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Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils

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ABSTRACT

Introduction: Asthma with adult onset and elevated blood eosinophils is a difficult-to-treat subgroup. This *post hoc* analysis evaluated reslizumab, an anti-interleukin-5 monoclonal antibody, in patients with late-onset eosinophilic asthma.

Methods: Data from two 52-week placebo-controlled trials of reslizumab IV 3 mg/kg every 4 weeks in patients aged 12–75 years with inadequately controlled asthma, ≥1 asthma exacerbation within 12 months, and screening blood eosinophils ≥400/μL (NCT01287039/NCT01285323) were stratified by age of asthma onset (<40 or ≥40 years). Annual clinical asthma exacerbation rates, change in lung function, and patient-reported outcomes were analyzed.

Results: 273 patients with late-onset asthma (placebo, n = 130; reslizumab, n = 143) and 658 with early-onset asthma (placebo, n = 336; reslizumab, n = 322) were included. Baseline demographics were similar between groups. The interaction between age at onset of asthma and effect of reslizumab on asthma exacerbations was statistically significant (p = 0.0083). Compared with placebo, reslizumab produced a 75% relative reduction in asthma exacerbations in patients with late-onset asthma (rate ratio [RR] 0.25; 95% confidence interval [CI], 0.16, 0.40), substantially larger than the reduction in earlier onset patients (RR 0.58; 95% CI, 0.44, 0.76). Similar findings were observed for other measures of asthma, including forced expiratory volume in 1 s (FEV_1). The adverse event profile of reslizumab was similar in patients with early- or late-onset asthma.

Conclusions: Compared with placebo, reslizumab produced larger reductions in asthma exacerbations and larger improvements in lung function in patients with late *versus* early-onset asthma.

1. Introduction

Asthma is a heterogeneous syndrome encompassing multiple phenotypes according to severity of symptoms, degree of airflow limitation, level of asthma control, frequency of exacerbations, nature of the underlying airway inflammation (eosinophilic or non-eosinophilic), and the age at onset of asthma [1]. Asthma developing for the first time in adulthood (late onset [LO]) represents a particularly difficult-to-treat subgroup of the severe asthma population, and is associated with a distinctive biology and phenotypic characteristics compared with asthma that develops in childhood [early onset]) [1–3]. The phase 3 reslizumab population represents mostly adult patients with uncontrolled asthma and an eosinophilic phenotype, and encompasses patients with early-onset asthma as well as with LO asthma [4].

Reslizumab is a high-affinity, humanized anti-interleukin (IL)-5 monoclonal (IgG4/κ) antibody, which inhibits activity within the IL-5 signaling pathway by reducing ligand-receptor interactions and reduces blood and tissue eosinophils in patients with asthma [5–7]. Add-on therapy with reslizumab (intravenous; IV) 3 mg/kg every 4 weeks (Q4W) was shown to produce significant reductions in the frequency of asthma exacerbations in two, replicate 52-week phase

Abbreviations: ACQ, Asthma Control Questionnaire; AE, adverse event; AQLQ, Asthma Quality of Life Questionnaire; ASUI, Asthma Symptom Utility Index; BMI, body mass index; CAE, clinical asthma exacerbation; CI, confidence interval; ER, emergency room; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IV, intravenous; LABA, long-acting beta agonist; LO, late onset; LS, least-squares; OCS, oral corticosteroids; PBO, placebo; Q4W, every 4 weeks; RES, reslizumab; RR, rate ratio; SD, standard deviation.

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3 safety and efficacy studies in symptomatic, exacerbation-prone asthma patients (≥12 years) with elevated blood eosinophils. In addition, treatment with reslizumab improved pulmonary function, patient-reported asthma control, symptoms and quality of life measures [4].

The current study aims to determine the efficacy of reslizumab treatment in patients with LO asthma by secondary analysis of pooled data from the two replicate 52-week exacerbation studies. An age cut-off of ≥40 years was primarily utilized based on previous studies, which suggest that this is a reasonable age boundary for defining LO disease in asthma [8,9]; other age cut-offs for LO asthma were also explored. Finally, the safety of reslizumab was evaluated according to the age at onset of asthma, in order to determine the benefit:risk ratio.

