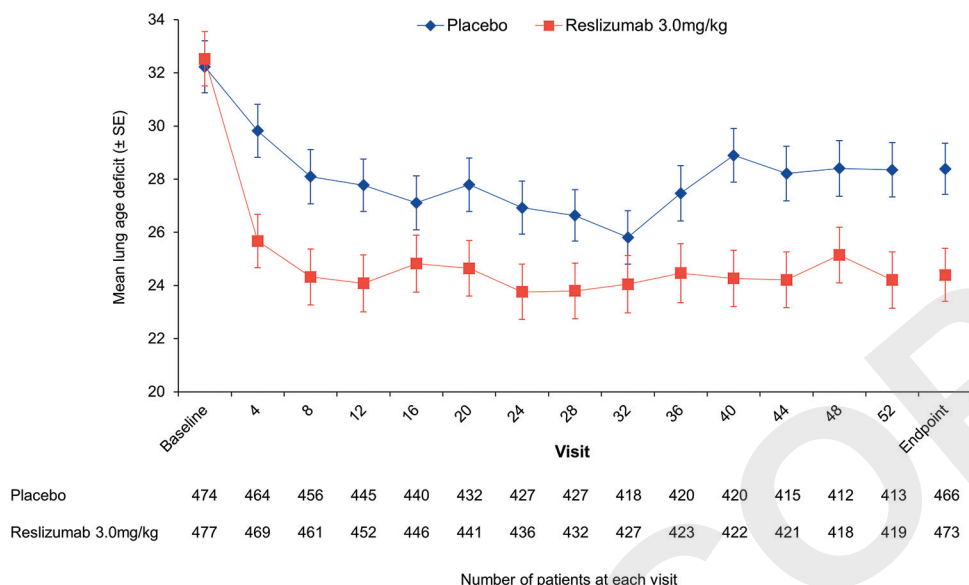


Figure 1. Lung-age deficit over 52 weeks of treatment. SE = Standard error; end point = the time point when the last observation was obtained at a postbaseline scheduled visit or early termination.

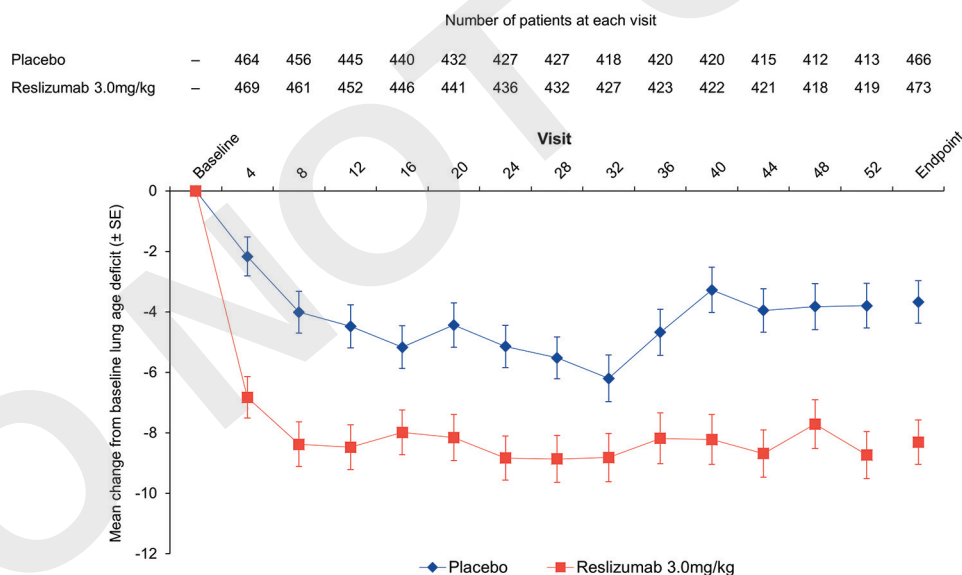


Figure 2. Change from baseline in lung-age deficit over 52 weeks of treatment. SE = Standard error; end point = the time point when the last observation was obtained at a postbaseline scheduled visit or early termination.