2. Methods

2.1. Study design and participants

Data for the analyses presented here originated from two replicate, randomized (1:1 ratio), placebo-controlled, double-blind, parallel-group phase 3 studies (studies 3082 [NCT01287039] and 3083 [NCT01285323]). Detailed methodology and results from the 3082 and 3083 trials have been previously reported [4]. In brief, patients received either reslizumab (3 mg/kg) or placebo administered IV Q4W for 52 weeks. At baseline, patients (12–75 years of age) were required to be diagnosed with asthma that was inadequately controlled on at least medium dose inhaled corticosteroid (ICS)-based therapy. All patients had increased blood eosinophil levels (≥400 cells/μL) at screening. Use of maintenance oral corticosteroids (OCS; ≤10 mg/kg/day of prednisone, or equivalent) was permitted.

The studies were 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.

2.2. Outcomes

The frequency of clinical asthma exacerbations (CAEs) over 52 weeks for reslizumab relative to placebo is represented by a rate ratio (RR). A CAE was defined by worsening lung function or asthma symptoms that required a medical intervention beyond usual care involving any of the following: systemic corticosteroid burst (≥3 days); increase in baseline ICS dose (doubling or more); an unscheduled visit to a doctor's office for urgent asthma treatment; an emergency room (ER) visit or a hospitalization for asthma [4]. Exacerbations requiring OCS or an ER visit/hospitalization were analyzed separately. Changes in the asthma impairment measures of forced expiratory volume in 1 s (FEV_1), Asthma Quality of Life Questionnaire (AQLQ), Asthma Control Questionnaire (ACQ)-6 and Asthma Symptom Utility Index (ASUI) over 52 weeks are also reported.

This is a *post hoc* analysis of pooled data from replicate 52-week asthma exacerbation studies (the 3082 and 3083 trials) by age of asthma onset ≥40 years (LO asthma); additional age of onset thresholds were also explored (≥age 18, 25, 30, and 35). Age of asthma onset (years) was determined from the patient's screening medical history information. The safety profiles for the patient populations from the 3082 and 3083 trials have already been reported by Castro and colleagues [4].

2.3. Statistical analyses

The ratio of CAE rate between the treatment groups and its 95%

Table 1
Patient demographics and baseline disease characteristics by age of asthma onset.

	Age of onset <40 years (n = 658)	Age of onset ≥40 years (n = 273)
Age, years, mean (SD)	42 (13)	58 (7)
Male, %	36	41
BMI, kg/m^2, mean (SD)	27.3 (5.9)	27.9 (5.3)
ICS[a] plus LABA, n (%)	545 (83)	221 (81)
Geographical location, n (%)		
USA	86 (13)	18 (7)
Europe	280 (43)	167 (61)
Asia	103 (16)	52 (19)
Other	189 (29)	36 (13)
OCS, n (%)	98 (15)	44 (16)
FEV_1 (L), mean (SD)	2.06 (0.79)	1.84 (0.64)
FEV_1% predicted, mean (SD)	66.5 (2.1)	67.8 (18.7)
ACQ6 score, mean (SD)	2.50 (0.93)	2.46 (0.87)
AQLQ score, mean (SD)	4.27 (1.10)	4.20 (1.02)
ASUI score, mean (SD)	0.65 (0.20)	0.62 (0.19)
Blood eosinophils, cells/μL		
Mean, SD	667 (693)	637 (467)
Median	500	500
Allergic disease by history[b], n (%)	438 (67)	134 (49)
Atopy (specific IgE)[c], n (%)	231 (69)	54 (41)
Chronic sinusitis + nasal polyps[d], n (%)	89 (14)	60 (22)
Number of exacerbations in previous 12 months mean (SD)	1.97 (1.82)	1.99 (1.99)

Values are for all randomized patients (placebo + reslizumab).
[a] Medium or high-dose ICS.
[b] Patient history of atopic dermatitis, or allergic rhinitis, or allergy shots.
[c] Presence of at least one ImmunoCAP test positive (≥0.35), study 3082 only.
[d] Based on patient history. SD = standard deviation; BMI = body mass index; ICS = inhaled corticosteroid; IgE = immunoglobulin E; LABA = long-acting beta agonist; OCS = oral systemic corticosteroids; FEV_1 = forced expiratory volume in 1 s; PBO = placebo; RES = reslizumab; ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ASUI = Asthma Symptom Utility Index.