ever, at all time points, greater improvements from baseline in the mean lung-age deficit were seen among patients treated with reslizumab compared with those on placebo (Fig. 2, Table 2). A significant effect of reslizumab versus placebo on the mean lung-age deficit was seen as early as the first measured time point, 4 weeks after the first dose of the study drug. At 4 weeks, the mean $\pm$ standard error (SE) change from baseline was -6.82 ± 0.69 years for reslizumab versus -2.17 ± 0.64 years for placebo, which represented a treatment difference of 5 years (95% CI, -6 to -3 ; $p < 0.0001$) (Fig. 2, Table 2). This improvement in the lung-age deficit was maintained through the 52-week treat-

ment period. At week 52, the mean $\pm$ SE improvement from baseline in the lung-age deficit in patients treated with reslizumab ($n = 419$) was -8.73 ± 0.78 years versus -3.80 ± 0.74 years among those who received placebo ($n = 413$). This represented a treatment difference of 5 years between the two groups after 52 weeks of treatment (95% CI, -7 to -3 ; $p < 0.0001$) (Fig. 2, Table 2).

Correlation Between the Change in Lung Age and AQLQ Score

The correlation between the change from baseline in lung age and AQLQ score among the overall popula-

Table 2 Change from baseline and treatment differences (reslizumab vs placebo) in lung-age deficit (years) at each time point

Wk	Mean $\pm$ SE Change from Baseline, y		Treatment Difference (reslizumab vs placebo), y	$\pm$ SE of Treatment Difference	95% CI	<i>p</i>
	Placebo (<i>n</i> = 476)	Reslizumab (<i>n</i> = 477)				
4	−2.17 (0.64)	−6.82 (0.69)	−5	0.88	−6 to −3	<0.0001
8	−4.01 (0.69)	−8.38 (0.74)	−4	0.95	−6 to −2	<0.0001
12	−4.48 (0.71)	−8.48 (0.74)	−4	0.96	−6 to −2	0.0001
16	−5.17 (0.71)	−7.99 (0.74)	−3	0.95	−5 to −1	0.0027
20	−4.44 (0.73)	−8.15 (0.76)	−4	0.96	−6 to −2	0.0001
24	−5.14 (0.70)	−8.83 (0.73)	−4	0.93	−5 to −2	0.0001
28	−5.52 (0.69)	−8.86 (0.78)	−3	0.94	−5 to −1	0.0006
32	−6.20 (0.77)	−8.82 (0.80)	−3	1.01	−4 to −0	0.0180
36	−4.68 (0.76)	−8.18 (0.84)	−4	1.04	−6 to −1	0.0008
40	−3.27 (0.75)	−8.22 (0.82)	−5	1.00	−7 to −3	<0.001
44	−3.95 (0.72)	−8.68 (0.78)	−5	0.96	−6 to −3	<0.0001
48	−3.82 (0.76)	−7.71 (0.81)	−4	1.00	−6 to −2	0.0004
52	−3.80 (0.74)	−8.73 (0.78)	−5	0.97	−7 to −3	<0.0001
End point*	−3.67 (0.70)	−8.31 (0.73)	−5	0.93	−6 to −3	<0.0001

SE = Standard error; CI = confidence interval.

* The time point at which last observation was obtained at a postbaseline scheduled visit or early termination.

tion and stratified by AQLQ response (response is a ≥ 0.5 increase in the AQLQ score) is shown in Table 3. For AQLQ responders who received placebo, there was no correlation seen at weeks 16 and 32, whereas a weak but statistically significant correlation was observed at week 52 (-0.12 ; $p = 0.0485$). In contrast, correlations between the change from baseline in lung age and AQLQ scores in AQLQ responders treated with reslizumab were all significant at weeks 16, 32, and 52 (-0.29 , -0.33 , and -0.29 at weeks 16, 32, and 52, respectively; $p < 0.0001$ in each case). This demonstrated that improvement in the AQLQ score significantly correlated with improvement in lung age among patients treated with reslizumab who had a clinically relevant response in quality of life (QoL). In the overall population (not stratified by the AQLQ response), correlation estimates with reslizumab were similar to those observed among AQLQ responders and were greater than with placebo at all time points (Table 3).