confidence interval (CI) were analyzed using a negative binomial model. The primary negative binomial model included the treatment group and randomization stratification factors (baseline usage of oral corticosteroid [yes or no] and geographical region [US or other]) as model factors and the logarithm of follow-up time excluding the summed duration of exacerbations in the treatment period as an offset variable. A 95% CI for the RR that excludes the value of 1 supports the claim that the RR is different than 1, namely, that reslizumab decreases the rate of exacerbations. Analysis of the overall change from baseline in the impairment measures of FEV_1, AQLQ, ACQ6, and ASUI over the 52-week treatment period was performed using a mixed-effect model for repeated measures including treatment, visit, treatment by visit interaction, region, OCS use at enrolment as fixed factors, and covariates for baseline value and patient as a random effect. Height and sex were also included as fixed effects for FEV_1.

3. Results

3.1. Patient disposition and baseline characteristics

Pooled data from 931 randomized patients from studies 3082 and 3083 were included in the *post hoc* analysis; 273 patients had LO asthma (placebo, n = 130; reslizumab, n = 143); whereas 658 patients had asthma with an onset <40 years of age (placebo, n = 336; reslizumab, n = 322).

Baseline demographics and disease characteristics are presented in Table 1. Baseline demographics and asthma control characteristics, including lung function, asthma exacerbation history, patient-reported asthma control, and quality of life scores were similar between the two groups. Baseline blood eosinophil levels were also similar between patients with LO asthma and patients with age of onset <40 years. Patients with LO asthma had a lower frequency of allergic disease and atopy compared with those with an age of onset <40 years. In contrast, a higher proportion of patients in the LO asthma group had chronic sinusitis with nasal polyps.

3.2. Efficacy outcomes: asthma exacerbations

Patients in the placebo arm with LO asthma had a higher background CAE rate compared with the overall population or patients with age of asthma onset <40 years of age: 2.26 *versus* 1.81 or 1.69 CAEs per patient per year, respectively. Based on an age cut-off of 40 years, patients with LO asthma experienced a relative reduction in asthma exacerbations of 75% with reslizumab that was larger than for the overall population and for patients with age of onset <40 years (Fig. 1A; p value for interaction between age group and treatment effect = 0.0083). A similar association was observed for exacerbations requiring OCS treatment (Fig. 1B). ER visits and hospitalizations due to asthma were relatively uncommon in these phase 3 clinical trials; however, exacerbations requiring an ER visit or hospitalization were reduced by 75% in the LO subgroup *versus* 34% for the overall population and 12% for asthmatics with age of onset <40 years (Fig. 1C).

The larger magnitude of reslizumab benefit in reducing CAEs in patients with LO asthma compared with the overall population and patients with early-onset asthma was consistently observed across a range of LO asthma age cut-offs (age of onset ≥18, 25, 30, 35 or 40 years; Fig. 2). Across this range of age cut-offs, reslizumab treatment reduced the rate of CAEs in patients with LO asthma by 68–75%.

3.3. Secondary efficacy outcomes

The magnitude of the improvement in FEV_1 from baseline over 52 weeks with reslizumab was similar across the overall population and in the subgroups of patients with an age at onset <40 years and those with LO asthma (224, 202, and 209 mL, respectively). However, the treatment difference for these groups *versus* placebo was largest for the LO asthma patients (110 mL, 88 mL, and 167 mL, respectively) due to the relatively smaller placebo effect observed in the LO subgroup compared with the early-onset asthma

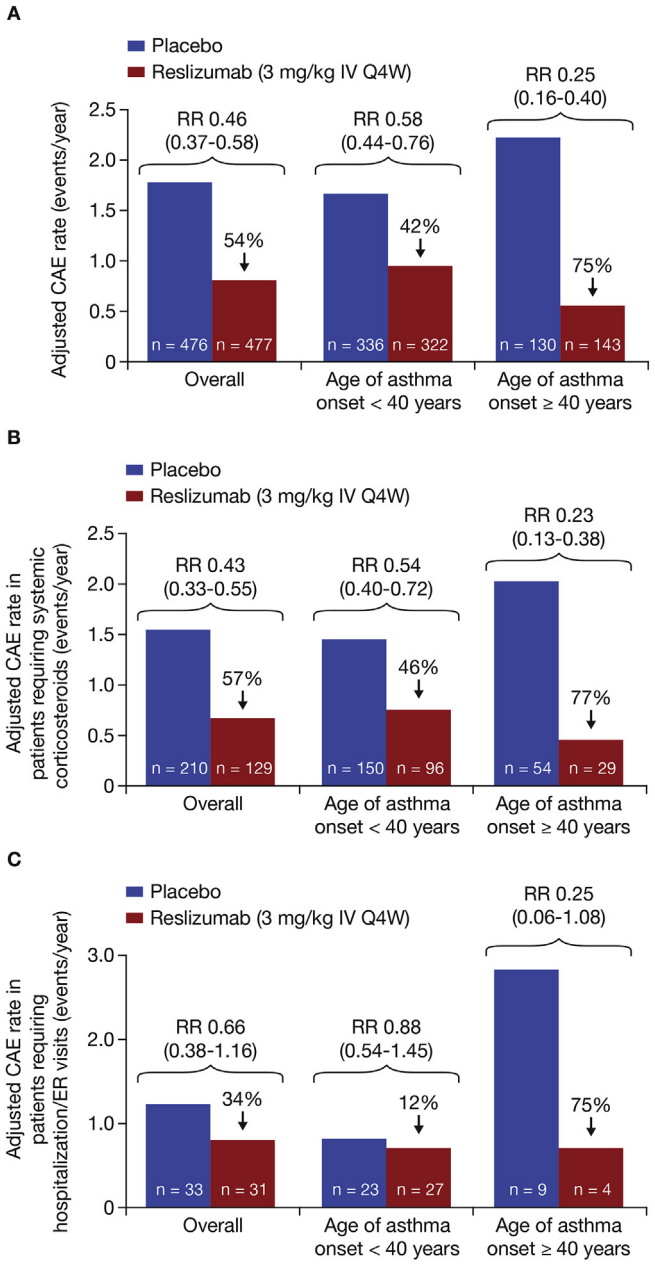

Fig. 1. Clinical asthma exacerbation (CAE) rate over 52 weeks (A), CAEs requiring systemic corticosteroids (B), and CAEs requiring hospitalization/ER visits (C) over 52 weeks by age of asthma onset. Values in brackets represent 95% CIs. The sample numbers for each subgroup are as follows: the total number of patients (A), the number of patients with at least one CAE requiring corticosteroids (B), and the number of patients with at least one CAE resulting in hospitalization/ER visits (C). ER = emergency room; RR = rate ratio; IV = intravenous; Q4W = every 4 weeks; CI = confidence interval.

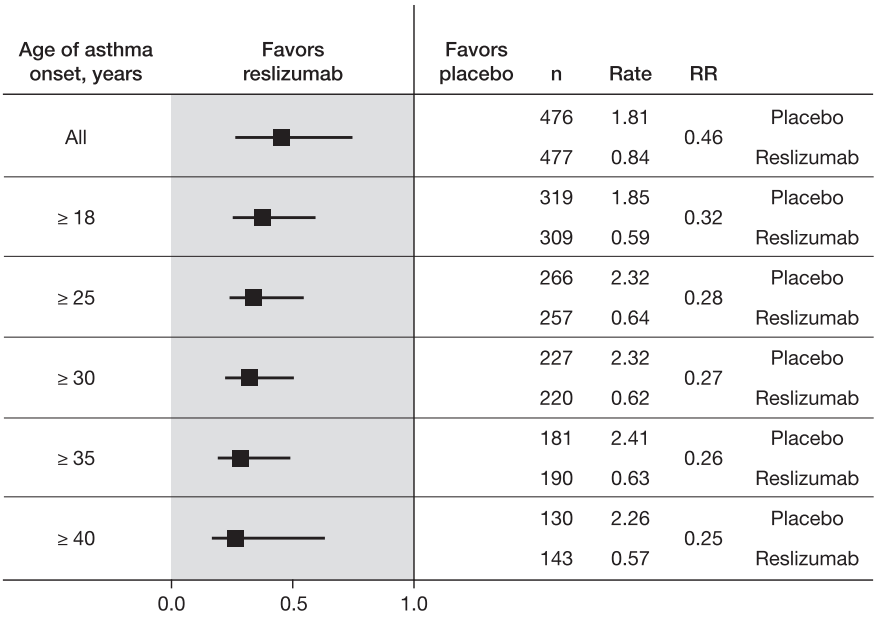

Fig. 2. Clinical asthma exacerbation (CAE) rates by age of asthma onset. RR = rate ratio.