Response Among Lung-Age Responders

Baseline demographics and clinical characteristics for lung-age responders (reduction of ≥ 5 years over 52 weeks) are shown in Table 4. At baseline, lung-age responders had a greater lung age deficit and slightly lower FEV₁ and FEV₁ % predicted compared with the overall population. Among lung-age responders, the proportion of patients who achieved a ≥ 0.5 increase in the AQLQ score and mean change from baseline in

AQLQ score at weeks 16, 32, and 52 was significantly greater for reslizumab than for placebo (Table 5). Greater improvements from baseline in the mean lung-age deficit with reslizumab compared with placebo were generally seen through the 52-week treatment period among lung-age responders (Table 6).

DISCUSSION

Increased blood and sputum eosinophil counts are recognized markers of asthma disease severity^{26,27} and are independent risk factors for future asthma exacerbations and decreased control.^{11,12,28,29} Over the past 2 decades, advances in our understanding of the pathophysiology of asthma led to the personalization of treatments that target specific pathways or mediators, such as eosinophils.³⁰ In the BREATH clinical program, IV reslizumab was investigated in two duplicate phase III, placebo-controlled clinical trials that included patients with inadequately controlled asthma and elevated blood eosinophil levels. IV reslizumab administered every 4 weeks achieved a $\geq 50\%$ reduction in asthma exacerbations and significantly improved multiple measures of asthma control, including FEV₁, asthma symptoms, and asthma-related QoL.²⁴

The present *post hoc* analysis included patients with moderate-to-severe and uncontrolled eosinophilic asthma, with a lung-age deficit at baseline of ~ 32 years. This deficit demonstrated that, on average, patient lung function was similar to that of someone 32 years

Table 3 Correlation between change from baseline in lung age and AQLQ score

	<i>n</i>	Correlation Estimate	95% CI	<i>p</i>
Overall population				
Wk 16				
Placebo	430	−0.106	−0.198 to −0.011	0.0293
Reslizumab	436	−0.310	−0.383 to −0.212	<0.0001
Wk 32				
Placebo	410	−0.159	−0.251 to −0.062	0.0013
Reslizumab	417	−0.342	−0.412 to −0.241	<0.0001
Wk 52				
Placebo	407	−0.187	−0.277 to −0.089	0.0002
Reslizumab	414	−0.284	−0.363 to −0.185	<0.0001
AQLQ responders (≥0.5 increase in AQLQ score)				
Wk 16				
Placebo	244	0.013	−0.113 to 0.138	0.8387
Reslizumab	289	−0.286	−0.388 to −0.176	<0.0001
Wk 32				
Placebo	262	−0.027	−0.148 to 0.094	0.6624
Reslizumab	301	−0.332	−0.429 to −0.228	<0.0001
Wk 52				
Placebo	262	−0.122	−0.239 to −0.0006	0.0485
Reslizumab	308	−0.292	−0.391 to −0.186	<0.0001

AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval.