subgroup (42 mL *versus* 114 mL) (Fig. 3). Similarly, improvements in the patient-reported outcomes of ACQ6 and ASUI were largest for LO asthmatics, whereas quality of life improvements were similar across the overall and LO subgroups (Table 2). The proportion of ACQ6 and AQLQ responders (ie, treatment difference from placebo ≥0.5 units) showed only slight differences between the overall population and LO asthma (79% *versus* 85% for ACQ6, and 73% *versus* 78% for AQLQ, respectively).

3.4. Safety

The most common adverse events (AEs) occurring among patients with LO asthma and those with an age of onset of asthma <40 years are shown in Table 3. Percentages of patients with at least one AE were similar in the two groups, and slightly higher with placebo than with reslizumab. Accordingly, most AEs (both system organ classes and preferred terms) affected similar percentages of patients with *versus* without LO asthma.

4. Discussion

Patients with LO asthma appear to represent a clinically distinctive and often severe form of the disease [10]. The defining age for LO of asthma varies in the literature, with early onset typically used to describe symptoms developing during childhood and LO asthma defined as asthma with onset in adulthood (broadly defined as after age 18 years or 40 years) [11,12]. The aim of this *post hoc* analysis of the pooled data from two replicate, phase 3 studies of reslizumab (3 mg/kg IV Q4W) in uncontrolled eosinophilic asthma was to assess the comparative efficacy of reslizumab in patients with LO asthma *versus* early-onset asthma.

Patients with inadequately controlled LO asthma, defined by age of onset ≥40 years, were more prone to asthma exacerbations than the overall population or patients with age of onset <40 years, based on higher exacerbation rates during placebo treatment; this result supports the observation that asthma is more severe in this subpopulation. Of note, placebo-treated patients with LO asthma also had a lower FEV_1 response to standard of care treatment compared with the overall population and patients with age of onset <40 years, which is also consistent with more severe disease (Fig. 3). LO asthma patients had a marked response to reslizumab (75% reduction in both CAEs and in events requiring a hospitalization or ER visit) that was larger than that observed for the overall study population or patients with age of onset <40 years (54% and 34% reduction, respectively). Treatment differences between reslizumab and placebo in measures of current asthma impairment were also numerically larger for LO patients compared with the overall population: lung function (FEV_1: 167 mL *versus* 110 mL), patient-reported asthma control (ACQ6: −0.363 *versus* −0.238) and patient-reported asthma symptoms (ASUI: 0.061 *versus* 0.049). Different definitions of LO asthma, ranging from age of onset of ≥18 years to ≥40 years of age, were tested and produced similarly large reductions in the rate of exacerbations with reslizumab relative to placebo. The safety profile of reslizumab was similar in LO asthma patients and those with an age of onset <40 years.

It is possible that differences in the pathobiology between the overall eosinophilic asthma population and those with LO asthma may contribute to the apparent differences in the magnitude of

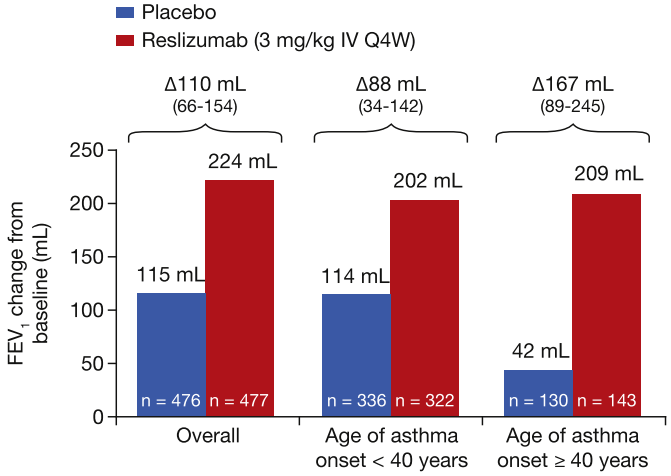

Fig. 3. Change in FEV_1 over 52 weeks by age of asthma onset. Values in brackets represent 95% CIs. FEV_1 = forced expiratory volume in 1 s; IV = intravenous; Q4W = every 4 weeks; CI = confidence interval.