older than a healthy, non-smoking individual of a corresponding age and sex. Treatment with reslizumab resulted in a reduction (improvement) in the lung-age deficit versus placebo of ~5 years at 52 weeks, which indicated a shift toward improved lung function with reslizumab. Importantly, the improvements were observed within 4 weeks of treatment and were sustained up to 52 weeks. Among lung-age responders (defined as those with a reduction of ≥5 years over 52 weeks), reductions in the lung-age deficit were generally greater with reslizumab than with placebo during the 52-week treatment period. We believe that these data represented the first assessment of improvements in lung age with an IL-5 inhibitor in patients with asthma. To our knowledge, currently, there is no threshold that determines whether a change in lung age over time is clinically meaningful. Because spirometric lung age is designed for use as a patient education tool and is derived from FEV₁ data, it could be proposed that clinically meaningful changes in FEV₁ represent clinically meaningful improvement in lung age. Our study was a *post hoc* analysis of previous data to assess changes in lung age with reslizumab and placebo, and so was not designed to determine thresholds of clinical significance for lung age. However, these factors will be valuable for the use of lung age as a patient educa-

tion tool, and future studies should be considered to validate the use of lung age in asthma and to establish thresholds for clinically meaningful differences.

Importantly, the improvement in lung age was associated with improvements in QoL. Among patients treated with reslizumab who experienced a clinically significant improvement in their QoL, the improvement in the AQLQ score was statistically significantly correlated with improved lung age at all measured time points. Correlation estimates with reslizumab were similar among the overall population and AQLQ responders, which suggested that the two variables continued to be related without reaching a detectable upper threshold. In lung-age responders, both the mean change from baseline in the AQLQ score and the proportion of patients who achieved an AQLQ response were significantly greater for patients treated with reslizumab compared with patients who received placebo. Previous reports of the correlation between lung function and QoL vary, from no effect to moderate correlations.^{31–34} The lack of a strong correlation may be because assessment of lung function reflects a single time point measurement, whereas QoL represents an average of days or weeks.³⁴ Overall, it seems that objective measures of lung function are only

Table 4 Baseline demographics and clinical characteristics among lung-age responders

	Placebo (<i>n</i> = 361)	Reslizumab 3.0 mg/kg (<i>n</i> = 396)	Total (<i>n</i> = 757)
Age, mean $\pm$ SD, y	46.4 $\pm$ 14.5	46.2 $\pm$ 13.8	46.3 $\pm$ 14.1
Males, <i>n</i> (%)	126 (35)	168 (42)	294 (39)
BMI, mean $\pm$ SD, kg/m ²	27.02 $\pm$ 5.50	27.12 $\pm$ 5.41	27.07 $\pm$ 5.45
Age of asthma onset, mean $\pm$ SD, y	28.2 $\pm$ 17.5	27.4 $\pm$ 18.4	27.8 $\pm$ 18.0
High-dose ICS use, <i>n</i> (%) [*]	164 (45)	170 (43)	334 (44)
OCS use, <i>n</i> (%)	58 (16)	64 (16)	122 (16)
LABA use, <i>n</i> (%)	292 (81)	335 (85)	627 (83)
Lung age, mean $\pm$ SD, y	82.2 $\pm$ 22.9	81.7 $\pm$ 22.5	82.0 $\pm$ 22.7
Lung-age deficit, mean $\pm$ SD, y	35.8 $\pm$ 20.2	35.5 $\pm$ 20.6	35.6 $\pm$ 20.4
FEV ₁ , mean $\pm$ SD			
Prebronchodilation, L	1.90 $\pm$ 0.72	1.96 $\pm$ 0.73	1.93 $\pm$ 0.72
% Predicted	64.07 $\pm$ 18.74	64.53 $\pm$ 18.50	64.31 $\pm$ 18.61
% Reversibility	28.62 $\pm$ 22.74	27.65 $\pm$ 16.08	28.12 $\pm$ 19.54
FVC, mean $\pm$ SD, L	2.95 $\pm$ 0.97	3.05 $\pm$ 1.00	3.00 $\pm$ 0.99
ACQ-6 score, mean $\pm$ SD	2.55 $\pm$ 0.91	2.48 $\pm$ 0.92	2.52 $\pm$ 0.91
Blood eosinophil count, mean $\pm$ SD, cells/Liter	0.66 $\pm$ 0.61	0.67 $\pm$ 0.64	0.67 $\pm$ 0.62
CAEs within the past 12 months, mean $\pm$ SD	2.16 $\pm$ 2.24	1.92 $\pm$ 1.64	2.03 $\pm$ 1.95

SD = Standard deviation; BMI = body mass index; ICS = inhaled corticosteroid; OCS = oral corticosteroid; LABA, long-acting β -agonist; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ACQ-6, Asthma Control Questionnaire-6; CAE, clinical asthma exacerbation.