treatment effect with reslizumab. Consistent with previous observations, patients in this study with LO asthma were more likely to have chronic sinusitis and nasal polyps, less atopy, and fewer comorbid allergic diseases compared with patients without LO asthma (Table 1) [2,10,13]. Indeed, a separate *post hoc* analysis using data from the same overall populations as the current analysis found that patients with nasal polyps and chronic sinusitis benefited most from reslizumab (*versus* the overall population) – this included an 83% reduction in the annual rate of CAEs relative to placebo ($p = 0.0002$) [14]. This provides further support for the use of reslizumab in patients with LO eosinophilic asthma.

Early-onset asthma may be described as being primarily driven by atopy and typified by type 2 cytokine expression (including IL-5) with consequential eosinophilia [15]. In contrast, in LO asthma (formerly called intrinsic asthma), the exogenous causes of the disease are largely unknown, although environmental stimuli such as oxidants (for example, chronic cigarette smoke exposure) or microbes might be involved. These agents may cause airway epithelial cells to secrete cytokines that activate innate lymphoid type 2 (ILC2) cells to produce IL-5 in an allergen-independent manner [2,16]. Moreover, increased numbers of IL-5-producing ILC2 cells have been observed in the airways of patients with severe LO asthma [17], as well as in patients with chronic rhinosinusitis and nasal polyps [16], despite treatment with high-dose ICS and even OCS, suggesting that ILC2 cells are relatively corticosteroid resistant. We put forward the hypothesis that the corticosteroid-resistant production of IL-5 by ILC2 cells underlies the persistent eosinophilic airway inflammation in LO asthmatics,

Table 2
Change from baseline in AQLQ, ACQ6 and ASUI over 52 weeks by age of asthma onset.

	Overall		Age of onset <40 years		Age of onset ≥40 years	
	Placebo (n = 476)	Reslizumab (n = 477)	Placebo (n = 336)	Reslizumab (n = 322)	Placebo (n = 130)	Reslizumab (n = 143)
ACQ6						
n			330	320	129	140
LS mean change from baseline	−0.85	−1.087	−0.805	−0.996	−0.977	−1.34
Treatment difference (95% CI)	−0.238 (−0.336, −0.140)		−0.191 (−0.309, −0.074)		−0.363 (−0.549, −0.177)	
AQLQ						
n			317	301	125	136
LS mean change from baseline	0.813	1.084	0.735	1.041	0.925	1.19
Treatment difference (95% CI)	0.272 (0.155, 0.388)		0.306 (0.166, 0.447)		0.265 (0.046, 0.484)	
ASUI						
n			323	315	129	138
LS mean change from baseline	0.122	0.171	0.104	0.149	0.165	0.226
Treatment difference (95% CI)	0.049 (0.033, 0.065)		0.046 (0.027, 0.064)		0.061 (0.031, 0.091)	

AQLQ = Asthma Quality of Life Questionnaire; ACQ = Asthma Control Questionnaire; ASUI = Asthma Symptom Utility Index; LS = least-squares; CI = confidence interval.

Table 3
Adverse events by age of asthma onset.