^{*}Defined as the patient receiving any one of the following daily doses: fluticasone >500 μ g, mometasone >440 μ g, budesonide >800 μ g, ciclesonide >320 μ g, beclomethasone >400 μ g, or triamcinolone >2000 μ g.

weakly to moderately correlated with subjective measures that describe how patients actually feel.³¹

This study showed that anti-IL-5 therapy can result in early and sustained improvement in lung age in appropriately selected patients with uncontrolled eosinophilic asthma. It was previously reported that improvements in lung function can occur rapidly with anti-IL-5 therapy, often within the first 4 weeks after the first dose,²⁴ and, therefore, can provide fast positive feedback to patients regarding the benefits of treatment compared with waiting 12 months to determine improvements in annual rates of asthma exacerbations. The concept of lung age offers a potentially valuable tool for the communication to patients of lung function benefits of treatment in a way that may be more readily understood than other measures of lung function, such as the FEV₁ % predicted. As such, this concept may have significant value as an educational tool in asthma and warrants further study. Effective asthma education is a critical part of asthma management, and one of the key components of asthma care, as acknowledged by international guidelines.²

Effective patient education should provide verbal, written, and schematic explanations of asthma that

best suit the language and health literacy of the patient.³⁵ Further, patient education should achieve a practical understanding of the concepts of inflammation, hyperreactivity, bronchoconstriction, and airway remodeling.³⁶ However, spirometric measurements of lung function are typically reported in absolute terms or as a percentage of predicted values based on a reference population, and this clinical language may prevent patients' understanding of the importance of lung function. By contrast, the lung-age concept may be more relatable because it presents spirometry results by using the age of an average healthy individual with similar spirometry results. For instance, the impact of a 47-year old being told he or she has the lung age of a healthy 79-year old, as would be the case in the present study (Table 1), may convey the concept of reduced lung function and the importance of treatment adherence in a more understandable way.

Lung age has been used as a motivational tool for smoking cessation and has improved biologically confirmed smoking cessation end points in clinic populations¹⁸ and randomized controlled trials.^{19,20} However, the potential of lung age as an asthma management tool remains largely unexplored.³⁷ As with smoking

Table 5 Proportion of patients achieving an AQLQ response and change from baseline in AQLQ score among lung-age responders

	Placebo (n = 361)	Reslizumab (n = 396)	Treatment Difference	p
Proportion of patients who achieved an AQLQ response, n (%)				
Wk 16	201 (58)	251 (67)	NA	0.0119
Wk 32	217 (65)	265 (72)		0.0443
Wk 52	211 (65)	269 (75)		0.0029
Change from baseline in AQLQ score, least square mean $\pm$ SE				
Wk 16	0.776 $\pm$ 0.082	0.978 $\pm$ 0.078	0.201 $\pm$ 0.075	0.0076
Wk 32	0.941 $\pm$ 0.082	1.181 $\pm$ 0.078	0.239 $\pm$ 0.076	0.0017
Wk 52	0.914 $\pm$ 0.083	1.243 $\pm$ 0.079	0.330 $\pm$ 0.078	<0.0001

AQLQ = Asthma Quality of Life Questionnaire; NA = not applicable; SE = standard error.

Table 6 Change from baseline and treatment differences (reslizumab vs placebo) in lung-age deficit (years) among lung-age responders

Wk	Mean $\pm$ SE Change from Baseline, y		Treatment Difference (reslizumab vs placebo), y	$\pm$ SE of Treatment Difference	95% CI	p
	Placebo (n = 361)	Reslizumab (n = 396)				
4	-7 $\pm$ 1.50	-13 $\pm$ 1.35	-6	1.44	-9 to -3	<0.0001
8	-12 $\pm$ 1.53	-16 $\pm$ 1.37	-4	1.49	-7 to -1	0.0068
12	-12 $\pm$ 1.54	-16 $\pm$ 1.38	-4	1.51	-7 to -1	0.0129
16	-12 $\pm$ 1.54	-16 $\pm$ 1.38	-4	1.50	-7 to -1	0.0152
20	-12 $\pm$ 1.52	-16 $\pm$ 1.36	-4	1.47	-7 to -1	0.0097
24	-14 $\pm$ 1.51	-16 $\pm$ 1.36	-3	1.46	-5 to 0	0.0825
28	-14 $\pm$ 1.49	-17 $\pm$ 1.34	-2	1.41	-5 to 0	0.0785
32	-15 $\pm$ 1.54	-17 $\pm$ 1.38	-2	1.52	-5 to 1	0.2602
36	-14 $\pm$ 1.54	-17 $\pm$ 1.38	-4	1.51	-7 to -1	0.0181
40	-14 $\pm$ 1.54	-17 $\pm$ 1.38	-3	1.51	-6 to 0	0.0230
44	-13 $\pm$ 1.47	-17 $\pm$ 1.33	-4	1.39	-7 to -1	0.0034
48	-13 $\pm$ 1.50	-17 $\pm$ 1.35	-3	1.44	-6 to -1	0.0170
52	-17 $\pm$ 1.40	-19 $\pm$ 1.26	-2	1.25	-5 to 0	0.0898
End point*	-18 $\pm$ 1.47	-20 $\pm$ 1.33	-2	1.25	-4 to 0	0.1027

SE = Standard error; CI = confidence interval.

* Time point at which the last observation was obtained at a postbaseline scheduled visit or early termination.

cessation,^{18,19} health-care professionals could consider lung age as part of an education program and intervention package in asthma. In addition to presenting FEV₁ % predicted values, an estimation of lung age may allow a benchmark to be set for a patient's asthma that is easy to understand and follow over time. Effective patient education has been shown to encourage adherence to asthma pharmacotherapy,^{35,38,39} which

leads to improved outcomes and reduced treatment costs.¹⁶

This study had a number of strengths and limitations. Limitations included the *post hoc* design. The analysis used the Morris and Temple equations, which are generally recognized and frequently used as the standard methodology for the determination of lung age. However, the Morris and Temple equations were

first developed in 1985 and are based on predictive equations from 1971.^{18,40} More recent equations were proposed, such as the Australian and Japanese Respiratory Society models.^{41–43} Calculation of lung age estimates by using the more recent equations resulted in differences compared with the Morris and Temple equations, which, perhaps, were attributable to cohort and period effects.^{41–43} As such, determination of lung age in our cohort when using these alternative equations may have yielded different results. Also, although the Morris and Temple equations adjust for sex, they do not correct for differences associated with ethnicity. The development of a lung-age equation that accounts for ethnicity may further enhance the value of lung age as a tool for patient education.

In acknowledging these limitations, our analysis comprised a large patient population and we believe it to be the first investigation of an IL-5 inhibitor on spirometric lung age in patients with moderate-to-severe eosinophilic asthma. Subsequent prospective studies should investigate whether using lung age as a communicative tool in addition to pharmacotherapy improves both lung age and treatment compliance in patients with moderate-to-severe eosinophilic asthma.

CONCLUSION

Reslizumab demonstrated effectiveness in reducing the lung-age deficit by an average of ~5 years in patients with moderate-to-severe and uncontrolled eosinophilic asthma, and that improvement in lung age correlated with improved QoL. Although the potential of lung age as an asthma management tool, to date, is largely unexplored, this concept provides an easy-to-understand indication of pulmonary function and could have substantial utility for patient education and the tracking of disease progression in asthma.

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