	Age of onset <40 years		Age of onset ≥40 years	
	Placebo (n = 336)	Reslizumab (n = 322)	Placebo (n = 130)	Reslizumab (n = 143)
At least one AE	285 (85)	255 (79)	114 (88)	110 (77)
Cardiac disorders	22 (7)	13 (4)	11 (8)	3 (2)
Gastrointestinal disorders	48 (14)	45 (14)	23 (18)	22 (15)
General disorders and administration site conditions	37 (11)	30 (9)	22 (17)	12 (8)
Fatigue	7 (2)	4 (1)	7 (5)	1 (<1)
Infections and infestations	201 (60)	173 (54)	81 (62)	69 (48)
Nasopharyngitis	66 (20)	49 (15)	23 (18)	24 (17)
Upper respiratory tract infection	31 (9)	30 (9)	15 (12)	15 (10)
Respiratory tract infection	6 (2)	8 (2)	7 (5)	7 (5)
Sinusitis	26 (8)	24 (7)	13 (10)	6 (4)
Urinary tract infection	15 (4)	14 (4)	6 (5)	5 (3)
Influenza	24 (7)	16 (5)	6 (5)	4 (3)
Pharyngitis	14 (4)	12 (4)	7 (5)	4 (3)
Bronchitis	29 (9)	13 (4)	6 (5)	2 (1)
Rhinitis	16 (5)	9 (3)	3 (2)	6 (4)
Injury, poisoning and procedural complications	33 (10)	22 (7)	10 (8)	13 (9)
Clinical laboratory results	33 (10)	29 (9)	9 (7)	16 (11)
Blood creatinine phosphokinase increased	7 (2)	6 (2)	4 (3)	8 (6)
Metabolism and nutrition disorders	18 (5)	18 (6)	8 (6)	9 (6)
Musculoskeletal and connective tissue disorders	48 (14)	44 (14)	18 (14)	21 (15)
Back pain	14 (4)	19 (6)	6 (5)	5 (3)
Nervous system disorders	58 (17)	49 (15)	21 (16)	26 (18)
Headache	34 (10)	35 (11)	12 (9)	16 (11)
Respiratory, thoracic and mediastinal disorders	199 (59)	152 (47)	79 (61)	59 (41)
Asthma	172 (51)	123 (38)	67 (52)	37 (26)
Dyspnea	10 (3)	6 (2)	7 (5)	6 (4)
Cough	12 (4)	12 (4)	8 (6)	2 (1)
Skin and subcutaneous tissue disorders	33 (10)	32 (10)	14 (11)	17 (12)
Vascular disorders	9 (3)	12 (4)	4 (3)	7 (5)

AE = adverse event. System organ classes and preferred terms reported in ≥5% of patients receiving either placebo or reslizumab (in either age of onset group) are shown. Data shown are numbers of patients (%).

and possibly explains the absence of a placebo effect in this group. Although the magnitude of tissue inflammation and blood eosinophilia can be similar in early and LO asthma (Table 1), IL-5 signaling is likely to underlie the greater proportion of symptom-related ICS-resistant signaling in LO asthma.

The main limitation of the study is that this *post hoc* analysis was not predefined and prospective controlled studies are needed to confirm these observations. However, the *post hoc* analysis was based upon a strong scientific rationale (ie, the presence of different endotypes of eosinophilic asthma according to the age at onset) [2]. Also, these observations are likely not applicable to patients with LO asthma who do not have an eosinophilic phenotype, as this was a requirement for inclusion. The parameter of age of asthma onset was necessarily patient reported and may therefore be imprecise. However, this approach clearly seems to identify a reslizumab-responsive LO asthma subgroup from the overall population and is consistent with the collection of a standard asthma history as would be used by healthcare professionals in everyday clinical practice. Finally, as this was a primarily adult population (age of inclusion for the phase 3 reslizumab trials was $\geq$12 years; however, only 25 patients age 12 to $\leq$17 years were randomized in the pooled dataset), the effect of reslizumab in adolescent patients with early-onset asthma remains to be elucidated.

In conclusion, patients with exacerbation-prone, LO asthma with elevated blood eosinophil levels ($\geq$400 cells/μL) and inadequately controlled symptoms responded particularly well to reslizumab, relative to the overall study population. These results contribute to our understanding of the heterogeneity of eosinophilic asthma and help to identify those patients most likely to achieve a clinically meaningful response to reslizumab.

Trial registry

ClinicalTrials.gov; NCT01287039 and NCT01285323.

Prior presentation

This analysis was previously presented, in part, at the European Respiratory Society International Congress, 2015.

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Conflict of interest

GB reports advisory board and speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Pfizer. MG reports being an employee and shareholder at Teva Pharmaceuticals. SW reports being an employee at Teva Pharmaceutical Industries Ltd. JZ reports being an employee at Teva Pharmaceuticals at the time of the analysis, interpretation of the data, and generation of this manuscript. JZ and GB are listed as co-inventors of a pending patent application entitled 'Use of reslizumab to treat moderate to severe eosinophilic asthma'.

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Guarantor statement: Guy Brusselle takes responsibility for the content of the manuscript, including the data and analysis.

Author contributions: GB, SW, MG and JZ were involved in data generation analysis and interpretation of the data and in preparation or critical revision of the manuscript. GB was a primary investigator and had full access to all the data in the studies and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the writing and revising of the manuscript and read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pupt.2017.01.011.

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